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Interakce proteinů HMGB s DNA a chromatinem

Interactions of HMGB proteins with DNA and chromatin

Komise pro obhajoby doktorských disertací v oboru *molekulární biologie*

Committee for the defense of DSc. thesis *in Molecular Biology*

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Content

1. Souhrn

HMGB patří do velké rodiny chromozomálních proteinů High Mobility Group (HMG), které se vyznačují přítomností DNA vazebné domény „HMG-box“, schopné rozpoznávat a vázat se na DNA odlišnou od Watson-Crickového B-typu. HMG-box se váže s vysokou afinitou nejen na ohnutou nebo odvinutou DNA, ale je schopen i ovlivňovat flexibilitu DNA mechanismem ohybu nebo smyčkováním. Proteiny HMGB (HMGB1-4) se vyskytují v buněčném jádře v relativně velkém množství (přibližně 1 molekula HMGB na 10-15 nukleozómů) a mají funkci „architektonických proteinů“, které ovlivňují v chromatinu celou řadu biologicky významných dějů jako např. transkripci, replikaci, rekombinaci, opravu DNA a genomovou stabilitu.

Nové poznatky v oblasti studia HMGB získané předkladatelem doktorské práce (DSc.): první izolace lidské genomové sekvence *HMGB1*; první izolace funkčních genů kódujících HMGB1 (ryby a paraziti); HMGB1 se váže v nukleozómech nejen na spojovací DNA (angl. linker DNA), ale i s korovými históny (angl. core histones); HMGB1 se váže s histonem H5 a je schopen tento histon vytěsnit z vazby s DNA; HMGB1 podporuje (nekovalentní) asociaci duplexů DNA prostřednictví jejich konců; HMGB1 ovlivňuje flexibilitu DNA smyčkováním (angl. DNA looping); schopnost HMGB1 ohýbat DNA je závislá na N- a C-koncových sekvencích HMG-box domény; kyselá doména HMGB1 (polyaniontová sekvence o délce 30 aminokyselin typu Asp/Glu) ovlivňuje schopnost HMGB1 se vázat s DNA a ohývat DNA nebo superspiralizovat DNA (za přítomnosti topoizomerázi I); HMGB1 a nádorově supresorový protein p53 se váží s vysokou afinitou a specifitou na hemikatenanové smyčky DNA (hcDNA); HMGB1 je schopen vytěsnit p53 navázaný na hcDNA; proteiny HMGB1/2 ovlivňují transkripční aktivitu (regulovanou p53/p73) pro-apoptického genu *Bax* v závislosti na funkčním stavu retinoblastoma proteinu pRb; HMGB1 stimuluje enzymatické spojování duplexů DNA; HMGB1 se váže s lidskou topoisomerázou IIα a stimuluje její katalytické vlastnosti mechanismem zvýšeného štěpení DNA; proteiny HMGB1/2 zvyšují buněčnou expresi lidské topoisomerázy IIα (pouze) v buňkách s nefunkčním retinoblastoma proteinem pRb mechanismem stimulace vazby transkripčního faktoru NF-Y na promotor genu topoisomerázy IIα.

2. Summary

HMGB proteins are members of the High Mobility Group (HMG) superfamily, possessing a unique DNA-binding domain, the HMG-box, which can bind non-B-type DNA structures (bent, kinked and unwound) with high affinity, and also distort DNA by bending/looping and unwinding. HMGBs (there are four HMGBs in mammals, HMGB1-4) are highly abundant and ubiquitously expressed non-histone proteins, acting as DNA chaperones influencing multiple processes in chromatin such as transcription, replication, recombination, DNA repair and genomic stability.

Novel findings by the applicant in the HMGB field of research (DSc. thesis): isolation a characterization of genes encoding HMGB1 (trout and parasites); HMGB1 interacts in nucleosomes not only with linker DNA but also with core histones (histone H3); HMGB1 interacts with histone H5 and displaces the linker histone from its binding to DNA; HMGB1 protein facilitates (non-covalent) association of DNA duplexes via their termini; HMGB1 promotes DNA flexibility by looping; the ability of HMGB1 to bend DNA depends on the N- and C-terminal flaking sequences of the HMG-box domains; the acidic C-tail of HMGB1 (a continuous run of 30 Asp/Glu residues) modulates the ability of the protein to bind, bend and supercoil DNA (by topoisomerase I); tumor suppressor protein p53 and HMGB1 bind hemicatenated DNA loops (hcDNA) with high affinity and specificity; HMGB1 can displace p53 from its binding to hcDNA; HMGB1/2 proteins interact with a novel member of p53 family, p73; HMGB1/2 proteins modulate p53/p73-dependent activity of the pro-apoptotic *Bax* promoter depending on the functional status of retinoblastoma tumor suppressor protein pRb; HMGB1 stimulates enzymatic ligation of DNA duplexes; HMGB1 interacts with human topoisomerase IIα and stimulates catalytic activities of human topoisomerase IIα via enhancement of DNA cleavage; HMGB1/2 proteins up-regulate cellular expression of human topoisomerase IIα in cells lacking functional pRb via stimulation of binding of transcription factor NF-Y to the *topoisomerase IIα* promoter.

