ACADEMY OF SCIENCES OF THE CZECH REPUBLIC

INSTITUTE OF BIOPHYSICS

RESEARCH REPORT
2001

BRNO 2002

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CONTENTS

I. INTRODUCTION

Research activities of the Institute issued from the scientific conception upgraded for the years 2001 - 2004 and from the research plan No. Z5004920, „Biophysical properties of living systems and their changes under the influence of environmental factors“. In addition, the Institute participated in two research plans in cooperation with Masaryk University - Faculty of Science and Faculty of Informatics.

Since the year 2001 the Institute is concerned with 3 new projects under the AS CR „The program of development of basic science research in the key areas of science“:

- K4055109 Physics, Chemistry and Informatics for Biological, Ecological and Medicinal Applications;
- K5011112 Molecular and Cellular Mechanisms of Important Diseases;
- K5052113 Structure, Expression and Interaction of the Genome.

At the same time, there is a continuation of one project of „The program for the support of advancement in research equipment in progressive fields of science“

- P1050128 Dynamics of Processes in Living and Inanimate Matter.

In January 2001 new Scientific Council of the Institute has been elected and consists of the following members: internal members - *V. Brabec* (chairman), *J. Hofmanová, F. Jelen, S. Kozubek, A. Lojek, J. Široký;* external members - *J. Doškař, A. Španová* (Masaryk University, Faculty of Science, Brno), *J. Šponer* (J. Heyrovský Institute of Physical Chemistry AS CR, Prague).

J. Šlotová has been elected the director of the Institute for the period of next four years, since July 1, 2001.

In the frame of the programme „The Day of Opened Doors“, aimed at the popularization of science, Laboratories of the Institute were visited by more than 200 visitors from schools of Brno who had the opportunity to get an acquaintance with the research in the field of electrochemistry of biomacromolecules, computer analysis and modelling of DNA, molecular cytology and cytokinetics, research of biophysical principles of the activity of anticancer drugs. Particular attention was devoted to the demonstration of unique scientific devices and research methods.

Furthermore, research activities were popularized in a series of articles in journals and newspapers, as well as in two videoprojects „Metamorphoses of Young Scientists“ (project of The Ministry of Education, Youth and Sports

of the Czech Republic, LP01055), and in the TV broadcast „Vědník“ (program of TV2, January 22, 2002).

The following researchers were awarded for their scientific activities:

B. Janoušek - The award of Josef Hlávka for extraordinary scientific results in the category of young scientists of the AS CR.

The Price of the Institute of Biophysics for young scientists were awarded:

N. Špačková for the set of publications on unusual structures in DNA - guanine quadruplexes;

V. Brázda for the set of publications dealing with the characterization of monoclonal antibodies raised against the protein p53 and with possibilities of their use in studies of p53 sequence-specific binding in linear and superhelical DNA;

C. Hofr for the set of publications on thermodynamical aspects of the molecular mechanism of anticancer activity of selected complexes of platinum a ruthenium.

S. Kozubek obtained the patent No. 288693 for „The Method of Determination of Cell Properties by Cytometry with a High Resolution and a Device for its Performance“ (July 20, 2001).

In 2001 finished the 1st stage of reconstruction works by establishing the extension of the Laboratory of Cytokinetics and, at the same time, the 2nd stage of complex reconstruction of some parts of the Institute, aimed at further expanding the laboratory space, commenced.

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MGR. IVANA VASILENKOVÁ* (SLOVAK REP.)	

*internal students

II. SCIENTIFIC ACTIVITIES

Individual Laboratories, grouped into five Programmes, undertake the research done by the Institute of Biophysics:

I. Biophysical Chemistry of Macromolecules

Laboratory of Biophysical Chemistry and Molecular Oncology - LBCMO
Prof. RNDr. Emil Paleček, DrSc.

Laboratory of Physics of Biomacromolecules - LBP
Prof. RNDr. Vladimír Vetterl, DrSc.

II. Biophysics of Nucleic Acid Complexes

Laboratory of Molecular Biophysics and Pharmacology - LMBP
doc. RNDr. Viktor Brabec, DrSc.

Laboratory of DNA Molecular Complexes - LDMC
RNDr. Jiří Fajkus, CSc.

Laboratory of Analysis of Chromosomal Proteins - LACP
RNDr. Michal Štros, CSc.

III. Biophysics and Bioinformatics of Genomes

Laboratory of CD Spectroscopy of Nucleic Acids - LSNA
RNDr. Michaela Vorlíčková, DrSc.

Laboratory of DNA Biophysics and Bioinformatics of Genomes - LDBGB
RNDr. Jaroslav Kypr, CSc.

Laboratory of Molecular Epigenetics - LME
RNDr. Aleš Kovařík, CSc.

IV. Molecular Cytology and Cytogenetics

Laboratory of Molecular Cytology and Cytometry - LMCC
RNDr. Stanislav Kozubek, DrSc.

Laboratory of Plant Development Genetics - LPDG
Prof. RNDr. Boris Vyskot, DrSc.

Laboratory of Plant Development Molecular Analysis - LMAPD
RNDr. Břetislav Brzobohatý, CSc.

V. Kinetics of Cell Populations

Laboratory of Cytokinetics - LC
doc. RNDr. Alois Kozubík, CSc.

Laboratory of Patophysiology of Free Radicals - LFRP
RNDr. Antonín Lojek, CSc.

Laboratory of Experimental Hematology - LEH
MUDr. Michal Hofer, CSc.

* * *

Laboratory of Computers and Information Systems - LCIS
RNDr. Josef Jursa, CSc.

The scientific projects were supported by grants from various grant agencies as follows:

Grant Agency of the Academy of Sciences of the Czech Republic

- 12 standard grants, 2 additional integration grants, 3 additional postgraduate grants
- 3 grants under the Programme for the Support of the Targeted Research and Development
- 3 grants under the Project for Development of Basic Science Research in the Key Areas of Science
- 1 grant under the Programme for the Support of Advancement in Research Equipment in Progressive Fields of Science

Grant Agency of the Czech Republic

- 21 individual grants; 19 of these had IBP scientists as principal investigators, whilst for the remaining 2 grants they were partial investigators
- 3 complex grants; 1 of them had IBP scientist as principal investigator, whilst for the remaining 2 grants they were partial investigators
- 13 postgraduate grants

Grant Agencies of Ministries of the Czech Republic

- Ministry of Health of the CR:
  - 5 grants; 4 of these grants had IBP scientists as principal investigators, 1 grant was as partial investigator
- Ministry of Industry and Trade of the CR:
  - 2 grants where the IBP scientists were partial investigators
- Ministry of Education, Youth and Sports of the CR:
  - "Research Centres" Programme - 2 grants where the IBP scientists were partial investigators
  - "Development of Universities" Programme - 4 grants where the IBP scientists were partial investigators
  - 4 grants under the "COST" Programme
  - 3 grants under the "KONTAKT" Programme

Foreign Grant Agencies

10 grants

PROGRAM I

BIOPHYSICAL CHEMISTRY OF MACROMOLECULES

LABORATORY OF BIOMACROMOLECULE PHYSICS (LBP)

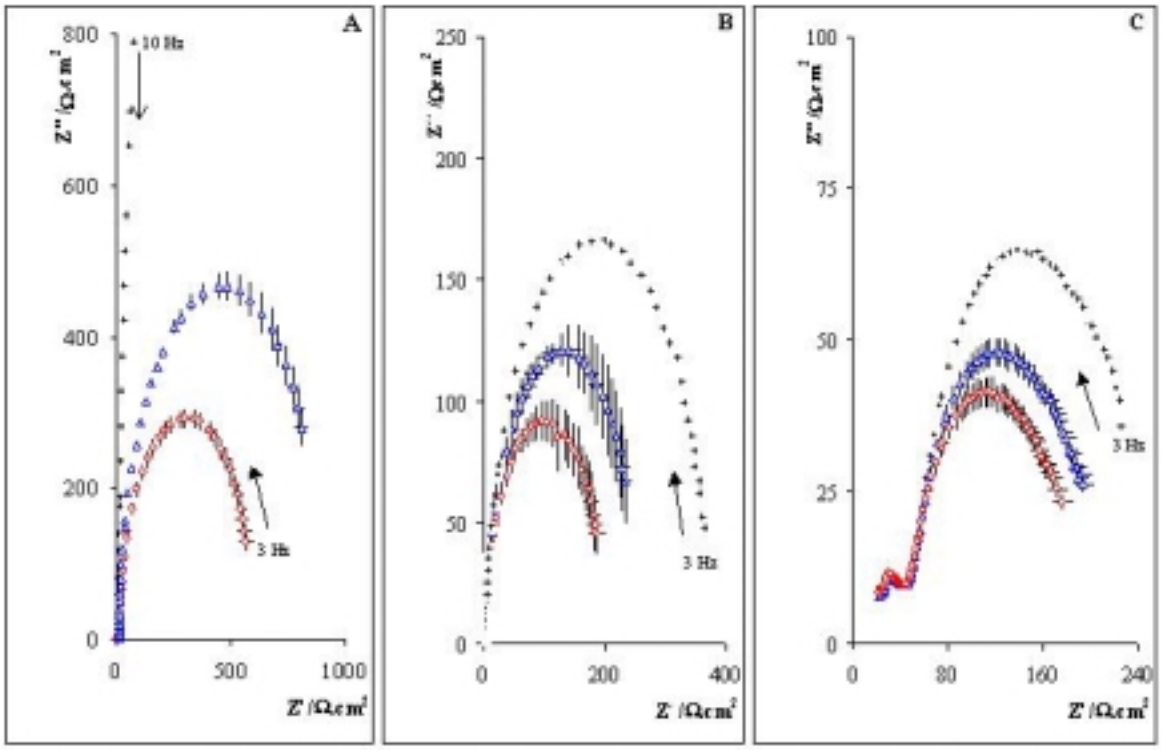
HEAD:	PROF. RNDR. VLADIMÍR VETTERL, DRSC.
SCIENTISTS:	RNDR. JIŘÍ ŠPONER, DRSC. MGR. VIKTOR DRAŽAN, PH.D.
RESEARCH FELLOW:	MGR. EVA RYCHTECKÁ
GRADUATE STUDENTS:	MGR. JANA RYCHTÁROVÁ MGR. NAĎA ŠPAČKOVÁ MGR. DIANA SMIEŠKOVÁ MGR. LUDĚK STRAŠÁK MGR. STANISLAV HASOŇ MGR. JAKUB DVOŘÁK
UNDERGRADUATE STUDENT:	JAN FOJT

I. Physical properties of the surface of different graphite electrodes and electrodes modified by a mercury thin film (thickness of the film was less than 5 μm) were studied by optical methods, cyclic voltammetry (CV) and electrochemical impedance spectroscopy (EIS). We have used the diffractive optical element (DOE) sensor for the study of the optical roughness of the above mentioned electrodes surfaces. The imaging properties of the DOE sensor obey the laws of hologram imagery. The CCD camera was used for visualisation of different surfaces of the graphite and graphite electrodes modified by mercury film. We have used the redox analytes ferri/ferrocyanide or cadmium to determine the electron – transfer constant k´ at the glassy carbon (GC), pyrolytic graphite (PG) in basal (horizontal axes) and edge (vertical axes) orientations or at the mercury film electrodes (MFE), respectively. The electric properties and electrochemical reactivity of these electrodes were studied by EIS measurements, i.e the frequency dependence of the impedance of electrode double layer. The thickness of the mercury film was about 2 μm. We have studied the dynamic of the mercury film formation by DOE sensor. Deposition of the mercury on different graphite surfaces during applied electromagnetic field was visualised by CCD camera.

II. The use of MFE for the study of electrochemical properties of nucleic acids and their components

a) The effect of optical roughnesses, anisotropy and electric conductivity of different graphite substrates covered with mercury film on the kinetics of formation of the two – dimensional (2D) condensed cytidine adlayers was studied. The kinetics of the formation of 2D physisorbed cytidine adlayer

from dilute adlayer of cytidine in acidic and alkaline solutions on the PGEbasal covered with a thin mercury film can be described by Avrami theorem of the nucleation and growth process. The formation of the 2D physisorbed cytidine adlayer on the PGEedge and GCE covered with mercury film is accompanied only by the adsorption process, the nucleation process is not observed.

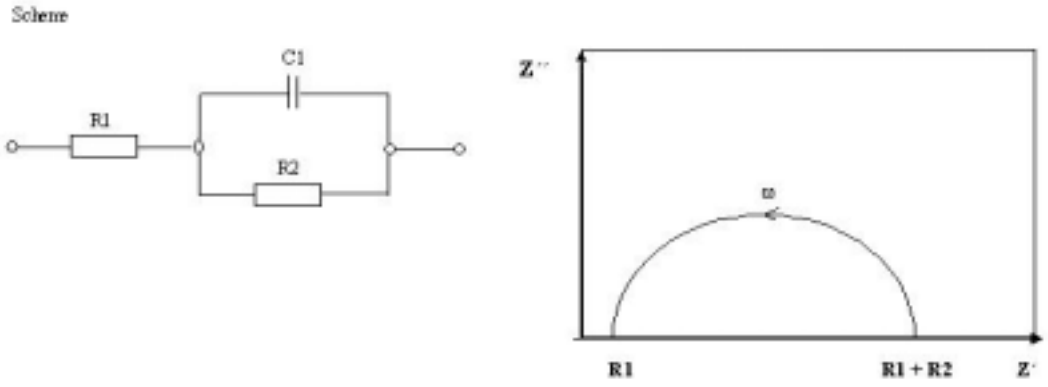


Complex impedance plots (Nyquist or Cole-Cole plots) of **(A)**, HMDE **(B)**, GCE|Hg and **(C)**, PGE|Hg. (+) bare electrodes, (Δ) electrodes modified by 100μg/ml native(ds)DNA and (O) 100μg/ml denatured (ss)DNA. The values are means ± standard deviations of 5 experiments. Frequency range was from 50 kHz to 3 Hz, ac voltage amplitude was 5mV.

b) The frequency dependence of the impedance of electrode double layer modified by nucleic acids measured with the GCE and PGEbasal covered with a mercury film at potential of the tensammetric peak 3 was studied. Providing that the mercury film-solution interface can be simulated by a parallel combination of C1 (double layer capacitance) and R2 (representing dielectric losses by tensammetric processes and/or charge transfer resistance by redox reactions) in series with the background electrolyte resistance R1 (see the scheme) the complex impedance plot should be a semicircle the radius of which is smaller with lower R2 values. It was observed that ssDNA has a smaller radius (lower R2) than the dsDNA. This result can be interpreted by a higher dielectric losses accompanying desorption of denatured DNA. With the HMDE and GCE|Hg the complex plane impedance plots of DNA exhibited arc shape, respectively (Fig. 1A,

B). With the PGEbasal|Hg (Fig. 1C) the complex plane impedance plots of DNA exhibited two arcs of different radius. The smaller arc (from 50 kHz to 10 kHz) is observed not only with PGE|Hg modified by DNA but with background electrolyte as well and thus obviously results from the kinetic processes taking place at the PGE|Hg - electrolyte interface at higher frequencies.

c) The interaction of echinomycin with nucleic acids on the MFE was studied. The capacitance measurement showed that echinomycin gived a pseudocapacitance redox peak strongly dependent on the a.c. voltage frequency at the potential of -0.53 V. Detection limit of echinomycin at the MFE was about 10 nM in the bulk of solution. We have found differences in the capacitance curves of ds and ssDNA. dsDNA complex with echinomycin produced specific echinomycin signal in agreement with the strong binding of echinomycin to dsDNA by bis-intercalation. Under the same conditions interaction of echinomycin with ssDNA resulted in almost no echinomycin signal suggesting only very weak interaction of echinomycin with ssDNA at the electrode surface. Our results demonstrate that echinomycin is suitable for finding differences between dsDNA and ssDNA at MFE using impedance (C-E curves and EIS) measurements.



GRANTS:

GA AS CR A4004002
Structure and interactions of nucleic acids and polypeptides at metal surfaces
Principal investigator: V. Vetterl, 2000 - 2002

GA AS CR A4004901
Analysis of the interactions of mutagens, carcinogens and anti-cancer drugs with biopolymers by means of electrochemical and biochemical methods
Principal investigator: F. Jelen, 1999 - 2001

GA AS CR K4055109
Physics, chemistry and informatics for biology, ecology and health application
Principal investigator: A. Holý, IOCHB AS CR, Prague, principal co-investigator: V. Vetterl, IBP AS CR, Brno, 2001 - 2004

GA CR 204/97/K084
Electrodes modified with nucleic acids and proteins. New tools in biochemical and biomedical research
Principal investigator: E. Paleček, principal co-investigators: O. Dračka, Fac. Sci. MU, Brno, L. Novotný, IPCH J.H. AS CR, Prague, B. Vojtěšek, MOÚ, Brno, 1997 - 2002

GA CR 203/00/P081
Adsorption of nucleic acid bases and their derivatives at electrodes
Principal investigator: V. Dražan, 2000 - 2002

GA CR 310/01/0816
Effect of low frequency electric and magnetic fields on biological systems
Principal investigator: V. Vetterl, 2001 - 2003

Research Centres of Ministry of Education, program LN00A016
Biomolecular centrum
Principal investigator: J. Šponer, 2000 - 2004

Support of the target research S5004107
Application of biophysical methods in biotechnological and clinical praxis
Principal investigator: V. Vetterl, 2001 - 2005

Grant Agency of the Ministry of Education, Youth and Physical Training of the Czech Republic, Fund of Universities Development MU 564
Innovation of teaching of bioelectrochemistry
Principal investigator: V. Vetterl, 2001

Grant Agency of the Ministry of Education, Youth and Physical Training of the Czech Republic, Fund of Universities Development MU 583
Adsorption of biopolymers at the interface solid metal electrode/solution
Principal investigator: S. Hasoň, 2001

Internal grant of the Faculty of Medicine, Palacký University, Olomouc, 11101104
Electrical model of membrane and its measurement
Principal investigator: D. Smiešková, 2001

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In the past year our work was concentrated mainly to two research fields:

A. Field I. *Properties of nucleic acids and proteins at surfaces and their application in DNA biodetectors.*

B. Field II. *Structure and interaction of DNA and proteins in oncological research especially with respect to the protein p53.*

Ad A. Our recent work was summarized in an invited article in *Analytical Chemistry*. We have achieved an important progress in the development of the DNA hybridization sensors by inventing the so-called 2-surface technique. In this technique the DNA hybridization is made at surface H (optimized for this purpose) and electrochemical detection at the detection electrode (DE); the DE can be chosen for the given purpose regardless of its suitability for the DNA hybridization. Using this technique we have been able to analyze longer target DNAs in excess of noncomplementary DNA. Such analysis was very difficult with the earlier techniques. Our attempts to combine this field with the field II continued and an important outcome of our efforts in this region can be expected in a near future.

Ad B. Our research on p53 interaction with and supercoiled DNA linear (including DNA damaged by antineoplastic drugs) continued. We have been interested in the roles of the individual protein domains in the p53 DNA. A considerable amount of work was done in collaboration with the Max Planck Institute of Biophysical Chemistry in Göttingen, involving mainly visualization of p53-DNA complexes.

Cyclic voltammetry of echinomycin and its interaction with double-stranded and single-stranded DNA adsorbed at the electrode

Interactions of echinomycin (Echi) with DNA was studied by cyclic voltammetry with hanging mercury drop electrode. Echinomycin was electrochemically active yielding several signals. Interaction of Echi with dsDNA attached to hanging mercury drop electrode resulted in high Echi signals suggesting a strong binding of Echi to dsDNA by bis-intercalation at the electrode surface. Under the same conditions interaction of Echi with ssDNA produced almost no Echi signal. This behavior is in agreement with a strong binding of Echi to dsDNA and a very weak binding of Echi to ssDNA observed earlier in solution. Echi thus appears to be a good candidate for redox indicator in electrochemical DNA hybridization sensors.

Voltammetric microanalysis of DNA adducts with osmium tetroxide,2,2'-bipyridine using a pyrolytic graphite electrode

DNA and synthetic polynucleotides modified with a complex of osmium tetroxide with 2,2'-bipyridine (Os,bipy) produce specific voltammetric signals at pyrolytic graphite electrodes. Based on a sufficient potential separation between the peaks of Os,bipy-modified DNA (DNA-Os,bipy) and of free Os,bipy, and using an adsorptive transfer stripping voltammetric procedure involving extraction of free Os,bipy from the electrode by chloroform, DNA-Os,bipy can be determined in an excess of the free reagent. Under certain conditions, 140 pg of DNA-Os,bipy can be detected after a 5 min accumulation period. This analysis displays a more favorable sensitivity

and a better selectivity for DNA structure than oxidation of DNA guanine moieties, and offers detection of osmium DNA markers at carbon electrodes.

Determination of nanogram quantities of osmium-labeled single stranded DNA by differential pulse stripping voltammetry

Earlier we showed that using differential pulse cathodic stripping voltammetry with hanging mercury drop electrode, single-stranded (ss) DNA modified with osmium tetroxide, pyridine reagent (Os,py) can be determined at concentrations down to about 10 to 5 ng/mL. Here we show that by exchanging Os,py for osmium tetroxide, 2,2‘-bipyridine (Os,bipy) and decreasing the pH of the background electrolyte from neutrality to about pH 4, ssDNA can be determined at concentrations lower by one order of magnitude. Determination of DNA at such low concentrations may find use in various areas of molecular biology and in biotechnologies, including the development of DNA sensors.

Voltammetry of two single-stranded isomeric -SH-marked oligonucleotides on mercury electrodes

Voltammetry of isomeric –SH-marked oligonucleotides depends on the dislocation of the electroactive components along the strand as well as on their adsorptivity with respect to adsorptivity of the other parts of the molecule.

DNA hybridization at microbeads with cathodic stripping voltammetric detection

In electrochemical DNA hybridization sensors generally a single-stranded probe DNA was immobilized at the electrode followed by hybridization with the target DNA and electrochemical detection of the hybridization event at the same electrode. In this type of experiments nonspecific adsorption of DNA at the electrode caused serious difficulties especially in the case of the analysis of long target DNAs. We propose a new technology in which DNA is hybridized at a surface H and the hybridization is detected at the detection electrode (DE). This technology significantly extends the choice of hybridization surfaces and DEs. Here we use paramagnetic Dynabeads Oligo$(dT)_{25}$ (DBT) as a transportable reactive surface H and a hanging mercury drop electrode as DE. We describe a label-free detection of DNA and RNA (selectively captured at DBT) based on the determination of adenines (at ppb levels, by cathodic stripping voltammetry) released from the nucleic acids by acid treatment. The DNA and RNA nonspecific adsorption at DBT is negligible, making thus possible to detect the hybridization event with a great specificity and sensitivity. Specific detection of the hybridization of polyribonucleotides, mRNA, oligodeoxynucleotides, and a DNA PCR product (226 base pairs) is demonstrated.

Electrochemical enzyme-linked immunoassay in a DNA hybridization sensor

Here we use another application of new technology in which DNA hybridization is performed on commercially available magnetic beads and detection on solid electrodes. Paramagnetic Dynabeads Oligo$(dT)_{25}$ (DBT) with covalently bound $(dT)_{25}$ probe are used for the hybridization with target DNA containing adenine stretches. Target DNA is modified with osmium tetroxide, 2,2'-bipyridine (Os,bipy) and the immunogenic DNA-Os,bipy adduct is determined by the enzyme-linked immunoassay with electrochemical detection. Electroinactive 1-naphthyl phosphate is used as a substrate and the electroactive product (1-naphthol) is measured on the carbon electrodes. Alternatively Os,bipy-modified target DNA can be determined directly by measuring the osmium signal on the pyrolytic graphite electrodes. A comparison between determinations of the 67-mer oligodeoxynucleotide on carbon electrodes using (a) the guanine oxidation signal, (b) direct determination of the DNA-Os,bipy adduct and (c) its electrochemical immunoassay showed immunoassay to be the most sensitive method. In combination with DBT, the DNA hybridization of long target deoxyoligonucleotides (such as 67- and 97-mers) and a DNA PCR product (226 base pairs) have been detected by immunoassay at high sensitivity and specificity.

Determination of glutathione-S-transferase traces in preparations of p53 C-terminal domain (aa 320-393)

Tumor suppressor protein p53 is often expressed as a fusion protein with Glutathione-S-Transferase (GST). Sensitive determination of GST in p53 samples is thus necessary. We propose a method for the determination of traces of GST in p53 C-terminus based on constant current chronopotentiometric stripping analysis (CPSA) with hanging mercury drop electrode (HMDE). GST produces a catalytic signal in cobalt-containing solutions due to cysteine residues. A large excess of the C-terminus does interfere with the determination because of lack of cysteines in the molecule. This method is simple and very sensitive and is capable of detecting < 1 % GST in the p53 sample.

Differential pulse adsorptive stripping voltammetry of osmium-modified peptides

Complexes of osmium tetroxide with nitrogen ligands were developed and used in our laboratory as probes of the DNA structure. Here we show that the complex of osmium tetroxide with 2,2-bipyridine (Os,bipy) can be used for modification and electrochemical detection of proteins at neutral pH. Salmon Luteinizing Hormone (SLH) containing two tryptophan (Trp) residues and Human Luteinizing Hormone (HLH) containing one Trp were modified by Os,bipy and measured by differential pulse adsorptive stripping voltammetry

(DPAdSV) at a hanging mercury drop electrode (HMDE). The intensity of the DPAdSV catalytic signals corresponded to the number of Trp residues in the peptide molecule. Decreasing pH of the background electrolyte from 6.6 to 3.8 led to the increase of DPAdSV signals suggesting that at pH 3.8 the DPAdSV detection limit might be well below 1 ng/mL. Our results suggest that Os,bipy is potentially useful for chemical modification of proteins.

Electrode potential-controlled DNA damage in the presence of copper ions and their complexes

Supercoiled (sc) DNA immobilized at the surface of a hanging mercury drop electrode was cleaved by reactive oxygen species generated by an electrochemically modulated reaction of copper ions, hydrogen peroxide and/or oxygen. The cleavage was observed in a certain potential region where redox cycling of DNA-bound Cu(II)/Cu(I) took place. In the presence of 1,10-phenanthroline, the maximum efficiency of DNA cleavage was shifted to more negative potentials and the effect was enhanced.

Silver electrode as a sensor for determination of zinc in cell cultivation medium

Use of the silver electrode as a sensor for the monitoring of zinc in cell growth media of cell is described. Zinc at silver electrodes provides specific voltammetric signal, which is affected by solution components. Signals of zinc ions in phosphate buffer solutions with and without cell growth media of were compared. Common DMEM cell culture medium was used for the cultivation of a cell line of v-myb-transformed chicken monoblasts and its variants expressing v-jun and c-jun in zinc-dependent manner. Electrochemical results showed zinc concentrations in the media coincide very well with the jun expression. With respect to the low toxicity of silver for eukaryotic cells, silver electrodes represent promising tools for the determination of zinc concentrations *in vivo* without the potential risk of a cell culture damage.

New ELISA technique for analysis of p53 protein - DNA binding properties

Tumour suppressor protein p53 is one of the most important factors in oncogenic research. Its function is associated with the ability to bind the DNA in a sequence-specific manner and to operate as a transcription factor. In present study we developed rapid and reliable method for analysing sequence specific binding of p53 protein to DNA based on modification of enzyme-linked immunosorbent assay (ELISA). In this p53/DNA - ELISA assay we use streptavidin coated microplates to catch oligonucleotides with p53 consensus sequences labelled by biotin. Our newly developed ELISA allows detection of p53/DNA complexes using different monoclonal antibodies recognising p53 protein. Using this method we can detect p53

binding activity to p53CON and activation of the p53 protein for DNA binding. Variations of the basic protocol are suitable to perform competition experiments and to study p53 binding to natural binding sequences, as shown in this paper. This modified DNA - ELISA assay is applicable for screening p53 binding properties from various sources in a short time.

Binding of "latent" and "active" protein p53 to cisplatin-damaged DNA fragments

Tumor suppressor protein p53 possesses two DNA binding sites. One is located within its core domain (responsible for sequence-specific DNA binding of the protein as well as for non-specific binding to internal segments of single- or double-stranded DNA molecules, and to certain kinds of non-B DNA structures). The other is contained in the protein C-terminus (site capable of binding to damaged DNA). Using electrophoretic mobility shift assay in agarose gels and immunoblotting analysis, binding of active, latent and *in vitro*-activated p53 to DNA fragments modified by antitumor cisplatin was studied. We found both latent and active p53 form bound to platinated random sequence DNA with a higher affinity than to unmodified DNA. The selectivity for platinated DNA was more pronounced in the latent form than in the active p53. Consistently with this observation the preference of the latent form for platinated DNA decreased after activation of latent p53 by phosphorylation at the PKC site within its C-terminus or by binding of a monoclonal antibody Bp53-10.1. Competition experiments, involving sequence-specific and non-specific oligonucleotides, suggested that the p53 core domain (responsible for the protein sequence-specific DNA binding) was the primary site of the active p53 binding to both unmodified and platinated DNA fragments. The latent protein selectively interacted with the platinated DNA probably via its C-terminus.

GRANTS:

GA CR 301/99/0692
Structural aspects of interactions of checkpoint proteins with DNA in cancer
Principal investigator: E. Paleček, 1999 - 2001

GA CR 204/97/K084
Electrodes modified with nucleic acids and proteins. New tools in biochemical and biomedical research
Principal investigator: E. Paleček, principal co-investigators: O. Dračka, Fac. Sci. MU, Brno, L. Novotný, IPCH J.H. AS CR, Prague, B. Vojtěšek, MOÚ, Brno, 1997 - 2002

GA CR 301/00/D001
Binding of human and mouse tumor suppressor protein P53 to linear and supercoiled DNAs
Principal investigator: V. Brázda, 2000 - 2003

GA CR 301/99/D078
Role of the p53 domains and the oligomerization state of the protein in its molecular interactions
Principal investigator: J. Paleček, 1999 - 2001

GA CR 204/00/D049
Influence of chemical modification of DNA and synthetic oligonucleotides on their electro-chemical behavior
Principal investigator: L. Havran, 2000 - 2003

GA AS CR K4055109
Physics, chemistry and informatics for biology, ecology and health application
Principal investigator: A. Holý, IOCHB AS CR, Prague, principal co-investigator: E. Paleček, IBP AS CR, Brno, 2001 - 2004

GA AS CR A4004901
Analysis of the interactions of mutagens, carcinogens and anti-cancer drugs with biopolymers by means of electrochemical and biochemical methods
Principal investigator: F. Jelen, 1999 - 2001

GA AS CR A4004108
Development of electrochemical biosensors for DNA damage
Principal investigator: M. Fojta, 2001 - 2003

GA AS CR A4004110
Binding of tumor suppressor protein p53 to DNA. The influence of DNA superhelicity and posttranslational modifications of the protein
Principal investigator: E. Paleček, 2001 - 2004

IGA MH CR NC5343-3/1999
Interactions of tumor suppressor protein P53 with damaged DNA and with lesions induced by anti-cancer drugs
Principal investigator: M. Fojta, 1999 - 2001

LBCMO participates on the projects of targeted reseach and development:

GA AS CR S5004107
Applications of biophysical methods in biotechnological and clinical praxis
Principal investigator: V. Vetterl, 2001 - 2005

GA AS CR S5004009
Untraditional therapeutic approaches in oncology
Principal investigator: A. Kozubík, 2000 - 2004

PROGRAM II

BIOPHYSICS OF NUCLEIC ACIDS COMPLEXES

LABORATORY OF MOLECULAR BIOPHYSICS AND PHARMACOLOGY (LMBP)

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Thermodynamic stability of DNA containing selected adducts of platinum anticancer drugs

Bifunctional polynuclear platinum compounds represent a novel class of metal-based antitumor drugs which are currently undergoing preclinical development. A typical agent is $[\{trans\text{-}PtCl(NH_3)_2\}_2H_2N(CH_2)_4NH_2]Cl_2$, (BBR3005) which coordinates to bases in DNA and forms various types of covalent cross-links. It also forms a 1,2-d(GpG) intrastrand adduct, the equivalent of the major DNA lesion of "classical" mononuclear cisplatin [cis-diamminedichloroplatinum(II)]. Differential scanning calorimetry and spectroscopic techniques were employed to characterize the influence of this

cross-link on the thermal stability and energetics of 20 base pairs DNA duplexes site-specifically modified by BBR3005. Thermal denaturation data revealed that the cross-link of BBR3005 reduced thermal and thermodynamical stability of the duplex noticeably more than that of "classical" cisplatin. The energetic consequences of the intrastrand cross-link at the d(GG) have been found to correlate with the character of conformational distortions induced in DNA by the cross-links of BBR3005 and cisplatin and with the data on the relationship between thermodynamic destabilization of the duplexes by the cross-links of the platinum complexes and their recognition and binding by damaged-DNA binding proteins (such as HMG-domain or tumor suppressor p53 proteins). It has been suggested that the results of the present work are consistent with different DNA binding modes of cisplatin and polynuclear bifunctional DNA-binding drugs, which might be relevant to their distinct biological effectiveness.

The effect of the single, site-specific interstrand cross-link formed by cisplatin or transplatin on the thermal stability and energetics of 20-base pairs DNA duplex has been also examined. The cross-linked or unplatinated 20-bp duplexes were investigated with the aid of differential scanning calorimetry, temperature-dependent UV absorption and circular dichroism. The cross-link of both platinum isomers increases the thermal stability of the modified duplexes by changing the molecularity of denaturation. The structural perturbation due to the interstrand cross-link of cisplatin increases entropy of the duplex and in this way entropically stabilizes the duplex. This entropic cross-link induced stabilization of the duplex is partially, but not completely compensated by the enthalpic destabilization of the duplex. The net result of these enthalpic and entropic effects is that the structural perturbation due to formation of the interstrand cross-link by cisplatin induces a decrease in duplex thermodynamic stability with this destabilization being enthalpic in origin. By contrast, the interstrand cross-link of transplatin is enthalpically almost neutral with the cross-link-induced destabilization being entirely entropic in origin. These differences are consistent with distinct conformational distortions induced by the interstrand cross-links of the two isomers. Importantly, for the duplex cross-linked by cisplatin relative to that cross-linked by transplatin, the compensating enthalpic and entropic effects almost completely offset the difference in cross-link-induced energetic destabilization. It has been proposed that the results of the present work further support the view that the impact of interstrand cross-links of cisplatin and transplatin on DNA is different which might be also associated with distinctly different antitumor effects of these platinum compounds.

Initiation of mammalian nucleotide excision repair: Double-check probing of DNA helix conformation by repair protein XPA and replication factor RPA

The XPA-RPA complex is required for initiation of mammalian nucleotide excision repair, but its molecular function during early stages of this DNA repair pathway was unknown. We have shown that XPA-RPA constitutes a universal sensor of nucleotide damage that operates through indirect readout of DNA conformations. XPA-RPA is guided by the synergism between two different DNA binding domains: XPA recognizes abnormal bending of the deoxyribose-phosphate backbone including that induced by platinum anticancer drugs whereas RPA recognizes base pair disruption. We have suggested that these two nucleic acid interaction modules are used to monitor integrity of the Watson-Crick helix by a double-check probing mechanism that confers an extremely wide recognition capacity for structural distortions. The versatility of double-check probing is confirmed by recognition and excision of platinum cross-links with divergent conformational effects.

Biophysical analysis of natural, double-helical DNA modified by anticancer heterocyclic complexes of ruthenium(III) in cell-free media

There have been efforts directed at the design of other transition-metal antitumor agents than only those derived from platinum. Possible advantages in using transition-metal ions other than platinum may involve additional coordination sites, alterations in ligand affinity and substitution kinetics, changes in oxidation state and photodynamic approaches to therapy. In the design of these new drugs, ruthenium complexes have raised great interest. Antitumor activity of metal-based compounds is frequently associated with their binding to DNA. These compounds form DNA adducts which block replication and transcription and induce programmed cell death. Interactions of cell components with these adducts are therefore very likely relevant to biological activity of these metal-based drugs. Modifications of natural DNA by three anticancer heterocyclic ruthenium(III) compounds were studied by methods of molecular biophysics. These methods include: DNA binding studies using atomic absorption spectrophotometry, inhibition of restriction endonucleases, mapping of DNA adducts by transcription assay, interstrand cross-linking employing gel electrophoresis under denaturing conditions, DNA unwinding studied by gel electrophoresis, circular dichroism analysis of B→Z transition in DNA and DNA melting curves measured by absorption spectrophotometry. The results indicate that the complexes HIm[trans-$Cl_4Im_2Ru^{III}$], HInd[trans-$Cl_4Ind_2Ru^{III}$] and Na[trans-$Cl_4Im(Me_2SO)Ru^{III}$] (Im and Ind stand for imidazole and indazole, respectively) coordinate irreversibly to DNA. Their DNA binding mode is, however, different from that of cisplatin. Interestingly, Na[trans-$Cl_4Im(Me_2SO)Ru^{III}$] binds to DNA

considerably faster than other two ruthenium compounds and cisplatin. In addition, when Na[trans-$Cl_4Im(Me_2SO)Ru^{III}$] binds to DNA it exhibits an enhanced base sequence specificity in comparison with other two ruthenium complexes. Na[trans-$Cl_4Im(Me_2SO)Ru^{III}$] also forms on double-helical DNA bifunctional intrastrand adducts capable of terminating RNA synthesis *in vitro* while capability of other two ruthenium compounds to form such adducts is markedly lower. This observation has been interpreted to mean that the bifunctional adducts of HInd[trans-$Cl_4Ind_2Ru^{III}$] and Na[trans-$Cl_4Im_2Ru^{III}$] formed on rigid double-helical DNA are sterically more crowded by their octahedral geometry than those of Na[trans-$Cl_4Im(Me_2SO)Ru^{III}$]. In addition, the adducts of all three ruthenium compounds affect conformation of DNA, Na[trans-$Cl_4Im(Me_2SO)Ru^{III}$] being most effective. It has been suggested that the altered DNA binding mode of ruthenium compounds in comparison with cisplatin might be an important factor responsible for altered cytostatic activity of this class of ruthenium compounds in tumor cells.