3. Contribution of the applicant to HMGB research

The eukaryotic genomic DNA must be highly condensed in a dynamic supramolecular nucleoprotein structure –chromatin- to fit into the cell nucleus and perform its function. The fundamental repeat unit of chromatin, the nucleosome, represents a structure formed by coiling of the DNA around histone octamers [consisting of the central $(H3/H4)_2$ tetramer and two peripheral H2A/H2B dimers] (1). Chromatin is characterized by repeating units of nucleosomes arranged in a beads-on-a-string nucleosomal chain, stabilized by histone H1 into the 30-nm chromatin fiber forming the higher-order chromatin structure (2). Modulation of chromatin folding and remodeling of the chromatin structure affects access of regulatory factors to their cognate DNA binding sites which is required for regulation of fidelity of gene expression and establishing a gene phenotype.

Histone H1 family (or linker histones) represents the major architectural proteins that can bind most of the nucleosomes in metazoan cells restricting access to transcription machinery and other DNA-dependent processes, such as suppressing chromatin remodeling (3). Many of the structural changes in chromatin are also mediated by a large and diverse superfamily of **HMG (High Mobility Group) proteins** that can bind to nucleosomes in a non-sequence specific manner (4). The HMG proteins have been subdivided into three distinct structural families: **HMGA** (the HMG-AT-hook family), **HMGN** (the HMG-nucleosome binding family), and **HMGB** (**the HMG-box family**) (5). Members of each family are abundantly and ubiquitously expressed in most eukaryotic cells, exhibit different structures and unique DNA or chromatin-binding motifs but they all affect the chromatin fiber as architectural factors. Association of HMG proteins is not confined to specific sites but it is rather highly dynamic, and the proteins can scan the potential chromatin binding sites and move from one chromatin site to another in a " hit and run" fashion (5).

This Introduction on HMGB proteins is based on recently published review articles by the applicant ((6) and Štros, 2009, in press)(**Refs. 1,4**), and outlines the current knowledge of structure and functioning of HMGB proteins with the emphasis on the contribution of the applicant to the HMGB field of research (all references are numbered consecutively. Applicant's original papers are indicated in the list of references in bold and highlighted in the text. However, numbering of references in

bold corresponds to the list of papers submitted for the DSc. thesis).

The HMG-box family

All members of the HMG-box family possess a DNA-binding domain (the HMG-box) related to a motif originally identified in vertebrate (canonical) HMGB proteins. Mammalian HMGbox-containing proteins are usually classified into two major groups distinguished by their abundance, function and DNA specificity (6)(**Ref. 4**). In general, two or more HMG-boxes are mostly found in abundant HMG-box proteins with little or no DNA sequence specificity (such as vertebrate HMGB1-4), albeit some *non*-sequence specific proteins contain a single HMG-box (reviewed in (6)). The second group of mammalian HMG-box proteins is highly diverse and consists of much less abundant proteins having mostly a single HMG-box (such as TCF/LEF-1, sex-determining factor SRY and SOX proteins, reviewed in (6)). The single HMG-box proteins recognize specific DNA sequences but the specificity is restricted due to the limited number of base-specific hydrogen bonds that can be formed within the minor groove. There are ~50 HMGbox-containing proteins of 15-193 kDa, with HMGB proteins representing only a small and specific subset of HMG-box proteins (6) (**Refs. 1,4**).

HMGB1 and HMGB2 were discovered ~35 years ago as abundant nonhistone DNA-binding proteins in calf thymus and their name originate from their (anomalous) high electrophoretic mobility in triton-urea gels (**High Mobility Group, HMG**) due to a high content of positively and negatively charged amino acid residues explaining their extractability in diluted solutions of acids (7). There are three canonical HMGB proteins in human and mice: HMGB1, HMGB2 and HMGB3 ((8), reviewed in (6) and refs. therein), and recently discovered HMGB4 (9). HMGB1-3 proteins have a molecular mass of ~25 KDa, contain two DNA-binding domains (the HMG-boxes A and B) and a long acidic C-terminal tail (**Fig. 1**). HMGB1-3 share more than 80% identity and mainly differ in the length of their acidic C-tails. HMGB4 protein has a molecular mass of ~21 kDa and also contains two HMG-boxes but lacks the acidic tail (9).

HMGB1 is the most abundant non-histone protein in the nucleus (approximately 1 molecule per 10–15 nucleosomes). HMGB1 is an evolutionarily highly conserved protein in mammals and amino acid sequences of all mammalian HMGB1 proteins

are virtually identical (>99%), implying similar biological functions in distinct organisms.