GRANTS:

GA CR 305/99/0695
Affection of conformation of DNA by antitumor metal complexes. Relations to the development of new anticancer drugs
Principal investigator: V. Brabec, 1999 - 2001

GA CR 301/98/P231
Reactions of DNA with platinum complexes containing aminophosphine ligands. Relation to the development of new antitumor platinum drugs
Principal investigator: K. Neplechová, 1998 - 2001

GA CR 301/00/0556
Dinuclear metal-based agents as agents cross-linking DNA and proteins
Principal investigator: R. Žaludová, 2000 - 2002

GA CR 305/00/D008
Reactions of antitumor trifunctional dinuclear platinum complexes with biomacromolecules
Principal investigator: H. Kostrhunová, 2000 - 2003

GA CR 202/01/D110
Microcalorimetric analysis of thermodynamic stability of DNA affected by anticancer platinum complexes
Principal investigator: C. Hofr, 9/2001 - 8/2004

GA AS CR K4055109
Physics, chemistry and informatics for biology, ecology and health application
Principal investigator: A. Holý, IOCHB AS CR, Prague, principal co-investigator: V. Brabec, IBP AS CR, Brno, 2001 - 2004

GA AS CR A7004805
Interactions of DNA with antitumor platinum drugs of the second generation
Principal investigator: O. Vrána, 1998 - 2001

GA AS CR A5004101
Structure, recognition and biochemistry of DNA modified by antitumor platinum drugs
Principal investigator: V. Brabec, 2001 - 2005

IGA MH CR NL6058-3/2000
Recognition and repair of DNA damaged by platinum antitumor drugs. Relations to the development of new anticancer drugs
Principal investigator: J. Kašpárková, 2000 - 2002

IGA MH CR NL6069-3/2000
Mutagenic effects of antitumor platinum drugs. Relations to the development of new anticancer drugs
Principal investigator: O. Vrána, 2000 - 2002

LABORATORY OF DNA MOLECULAR COMPLEXES (LDMC)

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GRADUATE STUDENTS:	ING. ZUZANA KUNICKÁ MUDR. JAN MALÁSKA MGR. MARIE SKLENIČKOVÁ MGR. MILAN KUCHAŘ MGR. LENKA SKŘÍŠOVSKÁ

*external co-worker

Laboratory is focused on structure-function relationships in complexes of proteins and nucleic acids which participate in metabolism of genetic material. Within this focus, a specific attention is paid to the analysis of eukaryotic chromosome ends (telomeres), to the study of their synthesis by means of telomerase or so called alternative mechanisms, and to the isolation and characterisation of telomere-binding proteins. While this work with plants concerns the basic research, with human cells and clinical samples is the research targeted to practical aspects of molecular diagnostics.

Following results have been achieved during work on individual projects:

A model of columnar structure of telomeric chromatin has been set up and published. In this model, the DNA is continuously wound in a parallel manner around the stacked histone octamers. In contrast to the previous models (solenoidal and "zig-zag") internucleosomal linkers in columnar structure are deformed in the same manner as the deformable part of the nucleosome DNAs. Due to the low energy of interaction between telomeric DNA and histone octamer, the structure is stabilised predominantly by stacking protein-protein interactions among histone octamers. Our model explains previously observed specific features of telomeric nucleosomes

(extremely short and regular periodicity of telomeric nucleosomes in the absence of sequentially determined nucleosome positioning, instability of short chromatin fragments which results in sliding of telomeric DNA along histone octamers, while longer chromatin fibres are stable) and corresponds to the absence of sequence-determined deformations on telomeric DNA. Formation of this structure proceeds cooperatively, and certain minimal length of chromatin fibre is required to achieve a thermodynamic ballance.

A detailed analysis of chromatin structure of two families of subtelomeric sequences from *Silene latifolia* (one of them, the 15Ssp sequence, has been newly described here) has been finished and relations among DNA sequence, its conformation anisotropy and chromatin structure have been discussed. Experimental data were compared to results of computer modelling.

Testing of the activity and expression of telomerase in solid tumor (namely colorectal and lung) samples has been finished. The results show presence of telomerase activity in 80-90% of samples tested. Expression of telomerase catalytic subunit (hTERT) mostly correlates with presence of activity, it was however observed also in several samples lacking telomerase activity. This could be explained by recently described presence of ectopic transcripts of hTERT which are alternatively spliced to one of deletion variants (hTERT α^-) of mRNA. This variant, besides lacking potential to produce active subunit, shows also inhibition of correctly spliced hTERT transcripts. To identify those cases, splicing profiles have been tested using multiplex RT-PCR with radioisotope labelling and PAGE analysis. It was found that cca 30% of controversial cases (absence of activity, presence of expression) can be attributed to the presence of hTERT α^- mRNA, while the rest is probably associated with posttranslational editing (e.g., inhibition of hTERT protein phosphorylation) or absence of factors involved in assembly of functional ribonucleoprotein telomerase complex.

GRANTS:

GA AS CR S5004010
Development of novel diagnostic techniques for oncology
Principal investigator: S. Kozubek, principal co-investigator: J. Fajkus, 2000 - 2004

GA AS CR C5004111
Characterisation of telomere chromatin proteins
Principal investigator: J. Fajkus, 2001

GA AS CR K5011112
Molecular and cellular basis of weight disorders
Principal investigator: P. Mareš, PGI AS CR, Prague, principal co-investigator: J. Fajkus, IBP AS CR, Brno, 2001 - 2004

GA CR 301/99/0045
Telomere dynamics in selected types of solid malignant tissues
Principal investigator: J. Fajkus, principal co-investigators: R. Vyzula, Faculty Hospital, Brno-Bohunice, L. Fajkusová, VÚZD, Brno, 1999 - 2001

QC 1164
Characterisation of potato genotypes by DNA fingerprinting method
Principal investigator: H. Polzerová, Potato Research Institute, Havlíčkův Brod, principal co-investigator: J. Fajkus, IBP AS CR, Brno, 2000 - 2003

The Leverhulme trust F/07476/G
Loss and gain of typical telomere repeats in a major radiation of monocots (UK)
Principal investigator: A. Leitch

MONBUSHO 116941196
Joint Research on Differentiation and Growth Specificity of Plant Cells
Principal investigator: H. Takahashi

MSM 143100008
Genomes and their function
Principal investigator: J. Relichová, Fac. Sci. MU, Brno, principal co-investigator: J. Fajkus, IBP AS CR, Brno

AV0Z5004920
Biophysical properties of living systems and their changes under the influence of environmental factors
Principal investigator: J. Šlotová, co-investigator: J. Fajkus, 1999 - 2003

LABORATORY OF ANALYSIS OF CHROMOSOMAL PROTEINS (LACP)

HEAD:	RNDR. MICHAL ŠTROS, CSC.
RESEARCH FELLOWS:	ING. ALENA BAČÍKOVÁ RNDR. DAGMAR ZACHOVÁ
GRADUATE STUDENT:	MGR. EVA MUSELÍKOVÁ
UNDERGRADUATE STUDENTS:	HANA STÁRKOVÁ JAN VRBSKÝ

We have continued the studies on the influence of nonhistone chromosomal protein HMGB1 on p53/p73-binding to DNA containing specific-binding sequences for p53. We have demonstrated that HMGB1 significantly stimulates binding of p53 or p73 to DNA without forming a ternary complex DNA-p53-HMGB1. Using transient transfections of H1299 or SAOS-2 cells we have discovered that HMGB1 has the capacity of the cell- and promoter-specific down- or up-regulation with respect to the *in vivo* transcriptional activity of different members of p53 family. Our finding suggests an existence of unknown cell-specific factor(s) which can modulate the ability of HMGB1 to affect p53/p73-dependent transactivation *in vivo*.

We show that the lysine-rich part of the linker region between A and B domains of HMG-1 (the 85 TKKKFKD 91 sequence) is a prerequisite for a preferential binding of the B domain to supercoiled DNA and for a high-affinity binding of the B domain to DNA containing a site-specific major 1,2-d(GpG) intrastrand DNA adduct of cisplatin. Mutation of Arg 97 to alanine significantly (>40-fold) reduces affinity of the B domain to cisplatin-modified DNA and inhibits the ability of the B domain to bend DNA (ligase-mediated circularization).

GRANTS:

GA CR 301/99/0691
Influence of chromosomal proteins HMG-1 and HMG-2 on transcription
Principal investigator: M. Štros, 1999 - 2001

GA AS CR A7004902
Involvement of chromosomal protein HMG-1 on DNA end-joining by human DNA ligases
Principal investigator: M. Štros, 1999 - 2001

GA AS CR A5004105
Understanding of DNA binding by RNA polymerase I transcription factor xUBF
Principal investigator: M. Štros, 2001 - 2005

GA AS CR K4055109
Physics, chemistry and informatics for biology, ecology and health application
Principal investigator: A. Holý, IOCHB AS CR, Prague, principal co-investigator: M. Štros, IBP AS CR, Brno, 2001 - 2004

PROGRAM III

BIOPHYSICS AND BIOINFORMATICS OF GENOMES

LABORATORY OF CD SPECTROSCOPY OF NUCLEIC ACIDS (LSNA)

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A-like guanine-guanine stacking in the aqueous DNA duplex of d(G_4C_4)

We have used CD spectroscopy, NMR spectroscopy and molecular dynamics to study conformational properties of a DNA duplex formed by the self-complementary octamer d(G_4C_4). Its unusual CD spectrum indicated A-like stacking of a half of bases whereas the other half stacks remained in a B-like fashion. Unrestrained molecular dynamics simulations converged to a stable B-like double helix of d(G_4C_4). However, the double helix contained a central hole whose size was a half of that occurring in structure A. In the canonical structure B, the hole does not exist at all because the base pairs cross the double helix center. The cytosine bases were stacked in the duplex of d(G_4C_4) like in structure B while stacking of the guanine bases displayed features characteristic for structure A. NMR spectroscopy revealed an increased tendency of the deoxyribose rings attached to the guanine bases to be puckered in an A-like fashion. The present analysis demonstrates a remarkable propensity of the guanine runs to stack in an A-like fashion even within the B-DNA framework. This property explains why the oligo(dG).oligo(dC) tracts so easily switch into structure A. Secondly, this property may influence replication because structure A is replicated more faithfully than structure B. Thirdly, the oligo(dG) runs might have played an important role in the early evolution when DNA took on functions that originally evolved on RNA. Fourthly, the present study extends the vocabulary of DNA secondary structures by the heteronomous duplex of d(G_4C_4) in which the B-like strand of oligo(dC) is bound to the A-like strand of oligo(dG).

Conserved guanine-guanine stacking in tetraplex and duplex DNA

Using a series of oligonucleotides d(C4G4), d(C3G4), d(C2G4), d(CG4) a d(G4) we have demonstrated that the duplexes of d(CnG4), (n=3,4) provide almost identical CD spectra as the parallel-stranded tetraplexes of d(CmG4), (m=0,1,2). CD spectroscopy is extremely sensitive to base stacking in DNA so that the above observation indicates that guanine-guanine stacking is essentially the same within the duplex of d(C4G4) and the tetraplex of d(G4). A very similar CD spectrum is also provided by the A-form of d(C4G4) induced by trifluorethanol. These results reveal that guanine-guanine stacking is a structural invariant conserved in various nucleic acids conformers. The structural invariance is likely to cohere with evolution of the genetic molecules and be important for fundamental functions, e.g. initiation of transcription.

Tetraplexes of the fragile X chromosome (GCC) repeat

UV absorption and CD spectroscopy, along with polyacrylamide gel electrophoresis, were used to study conformational properties of DNA fragments containing the trinucleotide repeat $(GCC)_n$, (n=4, 8, 16), whose expansion in genome is correlated with the fragile X chromosome syndrome. We have found that the conformational spectrum of the $(GCC)_n$ strand is wider than it has been shown so far. The $(GCC)_n$ strands adopt the hairpin described in literature under a wide range of salt concentrations (Figs. 1 and 2, green), but only at alkaline (>7.5) pH values. However, at neutral and slightly acid pH the $(GCC)_4$ and $(GCC)_8$ strands homodimerize (Fig. 1, blue). Our data suggest that the homodimer is a bimolecular tetraplex formed by two parallel-oriented hairpins held together by hemiprotonated inter-molecular $C.C^+$ pairs. The $(GCC)_{16}$ strand forms the same tetraplex intramolecularly (Fig. 2, blue). We have further shown that below pH 5 the $(GCC)_n$ strands generate intercalated cytosine tetraplexes. Their molecularity depends on the DNA strand length. They are tetramolecular with $(GCC)_4$, bimolecular with $(GCC)_8$, and monomolecular with $(GCC)_{16}$ (Figs. 1 and 2, red). The *i*-tetraplex formation is a complex and a slow process. The neutral tetraplex, on the other hand, arises with fast kinetics at physiological conditions. Thus it is a conformational alternative of the $(GCC)_n$ strand to its duplex with the complementary $(GGC)_n$ strand.

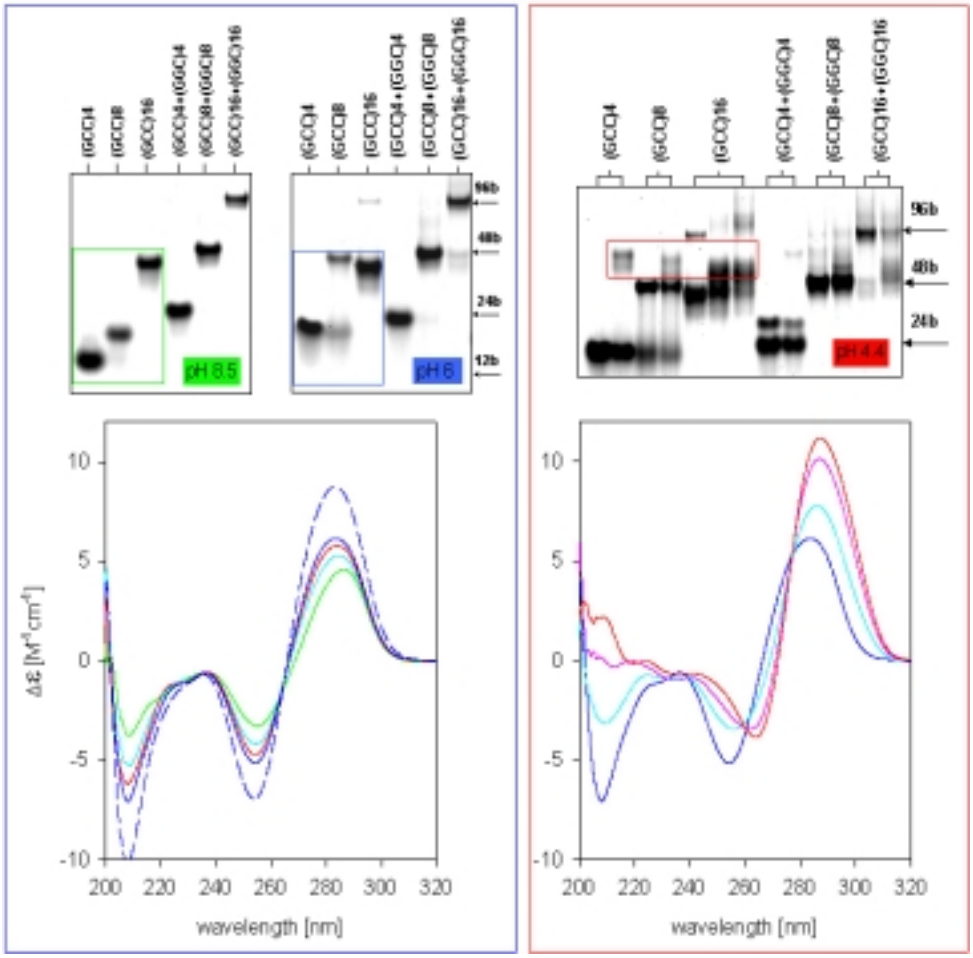

Figure 1

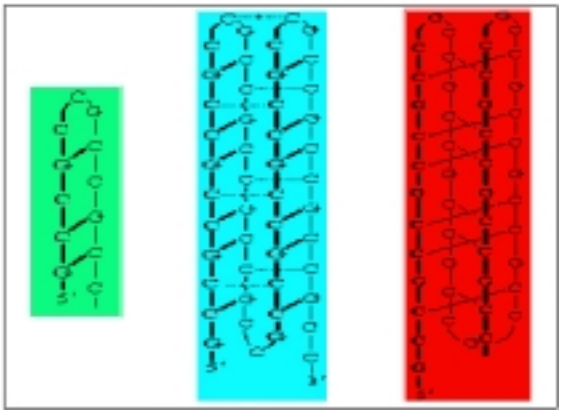

Figure 2

GRANTS:

GA CR 204/01/0561
Conformational polymorphism of DNA molecules containing trinucleotide repeats associated with genetic diseases
Principal investigator: M. Vorlíčková, 2001 - 2003

GA AS CR K5052113
Structure, expression and interaction of the genome
Principal investigator: V. Pačes, IMG AS CR, Prague, principal co-investigator: M. Vorlíčková, IBP AS CR, Brno, 2001 - 2004

LABORATORY OF DNA BIOPHYSICS AND GENOME BIOINFORMATICS (LDBGB)

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We showed, using CD spectroscopy and other methods, that dimethyl-sulphoxide stabilized a single-stranded conformer of DNA. This conformer exhibits a cooperative thermal denaturation, which is a characteristic property of an ordered DNA. The single-stranded conformer is not a hairpin. It is adopted by (GA)10, but not (TA)10, A20 or G20. This is the first example when the denaturing agent dimethylsulphoxide is shown to stabilize an ordered conformation of DNA. According to the available knowledge, the ordered single strand of DNA is a counterpart of an alpha helix, which inspires considerations about a common evolutionary ancestor of proteins and DNA.

We calculated geometrical parameters from the NDB database to reproduce the cartesian coordinates of the phosphorus atoms in the DNA sugar phosphate backbone. The differences were surprisingly small between the true and simulated structures, which means that the phosphorus atoms reflect a substantial part of the regularities governing the three dimensional structure of DNA. We wrote a software assigning the cartesian coordinates of the phosphorus atoms to any nucleotide sequence in DNA. The software is computationally so undemanding that we could easily simulate the whole genomes of not only plasmids, viruses and bacteria, but also eukaryotic organisms. We have already managed to simulate the tertiary structures of the DNA molecules of the human chromosomes 21 and 22 whose lengths are around 30 million nucleotides, i. e. 1 cm. The simulations are interesting in two respects. First, they demonstrate that the high degree of compaction characteristic for DNA molecules in the nuclei of human cells, is to a high

degree encoded in the DNA itself, i. e. in the absence of any protein. Secondly, the simulations indicate the existence of distinct domains in the tertiary structures of the human chromosome molecules of DNA. For example, the telomere constitutes a separate domain that is distinctly separated from the subtelomeric domain, and the subtelomeric domain is further separated from the main body of the molecule. We will elaborate further pieces of software to characterize and compare tertiary structures of megabase molecules of DNA. This software will be useful to trace the evolution and analyze functional properties of the human chromosomes.