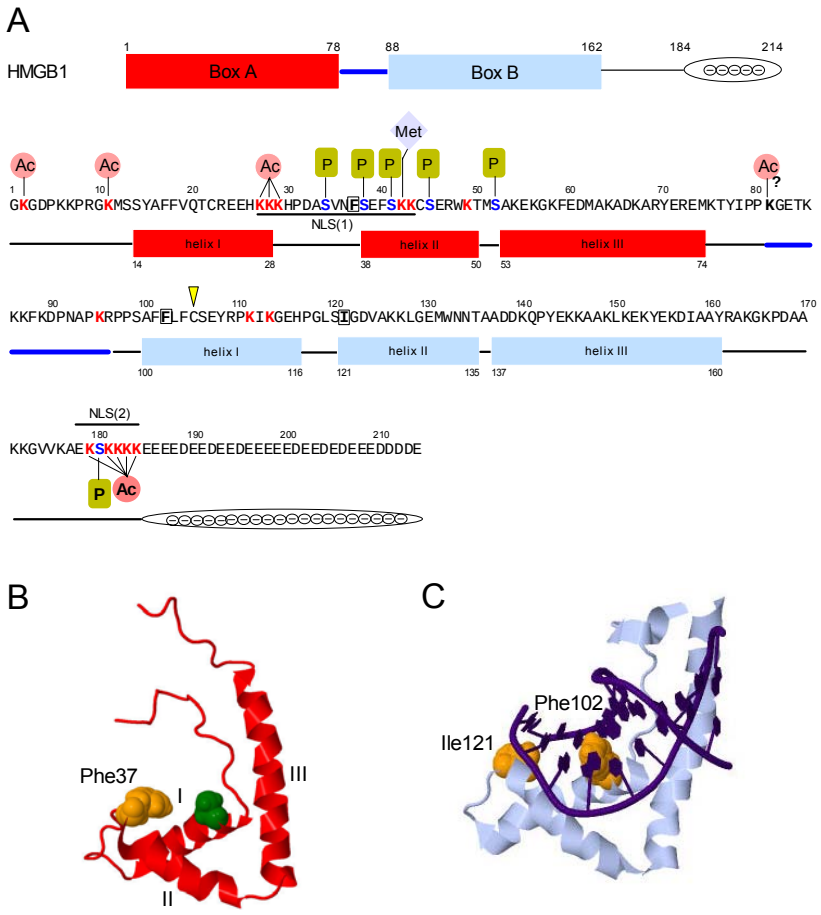

Fig. 1. Domain structure of HMGB1 and post-translational modifications. (A) Amino acid sequence and positions of the α-helices within HMGB1-boxes (box A in red and box B in blue) as determined by NMR spectroscopy (10,11). Acidic C-tail is indicated as oval with negative charges. NLS (1/2), putative nuclear localization signals (12).. Intercalating aa within HMGB1-box A (Phe37) and HMGB1-box B (Phe102/Ile121) are bold and framed. (B) Structure of the HMGB1-box A (11). (C) Structure of the HMGB1-box B bound to DNA (the depicted structure represents a part of the published tandem structure SRY.box-B with DNA, (13)). DNA is depicted in dark blue. Published in **Ref. 1**.

Structure of the HMG-box

The solution structures of individual HMG-boxes, A and B, of HMGB1 have been determined by NMR spectroscopy (10,11,14). An HMG-box contains ~75 amino acids and has a characteristic L-shaped fold consisting of three α-helices with an angle of ~80^{o} between the arms. The long arm includes the extended N-terminal strand and helix III (the minor wing), while the short arm is composed of helices I and II (the major wing) (**Fig. 1B**). The overall structure of the HMG-box is far more

conserved than the corresponding amino acid sequences of the different HMG-boxes The structures of free HMG-boxes or bound to DNA are similar (structures of other HMG-boxes are to be found at http://www.ncbi.nlm.nih.gov).

Interaction of HMGB proteins with DNA

Relatively soon after isolation of HMGB1 and HMGB2 (7) it was found that the proteins could bind DNA with a clear preference to noncanonical DNA structures such as single-stranded DNA (15), DNA containing cruciforms or bent structures (16), supercoiled DNA and Z-DNA (17). The highest affinity of HMGB1 to date was reported for hemicatenated DNA loops (K_D <0.2 × 10^{-12} M) (18-20) (**Refs. 6,7**), followed by DNA minicircles (1 × 10^{-10} M) (21), four-way junctions (1 × 10^{-9} M) (16) and DNA damaged by chromium(VI) adducts (~10^{-9} M) (22) as compared to the affinity of the protein to linear (B-type) DNA (5 × 10^{-5} M). HMGB1/2 proteins interact with DNA via their HMG-boxes, A and B. HMG-boxes A and B exhibit differences in their DNA binding and bending activities, partially due to the modulatory effect of their flanking sequences (23-30) (**Refs. 8,10,13**). Although individual HMGB-boxes can bind to DNA, the binding is enhanced when the two domains are covalently linked in the A+B di-domain (26,27,31,32) (**Ref. 10**).

A characteristic feature of HMGB1/2 proteins and all known HMG-boxes is binding to distorted (bent and unwound) DNA substrates ((6,33,34) and refs. therein) (**Ref. 4**). It seems likely that the DNA structures for which HMGBs exhibit in vitro high affinity (e.g., hemicatenanes, four-way junctions, minicircles or damaged DNA such as UV-irradiated DNA) may mimic their in vivo DNA binding sites (if they exist) due to high complementarities of their binding surfaces with the DNA-binding regions of the HMG-boxes.

Recognition of damaged DNA by HMGB1

Damaged DNA represents a high-affinity binding substrate for HMGB proteins. HMGB1/2 or individual HMG-boxes can preferentially bind to damaged DNA, such as that modified by various chemotherapeutic drugs including cisplatin-based drugs or triplex-directed psoralen ICLs and by a number of carcinogens [e.g., benzo[*a*]pyrene diol epoxide (BPDE), acetyl aminofluorene (AAF), ultraviolet radiation (UV)] with affinity constants 3×10^{-6} - 4×10^{-7}M (reviewed in (34)).

Evidence for a possible role of HMGB1 in the repair of damaged DNA emerged relatively recently. HMGB1 can interact functionally with several protein components involved in NER, base excision repair (BER), mismatch repair (MMR) in vitro, and V(D)J recombination ((35), reviewed in (34)(**Ref. 15**). Data are available indicating a possible involvement of HMGB1 in nonhomologous end-joining pathway (NHEJ) in vitro: HMGB1 can target catalytic subunit of DNA-dependent protein kinase (DNA-PK_{cs}) to DNA ends and stimulate DNA end-joining by enhancing ligation and association of DNA molecules via their ends (26,36-39)(**Refs. 11,13,14**). The stimulatory effect of HMGB1 on association of DNA molecules via their ends (39) (**Ref. 11**) is further promoted by HMGB1 acetylation (40), likely due to an increased affinity of the acetylated protein for DNA ends.

DNA bending/looping by HMGB proteins

DNA bending by HMGB1 and HMGB2 was initially demonstrated using ligase-mediated ring closure assays and by experiments in which the proteins could substitute for prokaryotic protein HU in promoting the assembly of the Hin invertasome (reviewed in (41)). The basis of DNA bending by the HMG-box is evident from the published HMGbox-DNA structures, demonstrating intercalation of bulky hydrophobic amino acid residues of the HMG-boxes between successive base-pairs within the DNA minor groove, accompanied with partial unwinding, widening of the minor groove and bending towards the major grove (reviewed in (33)). Intercalating residues of the HMG-box are flanked by conserved basic residues that bind to the phosphodiester bond of DNA to stabilize the complex (41), and the DNA bending/binding is further modulated by the N- and C-terminal flanking sequences of the HMG-box ((26,33,41)(**Ref. 13**) and refs. therein). HMGB1 has three intercalating residues: Phe102 and Ile121 in the box B, and Phe37 in the box A (**Fig. 1**). HMG-box B, and much less HMG-box A, of HMGB1/2 proteins is responsible for DNA bending (25,26,42-44)(**Ref. 13**), a likely consequence of the lack of the “primary” intercalating residue within the HMG-box A (33) (**Fig. 1**).

The importance of intercalation residues of HMGB1 or other HMG-box proteins for DNA bending, supercoiling and binding to bent DNA has been established in numerous *in vitro* assays (45-50)(**Refs. 2, 3, 12**)**.** Mutation of three intercalating residues of HMGB1 resulted in decreased mobility of HMGB1 in living cells and prevented HMGB1 binding to chromatin (51). Intercalating residues of HMGB1 are

also required for stimulation of progesterone receptor (PR) transcriptional activity in cells but not for complex formation of HMGB1-PR or enhancement of PR-DNA binding (52). Similarly, mutation of intercalating residues of HMGB1 significantly reduced the ability of HMGB1 to transactivate the human *topoisomerase IIα* gene promoter *in vivo*, possibly due to impaired ability of HMGB1 to bend DNA (53)(**Ref. 2**).

We have discovered that HMGB1 protein and its individual HMG-boxes could also enhance DNA flexibility by looping (electron microscopy) (24,44)(**Refs. 17, 18**). It appears now that all HMG-boxes (either individual or arranged in tandems or multi-domain proteins) are capable of DNA bending/looping (54). DNA bending/looping by HMGBs provides a mechanism by which the proteins promote activity of various gene promoters by enhancement of binding of transcription factors and/or bringing distant regulatory sequences into close proximity.

Modulation of HMGB binding by the acidic C-tail

The acidic C-tails of vertebrate HMGB1-3 consist of consecutive runs of only Glu/Asp residues: 30, 22 and 20 residues for HMGB1, HMGB2 and HMGB3, respectively. The amino sequences of acidic tails are highly conserved among different species and appear to be unstructured (reviewed in (6) (**Refs. 1, 4**). Apart from the canonical HMGB1-3, the only human HMG-box proteins containing the acidic tails are HMG4L, HMG1L10, SP100-HMG, UBF and SSRP-1 (reviewed in (6) (**Ref. 4**)).

We have for the first time demonstrated that the acidic tail of vertebrate HMGB1 down-regulates binding of the two tandem HMGB1-boxes to linear and supercoiled DNA, as well as the ability of the protein to introduce negative supercoils into the closed circular DNA in the presence of topoisomerase I (24)(**Ref. 18**). HMGB1 binding to DNA can also be fine-tuned by acetylation which is dependent on the acidic tail (55).

The fact that the affinity of HMGB1 for highly distorted DNA substrates such as minicircles (21,28,56) and hemicatenated loops (19,20)(**Refs. 6,7**) is very little affected by the acidic tail can be related to high complementarities between the DNA-binding surface of the HMGB-box and the bent DNA substrates. Interestingly, the acidic tail affects structure and binding properties of the HMG-box B when linked to the acidic tail, as revealed by the loss of the secondary and tertiary structures and inhibition of DNA binding properties of the HMGB1 peptide (57). The latter also

explains the reported inability of the latter peptide to enhance DNA binding of p53 (58,59) or to interact with p53 (58,59), as compared to the HMG-box B *not* linked to the acidic C-tail (19)(**Ref. 7**).