We performed a variation analysis of the nucleotide distributions along DNA molecules of all 24 human chromosomes, 6 chromosomes of *Caenorhabditis elegans* and the chromosome of *Escherichia coli*. We found that the distributions were about five times more heterogeneous compared to the randomized sequences on the isochore length (100kb) as well as smaller (10kb) and larger (1Mb) scales. This statement generally holds for all 31 analyzed molecules. Hence the nucleotide distribution homogeneity/heterogeneity does not discriminate among the man, worm and the bacterium. In addition, properties of the genomic (G+C) distributions do not substantially differ from the (A+G) or (A+C) distributions on the isochore length scale. The genomic distributions of the particular nucleotides A, C, G and T are already highly heterogenous. Hence the (G+C) distribution heterogeneity neither is a useful property to characterize long range genome structures. The original definition of the isochores in terms of very long genomic blocks unique for higher eukaryotes where the (G+C) distribution is homogenous, is untenable in the light of the above results.

GRANTS:

GA AS CR A5004802
Biophysical analysis of selected regions of the human genome
Principal investigator: J. Kypr, 1998 - 2002

GA AS CR K5052113
Structure, expression and interaction of the genome
Principal investigator: V. Pačes, IMG AS CR, Prague, principal co-investigator: J. Kypr, IBP AS CR, Brno, 2001 - 2004

GA CR 204/00/D012
Correlations and variations of nucleotide and short oligonucleotide distributions in the genome of *Caenorhabditis elegans*
Principal investigator: D. Häring, 2000 - 2003

GA CR 301/01/0590
Structural properties and expansion of mononucleotide and dinucleotide microsatellites of the human genome
Principal investigator: J. Kypr, 2001 - 2003

LABORATORY OF MOLECULAR EPIGENETICS (LME)

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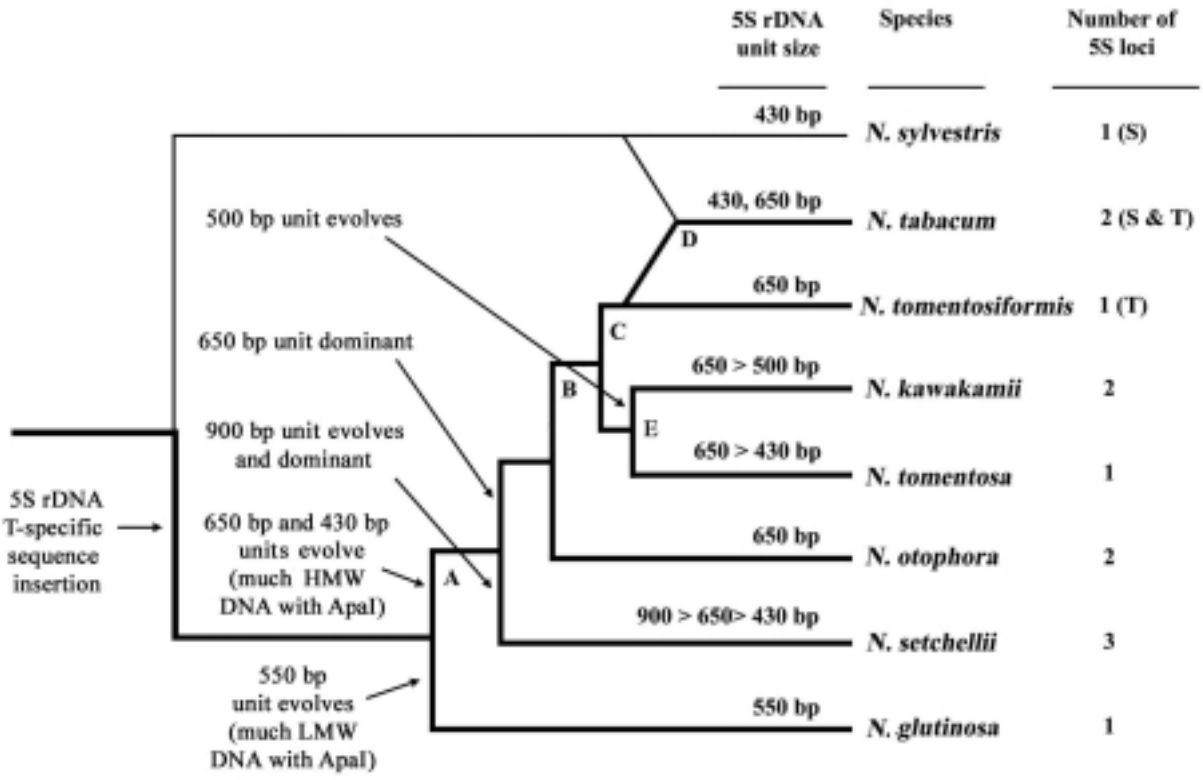
Prokaryotic insertion elements as frequent contaminats of nucleotide databases

During recloning of *Nicotiana tabacum* L. repetitive sequence R8.3 in *Escherichia coli*, a modified clone differing from the original by insertion of IS10 sequence was unintentionally produced. The insert was flanked by a 9 bp direct repeat of R8.3 sequence, the 9 bp duplication of acceptor DNA in the site of insertion being a characteristic event of IS10 transposition. A database search using the FASTA program showed IS10 and other prokaryotic IS elements inserted into numerous eukaryotic clones. Unexpectedly, the IS10 which is not a natural component of *E. coli* genome appeared to be the far most frequent contamination of DNA database out of several IS sequences tested. In GenEMBL the IS10 yielded positive scores with more than 500 eukaryotic clones. The insertions of shortened IS10 sequences having only one intact terminal inverted repeat were commonly found. Most full-length IS10 insertions (32 out of 40 analyzed) were flanked by 9 bp direct repeats having a consensus 5'-NPuCNNNGPyN-3' with a strong preference for 5-TGCTNAGNN-3'. One insertion was flanked by an inverted repeat of more than 400 bp in length. PCR amplification and Southern blot hybridization revealed the presence of IS10 sequences in Escherichia coli strains commonly used for DNA cloning including those reported to be Tn10-free. No IS10-specific PCR product was obtained with N. tabacum or human DNA. Our data suggest that transposition of IS10 elements may accompany cloning steps, particularly into large BAC vectors. This might lead to relatively frequent contamination of DNA databases by this bacterial sequence. It is estimated that approximately every thousandth eukaryotic clone in a database contains IS contamination. We recommend checking submitted sequences for the presence IS10 and other IS elements. In addition, DNA databases should be corrected by removing contaminating IS sequences.

Evolution of 5S rDNA in Nicotiana

Nicotiana tabacum (tobacco, Solanaceae) has two 5S ribosomal DNA (rDNA) families, one of unit length c. 646 bp and the other c. 430 bp that differ in the length of the 5S rDNA non transcribed spacer (NTS). The long 5S rDNA family, found on the T genome of tobacco and in *N. tomentosiformis,* contains a GC rich 140 bp subregion that is absent in the short family. We demonstrated the presence of the GC rich subregion in a range of Nicotiana species (including few members of distantly related Alatae), but it was absent in *N. sylvestris, N. longiflora* and in two closely related genera, Petunia and Solanum. These data suggest ancient origin of this subregion of NTS that have evolved with the genus Nicotiana. The length polymorphisms of NTS allowed us to demonstrate patterns of evolution in the 5S rDNA unit cluster in relation to a phylogenetic reconstruction of species relationships in section Tomentosae (see figure below) Certainly the replacement of 5S rDNA units, perhaps by gene conversion, has occurred repeatedly in the evolution of Nicotiana.



The phylogenetic scheme of the evolution of 5S rDNA in section *Tomentosae.*

Molecular and structural characterisation of plant satellite sequences

Highly repeated satellite DNA (stDNA) of citric plants was characterized by cloning and sequencing 10 to 14 repeats of each plant *(Citrus limon, C. sinensis, C. ichangensis, Poncirus trifoliata).* The monomers are mostly 181 ± 2 bp in length with a GC-content between 60 to 68 %, respectively (significantly higher than average GC content of the citrus group genomes). Similarity among the repeats indicate that they belong to a satellite family that underwent species-specific modifications which are reflected in their phylogenetic relationships. Curvature provoked by dA-stretches of the repeats analyzed by gel shifts revealed structural conservation although the nucleotide sequences vary among species, therewith probably supporting the heterochromatic structure of stDNA. We show that the species-specific modification of the satellite consensus involves changes in position and number of dA tracts. Molecule shapes of satellite oligomeres predicted by computer modeling were in a good agreement with phylogenetic tree.

GRANTS:

GA AS CR S5004010
Development of new diagnostic tools in oncology
Principal investigator: S. Kozubek, principal co-investigator: A. Kovařík, 2000 - 2004

GA AS CR K5052113
Structure, expression and interaction of the genome
Principal investigator: V. Pačes, IMG AS CR, Prague, principal co-investigator: A. Kovařík, IBP AS CR, Brno, 2001 - 2004

GA CR 204/99/D001
Mechanisms of DNA methylation and demethylation in higher plants
Principal investigator: J. Fulneček, 1999 - 2001

GA CR 521/00/0037
The role of epigenetic factors in regulation of gene expression in higher plants
Principal investigator: A. Kovařík, principal co-investigator: A. Holý, IOCHB AS CR, Prague, 2001 - 2003

GA CR 204/01/0313
Evolution and mutual interactions between homologous loci in allopolyploid genomes
Principal investigator: R. Matyášek, 2001 - 2003

GA CR 521/01/P042
Regulation of posttranscriptional gene silencing in transgenic plants
Principal investigator: M. Fojtová, 2001 - 2003

PROGRAM IV

MOLECULAR CYTOLOGY AND CYTOGENETICS

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*external co-worker

Using repeated dual-color hybridization, internal structure of chromosome domains and their topology in the cell nucleus were investigated in detail for two "euchromatic" chromosomes (9 and 17) containing a large number of expressed genes, as well as for two "heterochromatic" chromosomes (8 and 13). The positions of chromosome domains were visualized in parallel with centromeres and selected loci (*c-MYC, ABL, RB, TP53, RARa*, as well as *iso-p,* and *iso-q*). This approach allowed reallocation and reacquisition of a large number (~500) of 3D images for each chromosome.

The results obtained with chromosomes 17 and 9 are shown in Figure 1A, B. Different results were obtained for chromosomes 8 (Figure 1C) and 13 (not shown). In Figure 1A-C, the fluorescence center of the domain was positioned by 3D-rotation to the *x*-axis and the whole chromosome was shifted along the *x*-axis to the domain medium position. In this way, the fluctuations of spatial positions of genetic loci related to the chromosome as a whole were removed. In order to show the real values of mutual distances between genetic elements, the *x-y* positions of genes and centromeres are shown only for such nuclei where *z* coordinates were near the central plane. The points, therefore, represent the genetic elements in a narrow slice through the central plane of the nucleus after its rotation. For the centromeres of

chromosomes 9 and 17 the distance distributions in the *x*-direction are narrower and shifted towards the nuclear membrane as compared with corresponding genes (upper left panel).

The medium positions of the investigated genes on chromosomes 9 and 17 are closer to the center of the nucleus, as compared with the domain fluorescence center; on the other hand, centromeres are located near the nuclear periphery (Figure 1A-B). The differences between the radial locations of genes and centromeres are much smaller for chromosomes 8 and 13 (shown for chromosome 8 in Figure 1C).

The nuclear location of genetic elements of the chromosome 17 was investigated using repeated hybridization (Figure 1D). It was found that *TP53, RARa*, and *iso-q* are located close to the nuclear center (at 50, 55, and 57% of radius from the nuclear center, respectively). Centromeres and *iso-p* were found close to the nuclear periphery (at 75 and 78%).

Nuclear distances between couples of genes located on different arms of the chromosome 17 (*RARa and TP53; iso-q* and *TP53*) are shorter than the distances between these genes and centromere of the chromosome 17 in spite of the larger molecular distances between these genes as compared to gene-to-centromere distances (Figure 1E). For example, the mean distances between *C17* and the *TP53* and *RARa* genes is 3.1±0.09 and 2.8 ± 0.07 μm, respectively, while the mean distance between both genes is only 2.3 ± 0.09 μm. Similar situation was observed in the case of *iso-q* and *TP53* (Figure 1E). In addition, the distance between both telomeres of the chromosomes 8, 9, and 19 was also shorter as compared to the distances of telomeres to centromere (unpublished results). The locations of all investigated genes, with an exception of *iso-p*, were not close to centromeres (Figure 3F). The *iso-p* locus (located very close to the centromere) displayed the medium position still closer to the nuclear membrane than to the centromere.

Radial distributions of the fluorescence weight centers of chromosome domains, measured in 3D for cell nuclei of human Go-lymphocytes, were determined for 22 chromosomes (Figure 2A). The most central location was found for chromosomes 16, 19, and 22; the most peripheral for chromosomes 3, 4, 8, and 18 (Figure 2B). In Figure 2B, the average 3D positions of the chromosome fluorescence weight centers are presented for human Go-lymphocytes and HT-29 colon carcinoma cells relative to G-band content. For comparison, 2D membrane-to-domain distances are shown for human granulocytes and lymphoblasts. Interestingly, the ratio between R and G-bands (R/G content) can be related to a chromosome location. The center-to-chromosome distance is approximately proportional to the G-band content for Go-lymphocytes, granulocytes, HT-29 cells, and lymphoblasts. Differences in the distance distributions reported for various cell types may

be related mainly to the procedure for determination of nuclear parameters, or to the normalization used by different laboratories. Comparison of the positions of individual chromosomes obtained in parallel measurements (Go-lymphocytes and HT-29 cells) indicated that the nuclear positions for the majority of chromosomes are very similar for both cell lines (Figure 2B). In these two cell types differences in center-to-chromosome distances, larger than 10% of the local radius, were found for chromosome 5. Moreover, in granulocytes, contrary to Go-lymphocytes and HT-29 cells, chromosome 16 domain is located much closer to the nuclear periphery than expected.

The central nuclear location of genes belonging to highly expressed gene regions, as well as the central nuclear location of chromosome domains rich in highly expressed genes, strongly suggest that the highly expressed gene regions themselves are located near the nuclear center. In addition, we have demonstrated that the central nuclear location of highly expressed chromosome regions is conserved in different cell types, in agreement with previous findings of Caron *et al.* (Science, 2001, 291, 1289-1292) that clusters of highly expressed genes (RIDGEs) reside at the same chromosome location in various cell types. These results indicate that the mechanism through which functional nuclear organization of chromatin is established and maintained consists in the arrangement of highly expressed genes to clusters located to specific regions of individual chromosomes that is strikingly similar in different cell types. Thus, two principal compartments composed of regions with high gene expression (RIDGEs) and regions with low gene expression (RILGEs) to which multiple regions of individual chromosomes contribute, are established in cell nuclei. Tissue specific genes do not seem to influence the basic location of a chromosome, however, induced transcription of some gene(s) can lead to the changes of the structure of the locus and its nuclear location. This was shown for MHC region involving about 3 Mbp.

Multiple regions of a chromosome, contributing to the RIDGE and RILGE compartments, define chromosome subdomains. The chromosome positions of RIDGEs at specific regions and their separation by RILGEs is responsible for bending of chromosome and the structure of chromosome domain. Therefore, two genetic elements of a particular subdomain might exist closer to each other than the elements located in different subdomains, depending on the chromosomal positions of RIDGEs and RILGEs. Indeed, we have demonstrated that the *RARa* and *TP53* genes as well as *TP53* and *iso-q* are located closer to each other in comparison to their distances from centromere of the chromosome 17, despite the greater molecular distance between the genes located on the opposite arms of the chromosome. Our results show that, in general, there is no proportionality between the physical and molecular distance of two genetic elements of the same chromosome.

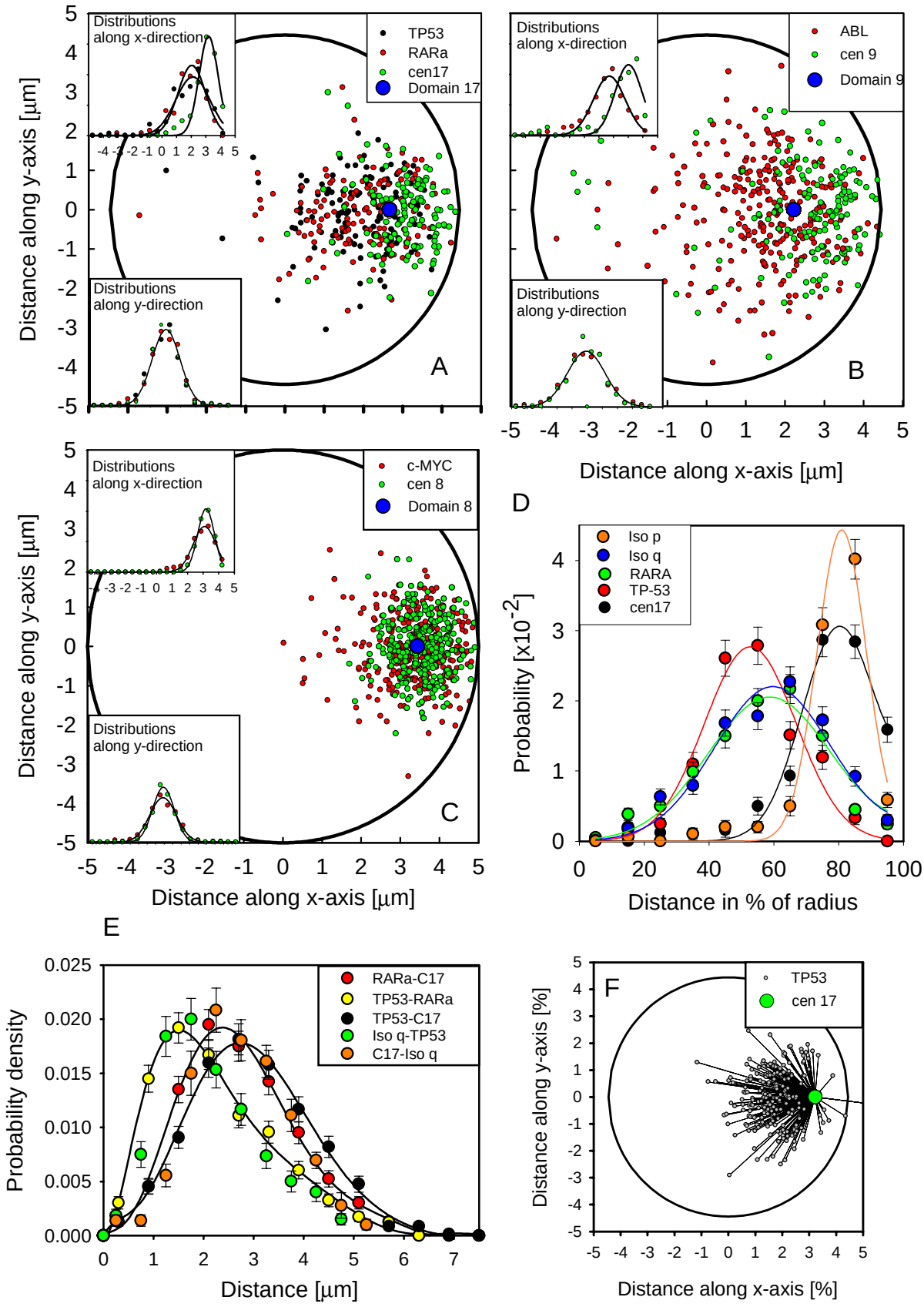

Figure 1. Structure of a chromosome domain in the nucleus.