Apart from intra-molecular interactions of the acidic tail with the HMG-boxes, the acidic C-tail of HMGB1 is also engaged in intermolecular interactions with proteins, mainly histones (60-63). The acidic tail of HMGB1/2 is then available for interactions with basic domains of histones (60-63)(**Ref. 20**), resulting in the weakening of their binding (or in the case of histone H1 in its displacement) in the nucleosomes (**Fig. 2**).

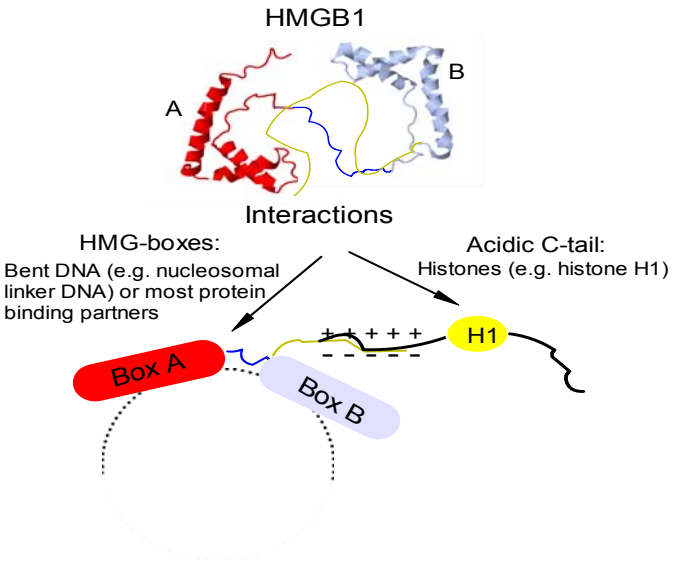

Fig. 2. Interactions of HMGB1 with DNA and proteins. The acidic tail of HMGB1 (in green) folds back and makes extensive intra-molecular contacts with the HMG-boxes, shielding their DNA binding surfaces from interactions with DNA. In the presence of bent DNA (**Ref. 4**), the intra-molecular interactions are disrupted leaving the HMG-boxes in open conformation available for DNA binding. Displacement of the acidic tail from interactions with the HMG-boxes of HMGB1 also occurs via binding of the acidic tail to basic domains of histones [interaction with the basic C-terminal domain (in black) of histone H1 is depicted]. Published in **Ref. 1**.

While the (intra-molecular) interactions of the acidic C-tail involve specific residues within the HMGB1-boxes (56,64), electrostatic (inter-molecular) interactions of the acidic C-tail with basic regions of proteins are likely less specific.

HMGB interactions with proteins

The function of HMGB-type proteins as architectural factors is determined not only by their DNA-binding properties (establishing proper DNA conformation), but also by

their ability to interact with a plethora of proteins to promote formation of complex nucleoprotein structures. HMGBs are involved in many biological transactions in the nucleus (6)(**Refs. 1,3**). Thus, the binding partners of HMGB1/2 *in vitro* include numerous proteins such as transcription factors, DNA repair proteins, site-specific recombination proteins, silencing complexes (transcriptional activators/repressors, co-repressors), viral proteins, nuclear importing proteins and histones (**Ref. 1**).

Depending on the type of the interacting protein, the protein binding domain of HMGBs may involve either the acidic C-tail and/or the HMG-box (**Ref. 1**). The acidic C-tail represents a typical binding region of HMGB1/2 proteins with linker histones.

HMGB proteins can promote transcription of numerous genes via different mechanisms. These include (i) direct binding of HMGB to nucleosomes (*see* Section 9), (ii) interaction with the TBP (TATA-binding protein)/TATA-box complex affecting recruitment of other general transctiption factors ((65-67), reviewed in (33,54)), and (iii) augmentation of binding affinity of a number of sequence-specific proteins to DNA *in vitro*. This can happen in many instances by direct binding of HMGB to the sequence-specific binding proteins such as p53/p73 (68)(**Refs. 7,9**), telomerase (**Ref. 4** and *unpublished*), NF-Y (53)(**Ref. 2**), topoisomerase IIα (50)(**Ref. 3**), octamer binding factors (Oct ½), NF-κB/Rel family, Hox domain proteins (HoxD9), SREBPs (Sterole-Regulatory Element-Binding Proteins), class I nuclear receptors