(A), (B) and (C) Structure of the chromosome 17 (A) 9 (B) and 8 (C) domains is shown. The x-axis was set to the fluorescence center of the domain and a thin section (1 μm) was cut in the central plane. Next, the whole chromosome was shifted to the medium position of the domain along the x-axis. The figures show the positioning of genes (red and black circles) and centromeres (green circles) relative to the center of the chromosome domain (blue circle) in the nucleus. The degree of variation in the x direction for the genes and centromeres is presented (upper left panel), as well as the degree of variation in the y direction (lower left panel).

(D) The center-to-locus distances for genetic elements of chromosome 17. The most central location was found for the TP53 gene, further for the iso q locus, and for the RARα gene. The centromere as well as the iso p locus were found near the nuclear periphery.

(E) The locus-to-locus distances for genetic elements of the chromosome 17. The centromere-to-TP53 (black circles), centromere-to-RARa (red circles), and centromere-to-iso q (orange circles) distances are, on average, longer than TP53-to-RARa, TP53-to-iso q, distances (yellow and green circles).

(F) The investigated genes do not approach the corresponding centromeres. The mutual positions of the TP53 genes relative to centromere 17 are shown.

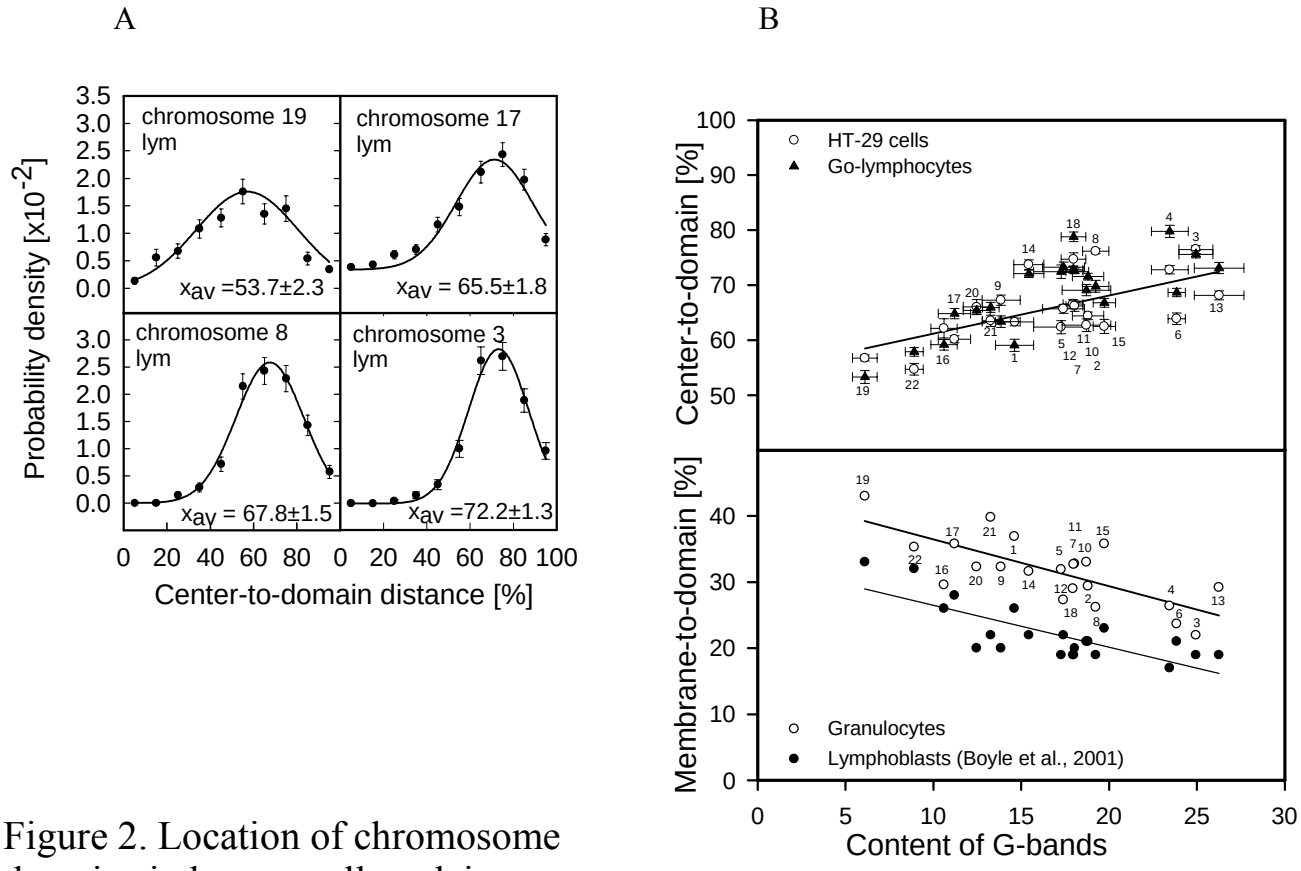

Figure 2. Location of chromosome domains in human cell nuclei.

(A) Radial 3D distributions of chromosome domains in cell nuclei of human G_o-lymphocytes are shown for 4 chromosomes. The mean values of the distributions and their standard errors are given in each panel.

(B) The dependence of the 3D distances between the nuclear center and the chromosome fluorescence center on the G-band content is shown for two cell types: G_o-lymphocytes (black triangles) and colon carcinoma cell line HT-29 (white circles). For comparison, the same dependence is included from our earlier 2D measurements for human blood granulocytes (white circles). 2D measurements for lymphoblasts are also shown (black circles).

GRANTS:

GA CR 202/98/P253
Changes of the structure of interphase nuclei of human leukemic cell lines after the influence of differentiating agents and radiation
Principal investigator: E. Bártová, guarantor: S. Kozubek, 1998 - 2001

GA CR 202/99/P008
Image analysis in the study of the structure of interphase cell nucleus
Principal investigator: M. Kozubek, FI MU, Brno, guarantor: E. Lukášová, 1999 - 2001

GA CR 202/99/0959
The use of multiple optical tweezers to controlled manipulation and rotation of microobjects
Principal investigator: M. Liška, VUT, Brno, principal co-investigator: E. Lukášová, 1999 - 2002

GA AS CR S5004010
Development of the new diagnostic techniques for oncology
Principal investigator: S. Kozubek, 2000 - 2004

GA AS CR B5004102
Nuclear topography of some protooncogenes in human neutrophils and leukemic cells
Principal investigator: E. Bártová, 2001-2003

GA AS CR K5052113
Structure, expression and interaction of the genome
Principal investigator: V. Pačes, IMG AS CR, Prague, principal co-investigator: S. Kozubek, IBP AS CR, Brno, 2001 - 2004

MH NC 5955-3
The topography of specific genetic loci in normal and malignant cell nuclei and its use for the diagnostics and treatment of solid tumors
Principal investigator: E. Lukášová, 2000 - 2002

LABORATORY OF PLANT DEVELOPMENTAL GENETICS (LPDG)

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(a) DNA methylation in plant development

1. Immunohistochemical study of DNA methylation dynamics during embryogenesis

We have studied global changes in DNA methylation during plant embryogenesis in *Silene latifolia* using an indirect immunohistochemical approach (Fig. 1). In the globular embryo, which is characterised by nearly non-differentiated cells, a low level of DNA methylation is present. In the heart stage, when basic body patterns are formed, the embryo forms highly methylated primordia of cotyledons and radicula, whereas the other parts of the embryo remain lowly DNA methylated. During the later embryo development, differentiation on the DNA methylation level proceeds together with the tissue differentiation. The fully developed embryo contains highly methylated root and shoot meristems, a lower level of DNA methylation is present in the provascular tissue and the lowest level takes place in the epidermal and subepidermal layers. The endosperm tissue of the fully differentiated but not mature seed contains a low level of DNA methylation, which rapidly increases during the seed maturation and desiccation. We conclude that plant embryos are subject to prominent, global DNA methylation dynamics, similarly as embryos in mammals.

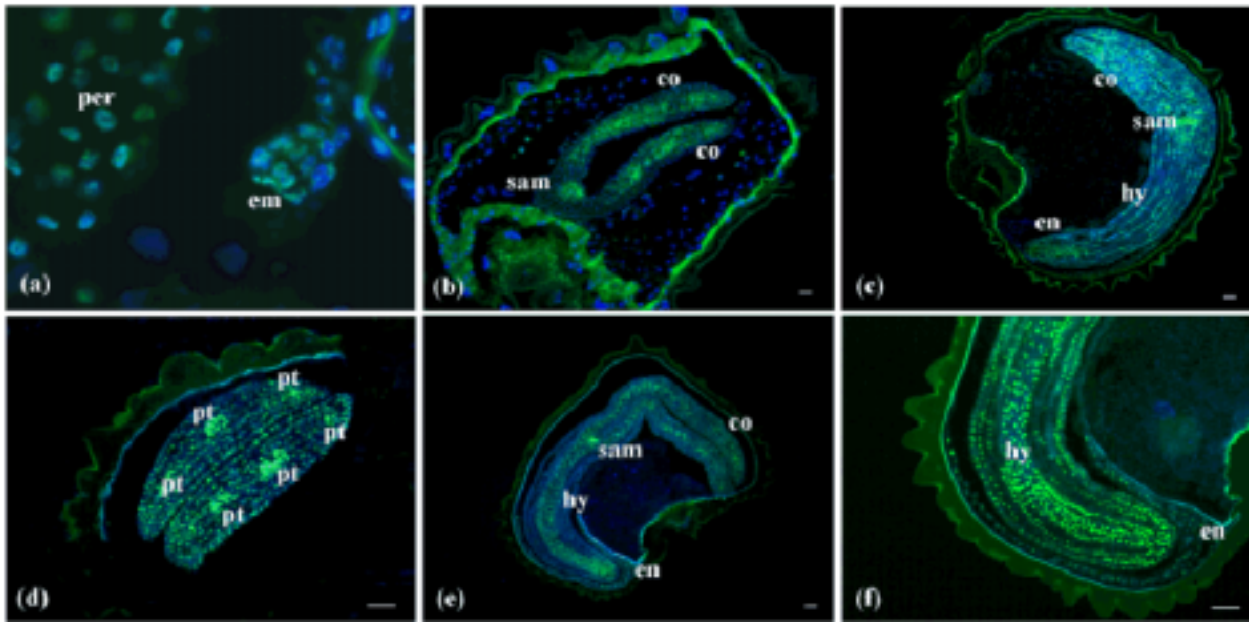

Figure 1. Immunohistochemical study of DNA methylation dynamics.

A primary antibody against 5-methylcytosine was detected with secondary FITC-labelled antibody (green signals). Slides were counterstained with DAPI (blue). Bars represent 100 µm. (a) Section of the globular embryo. Both the embryo (em) and perisperm (per) display a low level of DNA methylation. (b) A partial section of the late torpedo embryo. The highest intensity of the antibody signal is present in the shoot apical meristem (sam), a lower DNA methylation signal is localised to the cotyledons (co). (c) Labelling of the fully differentiated embryo with anti-5-methylcytosine antibody. A high DNA methylation signal is restricted to the shoot apical meristem (sam). The other parts of the embryo – cotyledons (co) and hypocotyl (hy) are rather less methylated. The lowest DNA methylation signal is present in the endosperm tissue (en). (d) A transversal section of the cotyledons of the fully differentiated embryo. The nuclei of the provascular tissue (pt) are labelled much higher than the nuclei of the epidermal and subepidermal layers. (e) Detection of the 5-methylcytosine in the mature dry seed. Prominent antibody signals are present in the shoot apical meristem (sam), less intensive signals are localised to the cotyledons (co) and hypocotyl (hy). (f) A partial section of the hypocotyl (hy) and endosperm (en) of the mature dry seed. Note the intensity of the anti-5-methylcytosine signal in the endosperm tissue.

2. Cytosine methylation pattern in a tissue specific gene

A possible role of DNA methylation in the transcriptional control of the *MROS1* gene (*Male Reproductive Organ Specific*) was checked by comparison of cytosine methylation patterns in a non-expressing tissue – leaves, and the tissue where this gene begins to be expressed – binucleate pollen. The genomic sequencing data obtained in leaf samples showed a significantly higher methylation level of a 150 bp long part of the 5' upstream region when compared to the neighboring 100 bp part of

transcribed region. However, the control role of this DNA hypermethylation cannot be stated since similar methylation patterns of 5' upstream region (presence of a 50 bp large hypermethylated part) were also found in binucleate pollen where the *MROS1* gene is transcribed. The hypermethylated region could represent a boundary which separates the *MROS1* gene from the global DNA methylation changes which occur in the vegetative nucleus of mature pollen grains. This research is realised in collaboration with Dr. Sachihiro Matsunaga (University of Tokyo).

(b) Structure and evolution of Silene genome and sex chromosomes

1. Construction and screening of BAC and phage genomic libraries

We screened a partial BAC library of *Silene latifolia* with the aim to find clones giving discrete signal in FISH on the sex chromosomes (collaboration with Dr. Sarah Grant, University of North Carolina; Prof. J. S. Heslop-Harrison, John Innnes Institute; Dr. Jiří Macas, Institute of Plant Molecular Biology). Such BACs would represent powerful tool in searching for autosomal progenitors of sex chromosomes in hermaphroditic *Silene* species. BAC library was screened with various probes (genomic DNA, cDNA, rDNA etc.) using colony hybridization manually or with robots arraying BACs onto membrane (Fig. 2a) and also using DNA microarrays. BAC clones strongly hybridizing with genomic DNA contained repetitive sequences and painted all chromosomes in FISH (Fig. 2b) while weakly hybridizing clones containing single- or low-copy sequences resulted in discrete signals in FISH (Fig. 2c).

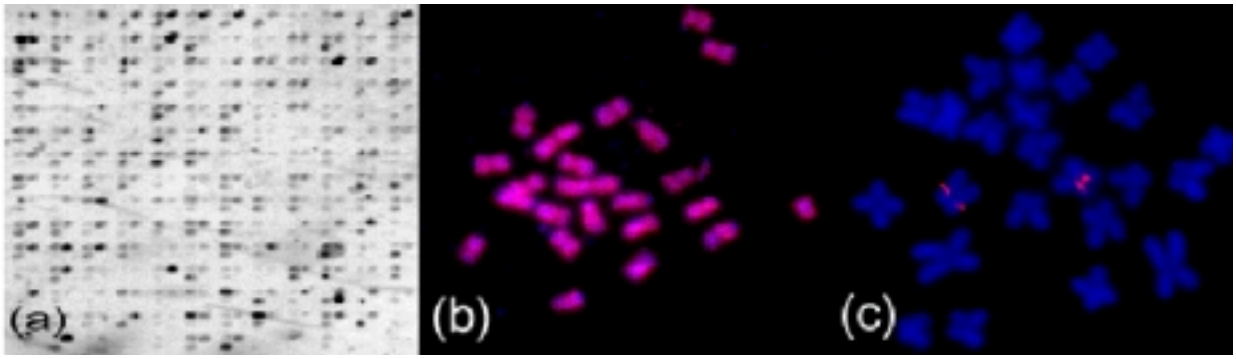

Figure 2. Hybridization of robotically arrayed BAC clones hybridized with labelled S. latifolia genomic DNA (a). Fluorescence in situ hybridization signals with BAC clones containing repetitive sequences (b) or single copy sequences only (c).

We also studied distribution of genes in *S. latifolia* genome. We used gene-rich *Arabidopsis thaliana* genomic DNA for interspecific FISH with *S. latifolia* chromosomes. Our previous results indicate that genes in large

S. latifolia genome and some other *Silene* genomes are homologous to *A. thaliana* genes and are mostly located in subtelomeric regions of all chromosomes.

2. Isolation and characterization of sex specific genes

We have isolated six sequences (DD3, DD7, DD14, DD26, DD44, DD51) by differential display method. We suppose that these sequences can play a role during male phenotype expression. All clones were localized in genome of *Silene latifolia* applying PCR on sorted chromosomes. We have used RT-PCR and Northern blot analysis to verify expression of cloned sequences. Only two (DD3, DD44) from six isolated sequences revealed differences in expression pattern between males and females or were localized on sex chromosomes. One of the DD3 alleles was localized using chosen primers on the Y chromosome and we have proved that this sequence is also expressed there. DD44 was localized on the sex chromosomes and is expressed both on the X and on the Y chromosome (Fig. 3a,b). The DD44 sequence was also localised on *S. latifolia* chromosomes using *in situ* hybridization (FISH). The probe for FISH was obtained by screening a genomic phage library (collaboration with Dr. Sarah Grant, University of North Carolina). The insert from a positive phage (16 kbp long) was recloned to pBR322 plasmid and labelled by Cy3-dUTP. DD44 probe was localised to the distal regions of longer arms of both the sex chromosomes, X and Y (Fig. 3c). The results are consistent with the segregation analysis showing the presence of X and Y linked copies in the *S. latifolia* genome. The precise cytological localisation was further confirmed using cultured cell deletion mutants; female *S. latifolia* cells possessing a deletion on the distal region of longer arm of the X chromosome and male cells with the completely missing shorter arm of the Y. The DD44 sequence is thus positioned in the pairing region of the sex chromosomes which otherwise do not pair during meiosis.

In collaboration with Prof. Ioan Negrutiu (ENS de Lyon) we have positioned three marker genes (*SLX1*, *SlX3*, *SlX4*) on the X chromosome in *Silene latifolia*. Relative distances between these genes were deduced from the percentage of recombination calculated for each gene pair by two different approaches – Haldane and Kossambi mapping function. Both methods suggest that the relative position of the three genes is *SlX1-SlX3-SlX4*. Considering the existence of interference between the genes, distance calculations by Haldane mapping function seems to be more precise – 27 cM between *SlX1* and *SlX3*, 49 cM between *SlX3* and *SlX4*. The statistical significance of the results was verified by standard error calculation. By this analysis we have generated the system of reference for other *Silene* species.