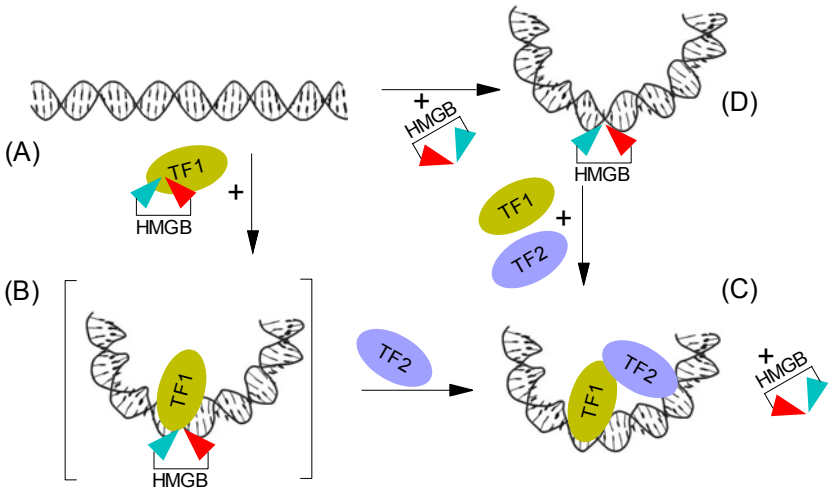

Fig.3. Putative role of HMGBs as architectural factors in transcription. (A) HMGB interacts with a transcription factor (TF1) and directs it to its specific-binding DNA site which is pre-bent by HMGB. (B) Ternary complex TF1-HMGB-DNA, most likely a fleeting intermediate (it is not clear whether the protein-protein contacts are retained upon binding to DNA). (C) Another transcription factor (TF2) is attracted to the complex TF1-DNA-HMGB, followed by the release of HMGB from the complex. (D)

Alternatively, the specific DNA sequence is bent by HMGB resulting in an enhanced binding of TF without direct interactions with HMGB. Published in **Ref. 1**.

(but *not* class II, (69) and refs. therein), Ets and other proteins (**Ref. 1**). One mechanism of HMGBs functioning as architectural factors in transcription assumes that HMGBs can facilitate binding of the sequence-specific proteins through direct interactions with transcription factors and pre-bending of the DNA target sequences (**Fig. 3A**). In only few cases, ternary complexes HMGB-protein-DNA have been detected. The absence of the ternary complexes may indicate the transient nature of these complexes, and this has led to a concept of a “hit-and-run” mechanism making the HMGB proteins “architects on hire” (**Fig. 3**, reviewed in (6,33,54,70,71)). It is likely that the ability of HMGBs to bind and bend DNA is a primary determinant of the stimulatory effect. The bent DNA can also recruit binding of additional transcription factor(s) (**Fig. 3C**) in close vicinity and facilitate their mutual contacts. HMGBs can also promote mutual interactions of transcription factors bound on distant regulatory sequences by enhancing DNA flexibility by looping and bringing the sequences into close proximity ((24,72,73) and refs. therein).

HMGB-mediated enhancement of transcription factor binding to DNA shown in **Fig. 3** depicts only nucleosome-free DNA for simplicity. In the cell, access of transcription factors to specific DNA sites on nucleosomes is facilitated by ATP-driven chromatin remodeling (resulting in loosening of the wrapped DNA and enhanced accessibility of transcription factors) which is enhanced by HMGBs (74).

HMGB1 gene and regulation

The organization of *HMGB* genes is very conserved during metazoan evolution (as revealed by comparison of DNA sequences encoding the HMGB proteins), the two HMGbox- containing HMGB proteins are only present in multicellular animals (from sponges onwards), and the *HMGB* gene appears to have arisen through the fusion of two different genes, each coding for one of the boxes (75). First functional HMGB1 genes were isolated and characterized from trout (76)(**Ref. 16**) and mouse (77). Apart from the functional, intron-containing, human *HMGB1* gene (78), human genome also contains a number of intron-less sequences of HMGB1 pseudogenes ((79) (**Ref. 19**), reviewed in (80)).

Human *HMGB1* gene has a strong TATA-less promoter and is down-regulated by a silencer and up-regulated by an enhancer in intron 1 (81). *HMGB1* transcription is also modulated by two members of p53 family, p53 and p73α (a splicing variant of p73). It is unclear whether there is a feed-back of HMGB1 protein on the synthesis of its own gene in the view of findings indicating that HMGB1 could interact with transcription factors affecting regulation of transcription of the *HMGB1* gene, p53 (19,82) and p73α (68)(**Ref. 9**).

Binding of histone H1 and HMGBs to nucleosomes

Histone H1 binds at the entry points into the nucleosome (~0.7 H1 molecule per nucleosome on average) and stabilizes it by "sealing" two turns of DNA around core histone octamer HMGB1 (which is ~10-15-fold less abundant than H1, (83)), like HMGB2, preferentially binds to the linker DNA, rather than the nucleosome core particles (84-86)(**Refs. 23,24**). HMGB1 protects nucleosomal linker DNA in reconstituted nucleosomes from micrococcal nuclease digestion on one side of the core particle and histone H1 on the opposite side of the core particle reconstituted on the same sequence (87,88). Although the two protected regions of linker DNA are on "opposite ends" of the nucleosomal DNA, those ends are probably closely juxtaposed in the nucleosome (88), explaining the competition of HMGB with histone H1 for nucleosomal-binding sites in vitro (86,89). While stable interactions of HMGBs with nucleosomes occur via binding to the linker DNA (74,84-86)(**Ref. 24**), binding of HMGB1 to the nucleosomal core particles can be detected upon protein-protein chemical cross-linking (90,91)(**Refs. 21,23**) or acetylation of the protein in vitro (92).

Histone H1 and HMGB proteins (like other members of the HMG superfamily), are required for the maintenance and dynamic changes of the chromatin structure by imposing steric hindrance on DNA and affecting DNA-octamer contacts (reviewed in (4,5,54) and refs. therein). Whereas histone H1 decreases nucleosome accessibility, HMG proteins (as well as other members of the HMG superfamily) decrease the compactness of the chromatin fiber and enhance the accessibility of chromatin targets to regulatory factors ((93) and refs. therein).