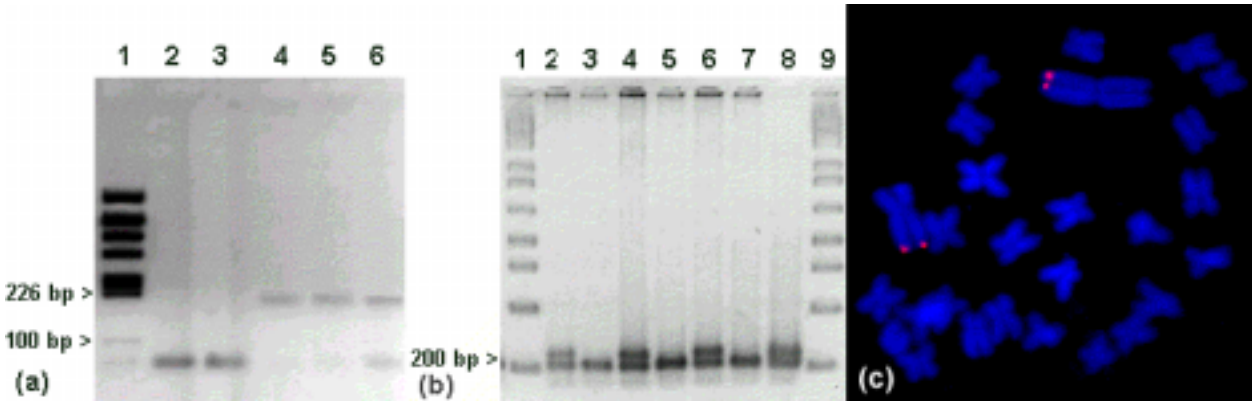

Figure 3. Characterization of DD44 gene. (a) PCR localization on sorted chromosomes with specific primers [1. DNA markers, 2. no template, 3. autosomes, 4. X chromosomes, 5. male genomic DNA, 6. female genomic DNA]. (b) Expression (RT-PCR) analysis with DD44 primers [1. DNA markers, 2. male RNA (leaves), 3. female RNA (leaves), 4. male RNA (flowers), 5. female RNA (flowers), 6. male RNA (buds), 7. female RNA (buds), 8. RNA (seedlings), 9. DNA markers]. (c) Localization of DD44 on S. latifolia sex chromosomes, male mitosis. DD44 is located to the subtelomeric region of longer arms of the sex chromosomes.

GRANTS:

GA AS CR A5004901
Nuclear structure and histone acetylation in plant cells
Principal investigator: B. Vyskot, 1999 - 2001

GA AS CR K5052113
Structure, expression and interaction of the genome
Principal investigator: V. Pačes, IMG AS CR, Prague, principal co-investigator: B. Vyskot, IBP AS CR, Brno, 2001 - 2004

GA CR 521/99/0696
Kinetics of DNA methylation in embryogenesis and seed germination
Principal investigator: B. Vyskot, 1999 - 2001

GA CR 521/96/K117
New methods for effective studying and mapping of crop plants
Principal investigator: J. Doležel, IEB AS CR, Olomouc, principal co-investigator: J. Široký, IBP AS CR, Brno, 1996 - 2001

LABORATORY OF MOLECULAR ANALYSIS OF PLANT DEVELOPMENT (LMAPD)

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RESEARCH FELLOW:	MGR. JAN NEJEDLÍK
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UNDERGRADUATE STUDENTS:	ALENA REKOVÁ, BC. PETR KLÍMA, BC.

*external co-worker

Biological function of a putative cytokinin receptor CKI1

Previously we have found that an insertion of an *En1* transposon in a gene *CKI1* results in a perturbation of sexual reproduction in *Arabidopsis thaliana*. Using light, electron scanning and laser confocal microscopy, we have shown that the defect in sexual reproduction is caused by an early block in ovule development. We have identified the position of the block by laser confocal microscopy. *CKI1* expression pattern was analyzed first by *in situ* RNA hybridization. The results are in a good agreement with the morphological analysis of the mutant phenotype. The results obtained by *in situ* RNA hybridization are being confirmed by analyzes of transcription activity of a putative *CKI1* promoter in transgenic plants harboring transcription fusion of the promoter with a *GUS* reporter gene. The corresponding binary vector was constructed and transgenic Arabidopsis plants harboring the fusion integrated in genomic DNA were prepared by vacuum infiltration. Preliminary analysis of the plants revealed that the promoter region has been chosen correctly, and it can be assumed that a detailed analyzes of the plants will confirm results obtained by *in situ* RNA hybridization. As a complementary approach, a histochemical *in situ* localization of the *CKI1*

gene product will be performed. To achieve this, CKI1 specific polyclonal antibodies were prepared. cDNA coding a part of a cytoplasmic CKI1 domain was cloned into a suitable vector, the protein was produced in a bacterial expression system and a purification scheme was developed. The highly purified antigen was used in four independent immunizations. Anti-CKI1 specific antibodies were purified on the immobilized CKI1 cytoplasmic domain used for immunization, and purity and sensitivity of the purified antibodies was analyzed first by Western blot. The antibodies will be used for histochemical analyzes of CKI1 distribution in Arabidopsis.

The role of cytokinin metabolism in plant growth and development

A transcription activation system based on a synthetic promoter pOp and a corresponding chimeric transcription activator LhG4 was employed to achieve regulatable expression of isopentenyl transferase, IPT, in transgenic tobacco. The system allowed us to analyze in detail developmental consequences of *ipt* activation in germination and early seedling development. We focused on analysis of (i) dynamics of changes in cytokinin metabolism upon *ipt* activation and (ii) subsequent chain of developmental alterations leading to transition from originally almost normal seedling to a completely distinct teratoma structure. We established a very similar system in Arabidospsis. Although the extent of changes in endogenous cytokinins in response to *ipt* activation was very similar in the two plant species, major differences in biological responses to the increased levels of endogenous cytokinins were found among tobacco and Arabidopsis. We are analyzing mechanisms underlying the different responses.

Cytokinins and auxins in regulation of plant development

The role of subcellular compartmentation of cytokinin metabolism in regulation of their biological activity is investigated. First, increased rate of cytokinin biosynthesis is triggered by induction of expression of a key enzyme of cytokinin biosynthesis, isopentenyl transferase, in tobacco protoplasts. The protoplasts are then fractionated and chloroplasts and vacuoles are isolated. Rate of sequestration and subsequent metabolic conversions in the chloroplasts and vacuoles of cytokinins originally synthesized in the cytoplasm are analyzed by LC-MS/MS. Second, feasibility of regulated cytokinin release from cytokinin-O-glucosides in individual subcellular compartments using a maize β-glucosidase, Zm-p60.1, specific for cytokinin-O-glucosides is analyzed. Zm-p60.1 is a plastid/chloroplast enzyme. Information specifying subcellular targeting in *Zm-p60.1* cDNA has been modified to achieve re-direction of individual Zm-p60.1 derivatives from plastids/chloroplasts into (i) the vacuole, and (ii) secretion into the extracellular space. The derivatives were placed under a control of a tetra-cycline-inducible promoter, and the resulting constructs were transformed

into tobacco. Upon induction, the changes in cytokinin metabolite spectra in intact protoplasts, and isolated chloroplasts and vacuoles are being analyzed by LC-MS/MS.

GRANTS:

GA AS CR A5004001
Transcription activation system for studying the relationship between cytokinin metabolism and action in Arabidopsis and tobacco
Principal investigator: B. Brzobohatý, principal co-investigators: A. Kuderová, Fac. Sci. MU, Brno; I. Macháčková, IEB AS CR, Prague, 2000 - 2002

GA AS CR K5052113
Structure, expression and interaction of the genome
Principal investigator: V. Pačes, IMG AS CR, Prague, principal co-investigator: B. Brzobohatý, IBP AS CR, Brno, 2001 - 2004

GA CR 206/96/K188
Cytokinins and auxins in regulation of plant development
Principal investigator: I. Macháčková, IEB AS CR, Prague, principal co-investigator: B. Brzobohatý, IBP AS CR, Brno, 1996 - 2001

ME CR LN00A081
Program Research Centres "Signalling pathways in plants"
Coordinator: I. Macháčková, IEB AS CR, Prague, participant: B. Brzobohatý, IBP AS CR, Brno, 2000 - 2004

PROGRAM V

KINETICS OF THE CELL POPULATIONS

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RESEARCH FELLOWS:	RNDR. JIŘINA HOLÁ MGR. JAROMÍRA NETÍKOVÁ
TECHNICAL ASSISTANT:	EVA KOUKALOVÁ
GRADUATE STUDENTS:	MGR. ZDENĚK ANDRYSÍK MGR. JIŘÍ PACHERNÍK MGR. JIŘÍ ŠTIKA MGR. ALENA VACULOVÁ MGR. KAREL SOUČEK MGR. KATEŘINA MINKSOVÁ
UNDERGRADUATE STUDENTS:	LENKA ŠINDLEROVÁ PETR ORSÁG PETRA RŮŽIČKOVÁ LENKA UHMANOVÁ

We have continued studies on interactions of cytokines TGF-β1 and TNF-α with inhibitors of metabolism of arachidonic acid (AA) in regulation of cytokinetics (proliferation, differentiation and apoptosis) in normal and tumor cell populations. These studies have been based on the hypothesis that both cytokines and cell membrane phosholipid derivatives play a key role in the regulation of the aforementioned processes. We have used an array of structurally diverse compounds blocking AA metabolism: eicosatetraynoic acid (ETYA, a competitive inhibitor of AA metabolism), nordihydro-guaiaretic acid (NDGA, lipoxygenase inhibitor), baicalein (12-lipoxygenase inhibitor), indomethacin (cyclooxygenase-1 and –2 inhibitor), niflumic acid (cyclooxygenase-2 inhibitor), and proadifen (cytochrome P450 inhibitors). The compounds were chosen because of their potential anti-tumorigenic effects.

Results of studies on effects of cytokines. We have studied the mechanism by which TGF-β1 potentiates myeloid differentiation of human leukemic cells (NB-4, HL-60), induced by all-trans retinoic acid (ATRA). Attention was paid especially to the role of Bcl-2 family proteins in inhibition of programmed cell death induced by ATRA and inhibited by TGF-β1. It was

shown that this effect does not depend on the expression of selected Bcl-2 family proteins. In addition, we have studied whether the potentiation of differentiation effects by TGF-β1 and ATRA co-treatment is related to changes in expression of TGF-βRI and TGF-βII receptors. However, no significant changes in expression of receptors were found. A number of novel clones of leukemia cell lines resistant to ATRA were prepared, in order to study possible interactions of ATRA and TGF-β1 effects.

Effects of TNF-α, TRAIL and Fas. Using the human leukemia U937 cell line, we have investigated the effect of dimethyl sulfoxide (DMSO) on apoptosis, induced by receptors of TNFR family. Both coincubation and preincubation of U937 cells with DMSO potentiated effects of anti-Fas monoclonal antibody, recombinant human TRAIL and TNF-α. DMSO did not affect expression of apoptosis-regulatory proteins, such as Mcl-1, Bcl-2, Bcl-X, Bax, cIAP-1, cIAP-2, XIAP, c-FLIP, caspase-3, caspase-8. However, it was found that DMSO significantly potentiates mitochondrial membrane depolarization.

The effects of TNF-α on colon carcinoma cells. It was shown that cells of human colon adenocarcinoma HT-29 line are relatively resistant to acute cytotoxic and antiproliferative effects of TNF-α although these effects can be potentiated by inhibition of proteosynthesis by cycloheximide. Inhibition of cell growth, apoptosis and decrease in cell viability were not apparent before 96 and 120 hours of treatment. However, in addition to this retarded effects TNF-α induced early events characteristic for apoptosis - activation of caspase-3, cleavage of poly/ADP-ribose)polymerase to its 89 kD fragment and production of reactive oxygen species (ROS).

Interaction of polyunsaturated fatty acids (PUFAs) with inductors of apoptosis. It was demonstrated that pretreatment with PUFAs of n-3 (docosahexaenoic acid) or n-6 types (arachidonic acid) sensitized HT-29 cells to acute apoptotic effects of sodium butyrate (NaBt), anti-Fas antibody (CH-11) or TNF-α. These effects were associated with increased production of ROS, lipid peroxidation and dissipation of mitochondrial potential.

The effects of inhibitors of AA metabolism. These effects were studied using specific inhibitors of AA metabolism with respect to the proliferation and death of undifferentiated or NaBt differentiated HT-29 cells. Differentiated cells were more sensitive to effects of inhibitors particularly those of cyclooxygenase. The effects of TNF-α were further investigated after the treatment of cells with NaBt or inhibitors of AA metabolism. While no changes in resistance to antiproliferative TNF-α effects were observed, cytokine promoted induction of cell death was significantly increased.

The effects of inhibitors of AA conversion by cyclooxygenases, lipoxygenases or cytochrome P450 were studied also with other cell populatins, such as murine fibrosarcoma G:5:113 cell line, human HaCaT keratinocytes and HL-60 cells. While the cyclooxygenase inhibitors (ibuprofen, flurbiprofen and diclophenac) did not significantly alter G:5:113 cells proliferation, the 5- and 12-lipoxygenase (NDGA, esculetin, baicalein) and cytochrome P450 inhibitors (proadifen) inhibited proliferation and induced specific changes in cell cycle, without inducing apoptosis. The cyclooxygenase inhibitors (indomethacin and piroxicam) had no effect on HaCaT cells, while ETYA (a competitive AA analogue), NDGA and esculetin inhibited cell proliferation and induced apoptosis (PARP cleavage). Esculetin induced morphological changes associated with F-actin re-distribution. The inhibitors had no effects on cytokeratin and E-cadherin expression.

Furthermore, we have studied effects of inhibitors on apoptosis induced by TNF-α. It was found that both indomethacin and NDGA induce apoptosis in HL-60 cells; however, in the case of NDGA this process was associated with depolarization of the mitochondrial membrane, cytochrome c release and caspase-3 activation. Both compounds synergistically potentiated apoptotic effects of TNF-α. However, they had no effect on apoptosis induced by anti-Fas antibody. Incubation of HL-60 cells with both inhibitors did not induce changes in expression of cytosolic phospholipase A_2, cyclooxygenase-2 and 5-lipoxygenase proteins. These findings can have implications in the area of supplementary anti-tumor therapy.

Results in the field of ecotoxicology. We have studied estrogenic effects of polycyclic aromatic hydrocarbons (PAH) *in vitro.* It was found that especially benzo[a]pyrene and benz[a]anthracene can activate estrogen receptor and potentiate the effects of natural estrogens (17β-estradiol). We have also studied effects of these compounds on activation of MAP kinases, Erk1/2, and their relation to estrogenic effects of PAH. We believe that these results contribute to the understanding of control processes in epithelial cells as well as to the understanding of adverse affects of environmental contaminants.

Results in the field of applied research and development. The current potential of five laboratories was further increasaed with the aim to contribute to the clinical praxis: Research on the role of DNA-binding sites of p53 protein in interaction with specific DNA structures, especially supercoiled (sc) DNA and chemically-altered DNA (Laboratory of Molecular Biophysics and Pharmacology) was extended to the *in vivo* level using the methodologies of the Laboratory of Cytokinetics and the Laboratory of Experimental Hematology; studies were aimed at understanding of mutual interactions

between experimentally-implanted tumor and host organism; special attention was payed to effects on hematopoiesis.

Our efforts also resulted in founding the Consortium of Infusia a.s., Faculty Hospital of Charles University, Hradec Králové and Laboratory of Cytokinetics. The goal is to develop and produce novel types of lipid emulsions for parenteral nutrition of patients.

GRANTS:

GA AS CR S5004009
Alternative therapeutic strategies in oncology
Principal investigator: A. Kozubík, 2000 - 2004

GA AS CR P1050128
Dynamics of processes in living and non-living matter - multifunctional equipment for fluorimetry, photometry and luminometry
Coordinator: K. Ulbrich, IMCH AS CR, Prague, principal co-investigator: A. Kozubík, IBP AS CR, Brno, 2001

GA AS CR K5011112
Molecular and cellular basis of weight disorders
Principal investigator: P. Mareš, PGI AS CR, Prague, principal co-investigator: A. Kozubík, IBP AS CR, Brno, 2001 - 2004

GA CR 524/99/0694
Polyunsaturated fatty acids and cytokines - their role in maintenance of homeostasis at the cell population level
Principal investigator: A. Kozubík, 1999 - 2001

GA CR 301/00/0563
Modulation of tumor cells defense: Definition and inhibition of survival mechanisms suppressing apoptosis mediated by Fas and employed by tumor cells
Principal investigator: M.A. Sheard, MOÚ, Brno, principal co-investigator: J. Vondráček, IBP AS CR, Brno, 2000 - 2002

GA CR 525/01/D076
Activation of MAP protein kinase pathways by polycyclic aromatic hydrocarbons *in vitro* - a potential nongenotoxic mechanism underlying the effects of environmental contaminants
Principal investigator: J. Vondráček, guarantor: A. Kozubík, 2001 - 2004

GA CR 305/01/0418
Cellular and molecular pharmacology of platinum and ruthenium anticancer drugs
Principal investigator: A. Kozubík, 2001 - 2003

GA CR 525/01/0419
Dietary lipid components in the regulation of cytokinetics of colonic epithelium
Principal investigator: J. Hofmanová, 2001 - 2003

IGA MH CR NC/6171-3
Changes of lipid metabolism and their effects in colorectal carcinoma patients - perspective use in nutritional support
Principal investigator: Z. Zadák, FN UK, Hradec Králové, principal co-investigator: J. Hofmanová, IBP AS CR, Brno, 2000 - 2002

MPO FD-K/033
Development of parenteral lipid emulsion and technical solution of its application
Principal investigator: INFUSIA a. s., Hořátev, principal co-investigator: A. Kozubík, IBP AS CR, Brno, 2001

University development foundation 0568/2001
The effects of polyunsaturated fatty acids on activity of cytokine TNF-α
Principal investigator: A. Vaculová, co-investigators: J. Hofmanová, IBP AS CR, Brno, V. Šimek, Fac. Sci. MU, Brno, 2001

University development foundation 567/2001
The effects of intracellular molecules on activity of cytokine TNF-α - student's research
Principal investigator: J. Štika, co-investigators: J. Hofmanová, M. Marek, E. Janouškovcová, Fac. Sci. MU, Brno, 2001

LABORATORY OF EXPERIMENTAL HEMATOLOGY (LEH)

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RESEARCH FELLOWS:	RNDR. JIŘINA HOLÁ MGR. JAROMÍRA NETÍKOVÁ ING. IVA PIPALOVÁ*
TECHNICAL ASSISTANT:	VĚRA REICHMANNOVÁ
GRADUATE STUDENT:	MGR. LENKA WEITEROVÁ

*external co-worker

In 2001, studies on pharmacological stimulation of hematopoiesis, damaged by combined action of ionizing radiation and cytostatic therapy, were performed. In the experiments, *in vivo* and *in vitro* techniques were used, cobalt irradiator Chisostat served as radiation source, cisplatin was employed a model cytostatic drug.