Early experiments revealed that vertebrate HMGB1 interacts (likely via the acidic C-tail) in vitro with histones H1 or H5 (60,63,94-96)(**Ref. 20**). Evidence for competition of HMGB1 with histone H1 for chromatin-binding sites (leading to weakening of H1 binding to chromatin or even its displacement) has recently been published from

microinjection of HMGB1 (or other members of the HMG superfamily) into living cells expressing histone H1 fused with green fluorescent protein (GFP) (93).

HMGB1 is the most mobile chromatin-associated protein and only 1-2 seconds is required to cross the nucleus (97), suggesting that binding of HMGB1 is rather dynamic. On the other hand, histone H1 is much less mobile protein in the nucleus, with an average binding time of each H1 molecule on chromatin being ~4 min (98). Interaction of HMGB1 with histone H1 or other nuclear proteins including transcriptional factors (such as glucocorticoid receptor) decreases each other´s mobility in chromatin (51,93,99).

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(numbering *in bold* correspond to the list original papers of the applicant submitted in the DSc. thesis)

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4. Detailed description of results

Applicant has recently extensively summarized in two invited review articles the current knowledge of HMGB and HMG-box proteins.

References:

(1) Štros, M., (2009) HMGB proteins: interactions with DNA and chromatin. *Biochimica Et Biophysica Acta-Genes Regulatory Mechanisms, in press.*

(4) Štros, M., Launholt, D. and Grasser, K.D. (2007) The HMG-box: a versatile Protein domain occurring in a wide variety of DNA-binding proteins. *Cellular and Molecular Life Sciences*, 64, 2590-2606.

Results obtained by the applicant in the HMGB field of research are dealing with the following topics: isolation and characterization of *HMGB1/2* genes; interactions of HMGB1/2 proteins with DNA, proteins and chromatin; regulatory effect of HMGB1/2 proteins on the activity of various enzymes and gene promoters. The results are outlined in details below, indicating applicant's papers in which the particular research has been published.

4.1.1. Isolation and characterization of genes encoding HMGB1 and HMGB2 proteins

We have isolated first genomic sequence of human *HMGB1* and detected a number of nonfunctional *HMGB1* retropseudogenes in the human genome. We have isolated and characterized first functional gene encoding HMGB1 protein (trout). We have also isolated first gene encoding HMGB1 in parasites (*Schistosoma mansoni* and *Schistosoma japonicum*).

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(19) Štros, M. and Dixon, G.H. (1993) A retropseudogene for nonhistone chromosomal protein HMG-1. *Biochimica Et Biophysica Acta*, **1172**, 231-235.
(16) Štros, M., Nishikawa, S. and Dixon, G.H. (1994) cDNA sequence and structure of a gene encoding trout testis High-Mobility-Group-1 protein. *European Journal of Biochemistry*, **225**, 581-591.
(5) de Oliveira, F.M.B., da Silva, I.C.D., Rumjanek, F.D., Dias-Neto, E.,Guimaraes, P.E.M., Verjovski-Almeida, S., **Štros, M**. and Fantappie, M.R. (2006) Cloning the genes and DNA binding properties of High Mobility Group B1 (HMGB1) proteins from the human blood flukes Schistosoma mansoni and Schistosoma japonicum. *Gene*, **377**, 33-45.

4.1.2. Binding of HMGB1 with nucleosomes

We have for the first time shown binding of HMGB1 and HMGB2 proteins to nucleosomes by gel electrophoresis. We have also detected HMGB2 binding to the linker DNA in nucleosomes using thermal denaturation. We have demonstrated the ability of HMGB1 and HMGB2 to interact with nucleosomes not only within the linker DNA but also via the core histones. Using photoaffinity cross-linking we have identified histone H3 as binding target of HMGB1 in nucleosomes.

References:

(21) Štros, M. (1987) Binding of nonhistone chromosomal protein HMG-1 to histone H3 in nucleosomes detected by photochemical cross-linking. *Biochemical and Biophysical Research Communications,* **147**, 301-308.
(22) Štros, M. and Kleinwachter, V. (1987) Thermal-denaturation and fluorescence study of nucleosomes containing nonhistone chromosomal protein HMGB2. *Biochimica Et Biophysica Acta*, **910**, 163-170.
(23) Štros, M. and Kolíbalová, A. (1987) Interactions of nonhistone protein-HMGB2 with core histones in nucleosomes and core particles revealed by chemical cross-linking. *European Journal of Biochemistry*, **162**, 111-118.
(24) Štros, M., Shick, V.V., Belyavsky, A.V. and Mirzabekov, A.D. (1985) Interactions of high mobility group proteins HMG-1 and HMG-2 with nucleosomes studied by gel-electrophoresis. *Molecular Biology Reports*, **10**, 221-226.

4.1.3. Modulation of linker histone-DNA interactions by HMGB1

We have found that HMGB1 could interact via the acidic C-tail (a continuous run of 30 Asp/Glu residues) with linker histone H5 and displace it from its binding to DNA (circular dichroism and chemical cross-linking).

References:

(20) Štros, M. and Vorlíčková, M. (1990) Nonhistone chromosomal protein HMG1 reduces the histone H5-induced changes in CD spectra of DNA - The acidic C-terminus of HMG1 is necessary for binding to H5. *International Journal of Biological Macromolecules*, **12**, 282-288.