Preceding studies showing the ability of drugs elevating extracellular adenosine (dipyridamole (DP) and adenosine monophosphate (AMP)) and granulocyte colony-stimulating factor (G-CSF) to potentiate mutually their stimulating actions on hematopoiesis damaged by exposure of experimental animals (mice) to ionizing radiation or cytostatic therapy were followed by a series of experiments in which hematopoietic system was deeply suppressed by combined exposure to both the damaging influences mentioned. Results of these experiments showed that also under these experimental conditions, the combination of DP, preventing the cellular uptake of adenosine, and AMP, a source of adenosine, with G-CSF may be advantageous. Such therapeutic procedure led to significant increase of numbers of hematopoietic progenitor cells for granulocytes and macropages (GM-CFC) in hematopoietic organs in early intervals after cessation of the treatment. This increase of GM-CFC numbers was succeeded in subsequent time intervals by an increase of the counts of mature granulocytes in the peripheral blood. Thus, the prerequisite for higher resistance of the experimental animals against infections accompanying myelosuppressive states of various origin has been reached. The findings described point out the possibility to use the drug combination of DP + AMP + G-CSF in human clinical practice.

Evaluation of the results of studies testing radio- and chemoprotective effects of adamantylamide dipeptide (AdDP) has been finished in 2001. Positive action of this immunomodulator on regeneration of suppressed hematopoiesis enables to consider further testing of AdDP, namely in clinical studies.

GRANTS:

GA CR 306/99/0027
Enhancement of G-CSF action by adenosine signalling: Testing of its potential clinical use in murine models
Principal investigator: M. Hofer, principal co-investigator: J. Vácha, LF MU, Brno, 1999 - 2001

GA AS CR K5011112
Molecular and cellular basis of weight disorders
Principal investigator: P. Mareš, PGI AS CR, Prague, principal co-investigator: M. Hofer, IBP AS CR, Brno, 2001 - 2004

GA MI PZ Z2/25/97
Radioprotective and chemoprotective effects of the immunomodulator adamantylamide dipeptide (AdDP)
Principal investigator: K. Mašek, IP AS CR, Prague, principal co-investigator: M. Hofer, IBP AS CR, Brno, 1997 - 2001

LABORATORY OF FREE RADICALS PATHOPHYSIOLOGY (LFRP)

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TECHNICAL ASSISTANTS:	BLANKA PANÁKOVÁ LENKA VYSTRČILOVÁ
RESEARCH FELLOW:	SYLVA POKORNÁ
GRADUATE STUDENTS:	MVDR. IVANA PAPEŽÍKOVÁ MGR. MARTINA PAVELKOVÁ MGR. DANIELA HRADILOVÁ MGR. LUCIE GALLOVÁ
UNDERGRADUATE STUDENTS:	EVA PRACHAŘOVÁ KATEŘINA MEJSTŘÍKOVÁ

Bacterial strain *Streptococcus mutans* was used to differentiate between extra- and intracellular reactive oxygen species production by human leukocytes. Significant differences were observed when comparing the chemiluminescence (CL) activity of the same number of cells in leukocyte rich plasma and in isolated leukocytes. The peak CL response of leukocyte rich plasma was higher than that of isolated leukocytes (8210 RLU vs. 5406 RLU for 2 x 10^5 cells). On the other hand, the CL reaction was much faster in isolated cells (2.2 min vs. 16.5 min). Additional flow cytometrical measurements showed *S. mutans* not being phagocytosed in the absence of opsonins. All the results obtained suggest an extracellular production of reactive oxygen species to be responsible for the *S. mutans*-induced CL activity of isolated leukocytes.

Systemic inflammatory responses following heart transplantation (HTx) and open heart surgery (OHS), both involving cardiopulmonary bypass, were compared. Interleukin (IL-6, IL-8, IL-10) plasma concentrations, lipid peroxidation, as well as blood phagocyte radical production during surgery and on the 1st and 7th post-operative days were evaluated in HTx patients (n=24) and in OHS patients (n=30). IL-6, IL-8 and IL-10 levels increased in both groups of patients during early reperfusion. They normalized within the first post-operative day in the HTx group, while the OHS patients' levels of IL-6 and IL-8 remained elevated on the 7th day after operation. IL-10 plasma levels were higher in HTx patients during reperfusion. Lipid peroxidation

was increased after operation in both groups of patients. Phagocyte activity was enhanced at reperfusion and at all other sampling times only in OHS patients. Both HTx and OHS are associated with increased oxidative stress and an enhanced production of pro- and anti-inflammatory cytokines. Differences in IL-10 production and phagocyte activity could be caused by a longer duration of ischemia and immunosuppressive therapy in HTx operations.

In vitro effects of recombinant IL-10, IL-6, IL-8 and TNF- alpha (400, 800, 1200, 1600 pg/ml) both separately and in combination, on the spontaneous and activated oxidative burst in human whole blood phagocytes was examined. IL-6, IL-8 and TNF-alpha induced significant increase in reactive oxygen species production and expression of CD11b, CD15, CD62L. Conversely, IL-10 had no effect on the oxidative burst of blood phagocytes and on the expression of adhesion molecules (CD11b, CD15, CD62L, CD31) on neutrophils and monocytes. Antiinflammatory effect of IL-10 was observed neither after its co-incubation with proinflammatory cytokines studied.

The effect of various ascorbic acid concentrations on the antioxidative properties of plasma and serum of laboratory rats was studied. Total antioxidative capacity of serum and plasma was evaluated using luminol-enhanced chemiluminiscence as an ability to scavenge peroxyl radicals. Synthetic ascorbic acid in the concentration range of 25 – 125 μM was added to plasma and serum samples. The ability of plasma and serum to scavenge peroxyl radicals increased proportionally with increasing concentration of ascorbic acid added. Antioxidative properties of ascorbic acid were proved also in systems generating the most important reactive oxygen species occuring in organisms - hydroxyl radicals generated by Fenton reaction and hydrogen peroxide.

A role of serotonine produced by platelets in inhibition of neutrophil oxidative burst was studied. Serotonine (0.1 a 0.5 μmol/l) inhibited neutrophil CL stimulated with Ca^{2+}-ionophore A23187 by 19 and 69%, resp. Serotonine in the concentration of 1 μmol/l decreased also the CL induced with FMLP (by 79%) and opsonised zymosan (by 39%). CL of various radicals produced chemically (in cell-free systems) was significantly reduced by serotonine in the concentration of 10 μmol/l (superoxide anion by 69%, hydroxyl radical by 34%) and 100 μmol/l (hydrogen peroxide by 63%). Extracellular concentration of serotonine increased to 0.2 μmol/l (0.125-0.355 μmol/l) after platelet activation, i.e. serotonine can participate in inhibition of CL. However, platelets inhibited CL significantly more efficiently than serotonine. It indicates that platelets release other substances which also contribute to the decrease in concentration of radicals in surrounding of activated neutrophils.

GRANTS:

GA CR 524/00/1223
Reactive oxygen and nitrogen metabolites generated by neutrophils under physiological and pathophysiological conditions
Principal investigator: A. Lojek, 2000 - 2002

GA CR 524/99/D022
The influence of different time of ischemia and reperfusion upon the development of reperfusion injury of intestine
Principal investigator: H. Čížová, guarantor: M. Číž, 1999 - 2001

GA CR 524/01/1219
Understanding and modulation of the antioxidative defence mechanisms in oxidative stress
Principal investigator: M. Číž, 2001 - 2003

GA AS CR K5011112
Molecular and cellular basis of weight disorders
Principal investigator: P. Mareš, PGI AS CR, Prague, principal co-investigator: A. Lojek, IBP AS CR, Brno, 2001 - 2004

Kontakt MŠMT CR 67
The influence of platelets on the respiratory burst of neutrophils
Principal investigator: A. Lojek, 2000 - 2001

RESEARCH CENTRE

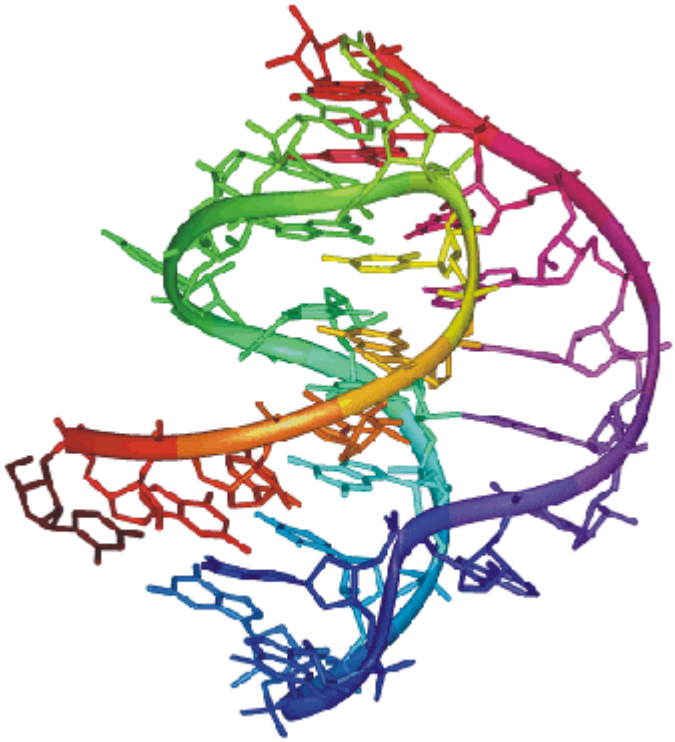
BIOMOLECULAR CENTRE

COORDINATOR:	MASARYK UNIVERSITY BRNO
PARTICIPANT:	INSTITUTE OF BIOPHYSICS AS CR BRNO
HEAD (IBP AS CR):	RNDR. JIŘÍ ŠPONER, DRSC.
GRADUATE STUDENT:	MGR. NAĎA ŠPAČKOVÁ

We have continued investigations of the structure and dynamics of DNA and RNA molecules with the aid of state-of the art computer simulations (molecular dynamics) combined with other advanced technologies such as *ab initio* quantum chemical calculations. Among others, we have finished and published an extensive study of the structure and dynamics of viral frameshifting pseudoknot of BWYV (see Fig.). This study revealed unique information regarding the initial stages of pseudoknot unfolding as well as unambiguously proved protonization of the key residuum C8. The simulations have revealed a number of highly structured hydration sites with residency times of individual water molecules on a scale of several nanoseconds, that is an order of magnitude longer than in the case of common hydration sites. Further, monovalent cation binding sites with occupancies above 50% of the time span have been found. Specific hydration and cation-binding sites evidently contribute to the unique three-dimensional structure of pseudoknots.

Important results were obtained in the course of studies of guanine quadruplex molecules. Simulations were used to characterize a wide range of four, three and double stranded DNA molecules that have been proposed to be possible kinetic intermediates in the process of quadruplex formation. Their thermodynamic stability has been characterized using advanced continuum solvent methods with a direct extraction of the data from the simulation trajectories. This analysis provides an atomic resolution picture of the quadruplex formation, considerably extended beyond the available experimental data.

We have initiated a broad study of additional RNA motifs rich in noncanonical base pairs such as the RNA E-loop. We have also carried out preliminary investigations of the conformational plasticity of lateral and diagonal thymidine loops of quadruplexes.



Structure of the viral pseudoknot BWYV (Beet Western Yellows Virus).

GRANT:

ME CR LN00A016
Program „Research Centre“ Biomolecular Centre
Coordinator: J. Koča, Fac. Sci. MU, Brno, participant: J. Šponer, IBP AS CR, Brno, 2000 - 2004

SIGNALLING PATHWAYS IN PLANTS

COORDINATOR:	INSTITUTE OF EXPERIMENTAL BOTANY AS CR PRAGUE
PARTICIPANT:	INSTITUTE OF BIOPHYSICS AS CR BRNO
HEAD (IBP AS CR):	RNDR. BŘETISLAV BRZOBOHATÝ, CSC.
SCIENTIST:	MGR. JAN ZOUHAR, PH.D.
GRADUATE STUDENTS:	MGR. JAN HEJÁTKO MGR. PETRA BORKOVCOVÁ MGR. HANA BUBENÍČKOVÁ

Biological function of a putative cytokinin receptor CKI1

Previously we have found that an insertion of an En1 transposon in a gene CKI1 results in a perturbation of sexual reproduction in *Arabidopsis thaliana*. Using light, electron scanning and laser confocal microscopy, we have shown that the defect in sexual reproduction is caused by an early block in ovule development. We have identified the position of the block by laser confocal microscopy. CKI1 expression pattern was analyzed first by in situ RNA hybridization. The results are in a good agreement with the morphological analysis of the mutant phenotype. The results obtained by in situ RNA hybridization are being confirmed by analyzes of transcription activity of a putative CKI1 promoter in transgenic plants harboring transcription fusion of the promoter with a GUS reporter gene. The corresponding binary vector was constructed and transgenic Arabidopsis plants harboring the fusion integrated in genomic DNA were prepared by vacuum infiltration. Preliminary analysis of the plants revealed that the promoter region has been chosen correctly, and it can be assumed that a detailed analyzes of the plants will confirm results obtained by in situ RNA hybridization. As a complementary approach, a histochemical in situ localization of the CKI1 gene product will be performed. To achieve this, CKI1 specific polyclonal antibodies were prepared. cDNA coding a part of a cytoplasmic CKI1 domain was cloned into a suitable vector, the protein was produced in a bacterial expression system and a purification scheme was developed. The highly purified antigen was used in four independent immunizations. Anti-CKI1 specific antibodies were purified on the immobilized CKI1 cytoplasmic domain used for immunization, and purity and sensitivity of the purified

antibodies was analyzed first by Western blot. The antibodies will be used for histochemical analyzes of CKI1 distribution in Arabidopsis.

GRANTS:

GA AS CR K5052113
Structure, expression and interaction of the genome
Principal investigator: V. Pačes, IMG AS CR, Prague, principal co-investigator: B. Brzobohatý, IBP AS CR, Brno, 2001 - 2004

ME CR LN00A081
Program „Research Centres“ Signalling pathways in plants
Coordinator: I. Macháčková, IEB AS CR, Prague, participant:
B. Brzobohatý, IBP AS CR, Brno, 2000 - 2004

LABORATORY OF COMPUTER AND INFORMATION SERVICES (LCIS)

HEAD:	RNDR. JOSEF JURSA, CSC.
TECHNICAL ASSISTANT:	LUKÁŠ POSÁDKA

Standard services of the laboratory:

- ✓ Operation, servicing and development of the IBP local area network (LAN)
- ✓ Operation of the connection of the IBP LAN to Brno Academic Computer Network (BACN) and to the Internet
- ✓ Cary on e-mail server
- ✓ Cary on www server of the IBP (http://www.ibp.cz) including data updating
- ✓ Current maintenance and development of computer technique (hardware and software), utilized by all projects solved at the IBP (servers, graphic workstations and simple PCs with Internet access), which is working under UNIX, MS Windows NT/2000 and MS Windows 95/98/ME operating systems
- ✓ Consulting and guidance services for individual projects (in a limited amount an expert help with solving computer technique and computer network connected problems).
- ✓ Operation and servicing of a ICCBnet (International Center for Cooperation in Bioinformatics network) national node of the Czech Republic - http://ICCBnet.ibp.cz
- ✓ Mirroring of the Protein Database (PDB) accessible through the Internet
- ✓ Sequence databases and accompanying software - Wisconsin GCG package - accessible to users from Academy of Sciences and universities in the Czech Republic
- ✓ Operation and servicing of a library server used by Academy of Sciences in Brno region

In 2001 the computer network of IBP and telephone connection was extended to newly built laboratories.

GRANTS:

Project UNESCO
Accessibility of biological databases for academic community in the Czech Republic through the National Node of the ICCBnet (International Center for Cooperation in Bioinformatics network), Czech Republic.
Principal investigator: J. Jursa

From the UNESCO grant there was bought a disk array for the database server of the National Node of the ICCBnet and there was extended software license of Wisconsin Package. From the point of view of the disk space and software licenses, operation of the server is ensured to the end of October 2003.

III. PUBLISHED REPORTS

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J. Heyrovský Memorial Symposium on Advances in Polarography and Related Methods, Praha, 30. 8. - 1. 9. 2000
In: Sborník, p. 62

Hašek, J., Malinská, K., Janatová, I., Paleček, J., Eder, S., Kohlwein, S. D.:
Interactions of the cytoskeleton with translation machinery in S. cerevisiae: implications for morphogenesis
VIII. Cytoskeletární klub, Vranovská Ves, 15. - 17. 3. 2000
In: Sborník, nestr.

Hašek, J., Paleček, J., Malinská, K., Eder, S., Janatová, I., Kohlwein, S. D.:
Role of elF3 interaction with cytoskeleton in yeast morphogenesis
Cell Biology of Plant and Fungal Tip Growth, Siena, Italy, 19. - 23. 6. 2000
In: Program and Abstracts, nestr.

Malinská, K., Paleček, J., Janatová, I., Kohlwein, S. D., Hašek, J.:
Rpg1p-Sla2p interaction: implications for localized protein synthesis in S. cerevisiae
Yeast Genetics & Molecular Biology Meeting, Washington, USA 25. - 30. 7. 2000
In: Program and Abstracts, p. 180

*Abstracts published in journals are mentioned too at part A.

E. OVERVIEW OF PUBLICATION ACTIVITIES IN 2001

1. Full-length papers	62
supplementary papers due to RR 2000	5
2. Short communications	8
3. Chapters in monographs	2
4. Articles popularizing science	1
5. Scientific lectures - presented in the CR	117
- presented abroad	99
6. Abstracts presented - conferences in the CR	103
- conferences abroad	85
supplementary abstracts due to RR 2000	4

IV. INTERNATIONAL CONTACTS

As always, international contacts were established in connection with research projects, supported by various grant agencies both from the Czech Republic and from abroad, on the basis of competitions organized by the Academy of Sciences of the Czech Republic (hereafter the Academy of Sciences CR or AS CR) or at the invitation of foreign institutions, etc.

An overview of international contacts in 2001 is provided in tables as follows:

Foreign guests

Country	AS CR competition	Grants	Other	Conferences
Argentina			1	
Austria		1	1	
Finland			1	
France	1		5	3
Germany	10		9	3
Great Britain		1	4	
Greece			2	2
Hungary			1	
Israel			2	1
Japan		1		
Netherlands		1		
Poland			2	1
Russia			1	1
Scotland		1		
Slovakia			5	2
Spain			1	
Switzerland				1
Uruguay			1	
USA		3	4	
Total	11	8	40	14

Travels of scientists abroad

Country	AS CR competition	Grants	Other sources
Austria		8	3
Belgium	1		3
Brazil		1	
Canada			2
Croatia		2	
Finland	2	2	1
France		3	4
Germany		8	7
Great Britain		3	4
Ireland		4	
Israel	3	4	
Italy		7	2
Japan			4
Netherlands		1	
Poland		2	
Portugal		3	1
Scotland		2	
Slovakia	9	13	10
South Africa		1	
Spain	1	6	1
Switzerland		1	
Ukraine			1
USA		5	5
Total	16	76	48

A. Overview of International Co-Operation of the Institute of Biophysics and Foreign Grants in 2001

Joint research based on direct agreements with foreign laboratories and projects which received grants from abroad continued as shown below.

1. Direct Agreements with Foreign Laboratories

FINLAND

University of Turku, Department of Biochemistry, Turku
A. Lojek - Role of phagocytes in the oxidative injury of animal cells and tissues

GERMANY

Max-Planck-Institut für Züchtungsforschung, Köln
B. Brzobohatý - Scientific research in the field of plant molecular biology

november AG, Erlangen
E. Paleček - Collaborative research and development agreement

GREAT BRITAIN

Queen Mary and Westfield College, University of London
A. Kovařík - Research in the field of plant genetics and epigenetics

ISRAEL

Weizmann Institute of Science, Rehovot
J. Fajkus - Analysis of the structure of plant chromosome termini

JAPAN

Chiba Cancer Center Research Institute, Division of Biochemistry, Chiba
M. Štros - A study on the effect of chromosomal proteins HMG1/2 on the binding of proteins of p53 family to DNA and on their role as transcriptional

USA

Virginia Commonwealth University, Richmond
V. Brabec - Mechanistic studies on new platinum clinical agents

2. Foreign Grants

FRANCE

CNRS/AS CR Collaboration, Ecole Normale Supérieure de Lyon
B. Vyskot (2000 - 2002) - Molecular analysis of sex chromosomes and dioecy in *Silene latifolia*

GERMANY

Volkswagen Stiftung
E. Paleček (1997 - 2001) - Tumor-Suppressor-Protein p53 und Seine Interaktionen mit DNA

Volkswagen Stiftung
M. Kozubek (FI MU), *E. Bártová* (IBP) (1999 - 2002) - Automated micro-axialtomography of tumour-correlated FISH pattern

GREAT BRITAIN

The Wellcome Trust, 062366/Z/00/Z
V. Brabec (2000 - 2003) - DNA interactions of platinum anticancer drugs. Relation to the development of new cytostatics

Royal Society, RS/PDF/BLL - Department of Plant Sciences, University of Oxford
B. Brzobohatý (1997 - 2001) - The role of cytokinin metabolism in plant growth and development

The Leverhulme trust F/07476/G
J. Fajkus (2001 - 2004) - Loss and gain of typical telomere repeats in a major radiation of monocots

GREECE

Program KONTAKT, Ministry of Education, Youth and Sports of the CR, Institute of Physical Chemistry "Demokritos", Athens
V. Brabec (2000 - 2001) - Molecular mechanism of anticancer activity of ruthenium complexes

JAPAN

MONBUSHO No. 11694196, Japan Ministry of Education
J. Fajkus, B. Vyskot (1999 - 2001) - Joint research on differentiation and growth specificity of plant cells

SLOVAKIA

Program KONTAKT, Ministry of Education, Youth and Sports of the CR, CR/SR co-operation, Institute of Experimental Pharmacology SAS, Bratislava
A. Lojek (2000 - 2001) - Influence of thrombocytes on oxidative flare-up of neutrophils

USA

Howard Hughes Medical Institute (HHMI), INTNL 55000313
J. Kašpárková (2001 - 2005) - Basis for new structure - pharmacological relationship of platinum antitumor drugs

National Institutes of Health (NIH), 1R01CA78754-01
V. Brabec (1998 - 2002) - Mechanistic studies on new platinum clinical agents

National Science Foundation USA/ Ministry of Education, Youth and Sports of the CR, Kontakt ME 380
B. Vyskot (2000 - 2002) - Evolution of sex chromosomes in *Silene*

OTHER FUNDING

COST D8, Chemistry of Metals in Medicine, D8/0012/97 (OC D8.40)
O. Vrána (1997 - 2001) - Platinum-linked nucleotides analogs as viruses inhibitors

COST D8, Chemistry of Metals in Medicine, D8/0017/97 (OC D8.50)
V. Brabec (1997 - 2001) - The development of ruthenium antitumor compounds

COST D8, Chemistry of Metals in Medicine, D8/0009/97 (OC D8.10)
V. Brabec (1997 - 2001) - Metal recognition of DNA and drug design

COST D20/003/00, the project involving 11 laboratories from 8 countries
V. Brabec - coordinator (2000 - 2004) - Biochemistry, structural and cellular biology of non-classical antitumor platinum compounds

B. Co-Operation with International Governmental and Non-Governmental Organizations

S. Kozubek worked as the chairman of the Czech Committee for Biophysics (IUPAB); *V. Brabec, E. Paleček, J. Šlotová* and *V. Vetterl* worked as members of this Committee.

B. Brzobohatý is a member of the Czech Committee for Molecular Biology and Biochemistry.

J. Šlotová is a representative of the CR in the ICSU. She participated in two experts' workshops for preparation 3 joint ICSU and UNESCO projects (Linz - February 2, 2001 and Vienna - August 2 - 4, 2001).

V. Brabec is a representative of the CR in the Managing Board of the European Program of Scientific and Technological Research, COST D8, and

a member of the Evaluation Commission of the 5th EU Framework Program in Brussels, Belgium.

J. Fajkus is a member of the Evaluation Commission of the 5th EU Framework Program in Brussels, Belgium.

S. Kozubek is a member of the Programs Advisory Committee, Joint Institute for Nuclear Research, Dubna, Russia and is a member of the Evaluation Commission of the 5th EU Framework Program in Brussels, Belgium.

M. Pospíšil is a member of the International Astronautical Academy (IAA).

C. International Conferences Organized by The Institute of Biophysics

✓ „Biophysics of the Genom and Its Interactions“ - Hlohovec u Břeclavi, October 15 - 17, 2001

organizer: Institute of Biophysics AS CR, Brno sponsored by International Union for Pure and Applied Biophysics, Academy of Sciences of the Czech Republic, Joint Institute for Nuclear Research, Dubna, Russia and Masaryk University Brno

✓ "Analytical Cytometry I" - Brno, June 3 - 6, 2001

organizer: Institute of Biophysics AS CR, Brno

✓ COST Action: D20 “Metal Compounds in the Treatment of Cancer“ - Florence, Italy, August 29, 2001

organizer: *V. Brabec* (coordinator)

Working Group Project: D20/0003/00 “Biochemistry, Structural and Cellular Biology of Non-Classical Antitumor Platinum Compounds”

✓ „17th International Conference on Plant Growth Substances“ - Brno, July 1 - 6, 2001

organizer: Mendel University of Agriculture and Forestry Brno, Brno, co-organizer: Institute of Biophysics AS CR, Brno

✓ „U.S.A. - Czech Republic Regional Workshop on the Plant Hormone Cytokinin“ - Prague, June 28 - 29, 2001

organizer: Institute of Experimental Botany AS CR, Prague, co-organizer: Institute of Biophysics AS CR, Brno

V. DOCTORAL STUDIES

A. Postgraduate Studies

Postgradual education of students took place on the basis of internal or external aspirantship (final year) and on doctoral studies.

(a) Aspirant studies

The following theses were defended before the Committee for Defending Candidate Theses in the field of biophysics:

Z. Hoferová (IP) / Influence of g-radiation and inhibitors of arachidonic acid metabolism on cytokinetics of mouse fibrosarcoma cell line G:5:113 *in vitro* and *in vivo*

I. Kejnovská (IBP) / Conformational properties of DNA strands containing $(CGA)_n$ motif and its analogs

T. Kubičárová (IBP) / Nucleic acid and protein interactions at electrode surfaces. Redox modulation of p53 DNA binding

M. Skalníková (FI MU) / Chromatin structure of higher order in interphase cell nuclei of human blood

E. Sýkorová (IBP) / Subtelomere - the beginning of chromosome end

(b) Postgraduate studies (PGS)

In 2001, the Institute of Biophysics successfully continued to participate in postgraduate education (doctoral studies) at universities, mainly at the Faculty of Science of Masaryk University in Brno. In total, sixty two students worked towards a doctor's degree at the IBP. Eighteen of them were external or combined postgraduate students and 44 of them were internal students.

Total number of students	External	Internal/ /combined	Year
14	0	14	I.
20	2	18	II.
9	3	6	III.
9	4	5	IV.
6	6	0	V.
4	3	1	graduates (accomplished studies)

PGS students belong to fields of specialization as follows:

biophysics (17)
molecular biology (22), 3 students accomplished their Doctor's Theses
genetics (6)
animal physiology (7)
immunology (4), 1 student accomplished his Doctor's Theses
environmental chemistry (1)
botany (2)
plant physiology (1)
microbiology (1)
oncology (1)

17 scientists of the IBP were appointed as PGS student advisors.

Doctoral Theses - undertaken at the IBP and defended in 2001:

M. Brázdová / Interactions of tumor suppressor protein p53 with supercoiled DNA: The roles of protein domains and influence of divalent ions

I. Koutná / Higher-order chromatin structure of tissue and blood cell nuclei and its relationship to gene expression

L. Kubala / Reaction of immune system cells on oxidative stress

J. Žlůvová / Dynamics of DNA methylation in ontogenesis

The following scientists of the IBP are members of PGS Branch Councils at the Faculty of Science of Masaryk University in Brno:

Branch Council for Physics: *V. Vetterl*
Branch Council for Biophysics: *M. Bezděk, V. Brabec, F. Jelen, E. Paleček, J. Šlotová, V. Vetterl, M. Vorlíčková*
Branch Council for Biology: *B. Vyskot*
Branch Council for Molecular and Cell Biology: *J. Fajkus, J. Kypr, E. Paleček, V. Vetterl*
Branch Council for Physiology and Developmental Biology of Animals: *J. Hofmanová, A. Kozubík*
Branch Council for Immunology: *M. Číž, A. Lojek*
Branch Council for Genetics: *M. Bezděk, E. Paleček, B. Vyskot*
Branch Council for Environmental Chemistry and Ecotoxicology: *J. Hofmanová, A. Kozubík*

In addition to this, IBP scientists are members of these of Branch Councils at other faculties:

Faculty of Medicine, Masaryk University in Brno:

BC for Biophysics: *V. Vetterl*
BC for Molecular Biology: *V. Vetterl*

Faculty of Medicine, Palacký University in Olomouc:

BC for Medical Biophysics: *V. Vetterl*

Faculty of Science, Palacký University in Olomouc:

BC for Physical and Analytical Chemistry: *E. Paleček, V. Vetterl, O. Vrána*

BC for Botany: *B. Vyskot*

Faculty of Science, Charles University in Prague:

BC for Anatomy and Physiology of Plants: *B. Vyskot*

Faculty of Mathematics and Physics, Charles University in Prague:

BC for Molecular and Biological Structures: *V. Brabec*

BC for Biophysics is in charge also at the Palacký University in Olomouc.

B. Membership in Scientific Institutions

M. Bezděk is a member of the Czech Committee for Transgenic Plants.

V. Brabec is an elected member of the General Assembly of the AS CR for the period 1998 - 2002 and he was a member of the Supervisory Committee of the AS CR General Assembly. He is a member of the Sub-branch Committee 301 "Molecular Biology, Genetics and Experimental Oncology" of the Grant Agency CR.

M. Fojta is a member of the Sub-branch Committee 204 "Molecular and Cellular Biology" of the Grant Agency CR.

M. Hofer is a member of the Branch Committee 3 "Medical Sciences" and a member of the Sub-branch Committee 305 "Physiology, pharmacology, toxicology" of the Grant Agency CR and is a member of the Branch Council for Theoretical Medical Fields and Pharmacy at the J. E. Purkyně Military Medical Academy in Hradec Králové.

J. Hofmanová is a member of the Branch Council 6 "Ecological and Biological Sciences" of the Grant Agency AS CR.

F. Jelen is a member of the Branch Council 4 "Chemical Sciences" of the Grant Agency AS CR.

J. Jursa is a member of the South Moravian Regional Committee for Computer Technology and a member of the Council for Computer Technology of the AS CR.

S. Kozubek was elected a member of the General Assembly of the AS CR for the period 1998 - 2002 and a member of the Programme Advisory Committee, Joint Institute of Nuclear Research Dubna, Dubna, Russia.

A. Kozubík is a member of the Scientific Council of the Masaryk Oncological Institute, Brno, a member of the Co-ordination Committee of the University Oncological Centre and a member of the Scientific Council of the programme RECETOX at the Faculty of Science, MU Brno.

J. Kypr is a member of the Branch Committee 3 “Medical Sciences” and a vice-chairman of the Sub-branch Committee 301 "Molecular Biology, Genetics and Experimental Oncology" of the Grant Agency CR.

A. Lojek is a member of the Sub-branch Committee 524 "Physiology and Pathology of Animals" of the Grant Agency CR.

E. Lukášová is a member of the Sub-branch Committee 202 "Physics" of the Grant Agency CR.

E. Paleček was elected as a member of the Scientific Council of the AS CR, is a member of the Branch Council 5 "Molecular and Cell Biology" of the Grant Agency AS CR, a member of the Supervisory Committee of the GA AS CR, a founding member of the Learned Society of the Czech Republic, a member of the Bioethical Committee at the Council of the Government of the CR for research and development, a member of the permanent working group (for biology and ecology) of the Accreditation Committee of the Government of CR for the Universities and a member of the Ministry of Education, Youth and Sport CR Committee for evaluating research plans and results of institutions for granting institutional support to research and development in science.

J. Široký is a member of the Branch Council 5 “Agricultural Science“ and a member of the Sub-branch Committee 521 “Plant Production, Genetics and Breeding“ of the Grant Agency CR.

J. Šlotová is a vice-chairman of the Council for International Affairs of the AS CR and a member of the General Assembly of the AS CR.

V. Vetterl is a member of the Board of the Fund of University Development to be a member of the F3 item "Innovation of Biomedicine Programs " and a member of the Branch Council 4 “Chemical Sciences” of the Grant Agency AS CR.

M. Vojtíšková is a member of the Council for qualification degrees in Genetics of the Ministry of health of the CR.

M. Vorlíčková is a member of the Branch Council 1 “Mathematical and Physical Sciences, Informatics” of the Grant Agency AS CR.

O. Vrána is a member of the Branch Council 5 "Molecular and Cellular Biology " of the Grant Agency AS CR.

B. Vyskot is a member of the Accreditation Committee of the Government of the CR for universities and chairman of its working group for biology and ecology.

Scientists of the Institute of Biophysics of the AS CR are members of boards for doctor's degrees in biophysics, biochemistry and immunology (*E. Paleček)* and candidate doctor degrees in biophysics (*E. Paleček* - chairman, *M. Bezděk*, *A. Vacek* - members).

V. Brabec is a member of the Slovak board for doctor's degrees in molecular biology.

The following scientists were members of editorial boards of scientific journals:

E. Paleček - General Physiology and Biophysics and Bioelectrochemistry and Bioenergetics

V. Vetterl - Český časopis pro fysiku (Czech Journal for Physics)

C. Membership in Scientific Societies

International Scientific Organizations and Societies

V. Brabec - member of the Biophysical Society USA and of the Society of Biological Inorganic Chemistry

V. Brázda - member of the Biochemical Society

B. Brzobohatý - member of the Federation of European Societies of Plant Physiology, of the Society for Experimental Biology and of the International Plant Growth Substances Association

M. Číž - member of the Society for Free Radical Research

H. Čížová - member of the Oxygen Society

J. Fajkus - member of the American Association for Microbiology, of the American Society for Health Aging (scientific consultant), of the British Royal Society for Aging and an expert for evaluation of the projects of 5FWP EC „Quality of Life"

J. Fulneček - member of the DNA Methylation Society

E. Frimlová - member of the Federation of European Societies of Plant Physiology

J. Hejátko - member of the American Society of Plant Biologists

M. Hofer - member of the Council of European Society for Radiation Biology

J. Hofmanová - member of the European Tissue Culture Society, of the International Society for Analytical Cytology and of the International Society for Predictive Oncology

S. Kozubek - member of the European Society for Radiation Biology, an expert for evaluation of the projects of 5FWP EC „Genetics and diseases of genetic origin“

A. Kozubík - member of the European Tissue Culture Society, of the Society for Leukocyte Biology (USA), of the International Society for Analytical Cytology and of the International Society for Predictive Oncology

A. Lojek - member of the Society for Free Radical Research

E. Paleček - member of the Bioelectrochemical Society and of the New York Academy of Sciences

M. Pospíšil - member of the International Astronautical Academy and of the European Society for Radiation Biology

J. Šlotová - representative of the Czech Republic in the ICSU

M. Štros - member of the American Society for Biochemistry and Molecular Biology

V. Vetterl - member of the Bioelectrochemical Society and of the International Society of Electrochemistry

M. Vorlíčková - member of the Biophysical Society USA

A. Vacek - member of the International Astronautical Academy

J. Zouhar - member of the American Society of Plant Biologists

National Scientific Organizations and Committees

M. Bezděk - member of the of the Czech Society for Biochemistry and Molecular Biology and of the of the Mendel Genetic Society

V. Brabec - member of the Czech Committee for Biophysics (IUPAB)

B. Brzobohatý - member of the Czech Committee for Biochemistry and Molecular Biology, of the Czech Society for Biochemistry and Molecular Biology and of the Society for Experimental Plant Biology

M. Číž - member of the Czech Society for Biochemistry and Molecular Biology

H. Čížová - member of the Czech Society for Biochemistry and Molecular Biology

M. Fojtová - member of the Society of Experimental Plant Biology

E. Frimlová - member of the Society for Experimental Plant Biology

M. Hofer - board member of the Czech Radiobiological Society at the Czech JEP Medical Society

J. Hofmanová - member of the of the Society for Tissue Cultivation at the Czech Oncological Society, of the Czech Radiobiological Society at the Czech JEP Medical Society and founding member of the Czech Society for Analytical Cytometry

B. Koukalová - member of the Mendel Genetic Society and of the Czech Biological Society

A. Kovařík - member of the Society of Experimental Plant Biology and of the Mendel Genetic Society

S. Kozubek - board member of the Czech Committee for Biophysics (IUPAB), board member of the Czech Radiobiological Society at the Czech JEP Medical Society, member of the National Committee for the Exploitation and Research of Cosmic Space and a member of the Advisory Board of the State Office for Nuclear Safety

A. Kozubík - member of the Society for Tissue Cultivation at the Czech Oncological society, of the Czech Radiobiological Society at the Czech JEP Medical Society and founding member of the Czech Society for Analytical Cytometry

L. Kubala - member of the Czech Society for Biochemistry and Molecular Biology

A. Lojek - member of the Czech Immunological Society

E. Paleček - member of the Czech Committee for Biophysics (IUPAB)

J. Šlotová - member of the Czech Committee for Biophysics (IUPAB)

M. Štros - member of the Czech Society for Biochemistry and Molecular Biology

V. Vetterl - board member of the of the Chemical Physics and Biophysics Branch of the Union of Czech and Slovak Mathematicians and Physicists and member of the Czech Committee for Biophysics (IUPAB)

M. Vorlíčková - member of the Czech Society for Biochemistry and Molecular Biology

O. Vrána - chairman of the Biophysical Section of the Czechoslovak Biological Society

J. Vondráček - member of the Czech Immunological Society and of the Czech Society for Biochemistry and Molecular Biology

B. Vyskot – board member of the Plant Biotechnology Section of the Czech Biotechnological Society