4.1.4. Discovery of a modulatory effect of highly Asp/Glu tail of HMGB1 on DNA binding

We have shown that the acidic C-tail of HMGB1 down-regulated the binding properties of HMGB1 to linear and supercoiled DNA. The acidic C-tail also modulated the ability of HMGB1 to introduce negative supercoils into closed circular DNA in the presence of topoisomerase I.

References:

(18) Štros, M., Štokrová, J. and Thomas, J.O. (1994) DNA looping by the HMG-box domains of HMG1 and modulation of DNA-binding by the acidic C-terminal domain. *Nucleic Acids Research*, **22**, 1044-1051.

4.1.5. Elucidation of a mechanism of DNA bending and recognition of bent DNA by HMGB1

We have found that binding of HMG-box domain B to bent DNA (such as DNA modified with anticancer drug cisplatin or supercoiled DNA), as well as the ability of the HMG-box to bend DNA, critically depended on a short stretch of basic residues within the N-terminal strand of the HMG-box. Alanine mutagenesis of the HMG-box domain B identified amino acid residues of the extended N-terminal strand and helix I involved in DNA binding and supercoiling. Mutations of most of the amino acid residues severely impaired the topoisomerase I-mediated DNA supercoiling by HMGB1 and changed the sign of supercoiling from negative to positive.

References:

(8) Kašpárková, J., Delalande, O., **Štros, M**., Elizondo-Riojas, M.A., Vojtíšková, M., Kozelka, J. and Brabec, V. (2003) Recognition of DNA interstrand cross-link of antitumor cisplatin by HMGB1 protein. *Biochemistry*, **42**, 1234-1244.

(10) Štros, M. (2001) Two mutations of basic residues within the N-terminus of HMG-1 B domain with different effects on DNA supercoiling and binding to bent DNA. *Biochemistry*, **40**, 4769-4779.

(13) Štros, M. (1998) DNA bending by the chromosomal protein HMG1 and its high mobility group box domains - Effect of flanking sequences. *Journal of Biological Chemistry*, **273**, 10355-10361.

4.1.6. Discovery of association of DNA duplexes by HMGB1

We have found that HMGB1 could (non-covalently) associate DNA duplexes. Association of DNA (either intermolecular in diluted solutions or intermolecular under conditions of “molecular crowding”) by HMGB1 occurred mainly via the DNA termini, irrespective the nature of the ends. We have also observed stimulatory effect of HMGB1 on enzymatic ligation of DNA duplexes. The above findings finding may suggest an involvement of HMGB1 in NHEJ (non-homologous end-joining) repair pathway.

References:

(11) Štros, M., Cherny, D. and Jovin, T.M. (2000) HMG1 protein stimulates DNA end joining by promoting association of DNA molecules via their ends. *European Journal of Biochemistry*, **267**, 4088-4097.

(13) **Štros, M.** (1998) DNA bending by the chromosomal protein HMG1 and its high mobility group box domains - Effect of flanking sequences. *Journal of Biological Chemistry*, **273**, 10355-10361.
(14) **Štros, M.** and Reich, J. (1998) Formation of large nucleoproteincomplexes upon binding of the high-mobility-group (HMG) box B domain of HMG1 protein to supercoiled DNA. *European Journal of Biochemistry*, **251**, 427-434.

4.1.7. Discovery of DNA looping by HMGB1

We have discovered that HMGB1 could manipulate DNA by looping. DNA looping was mediated via the HMG-boxes of HMGB1 and occurred independently of the looped DNA sequence. It is now accepted that the ability of HMGB1 to loop DNA is a general property of all proteins containing the HMG-box domain. DNA looping by HMGB1 explains several architectural functions of HMGB1 in chromatin, such as ”communication” between distant regulatory DNA sequences with bound transcription factors.

References:

(17) **Štros, M.**, Reich, J. and Kolíbalová, A. (1994) Calcium-binding to HMG1 protein induces DNA looping by the HMG-box domains. *Febs Letters*, **344**, 201-206.
(18) **Štros, M.**, Štokrová, J. and Thomas, J.O. (1994) DNA looping by the HMG-box domains of HMG1 and modulation of DNA-binding by the acidic C-terminal domain. *Nucleic Acids Research*, **22**, 1044-1051.

4.1.8. High-affinity binding of tumor-suppressor protein p53 to hemicatenated DNA loops and modulation of the p53-DNA binding by HMGB1

We have found that tumor suppressor protein p53, like HMGB1, can bind hemicatenated DNA loops (a novel DNA structure that forms a DNA loop maintained at its base by a hemicatenane, hcDNA) with high affinity and specificity. HMGB1 could displace p53 from its binding to hcDNA. We have demonstrated that the hemicatenane, and *not* the DNA loop, was the main determinant of the affinity of HMGB1 or p53 for hcDNA. Our results point to a tight structural fit between HMGB1 and DNA hemicatenanes under physiological conditions, and suggest that one of the nuclear functions of HMGB1 could be linked to the possible presence of hemicatenanes in the cell.

References:

(6) Jaouen, S., de Koning, L., Gaillard, C., Muselíková-Polanská, E., **Štros, M.** and Strauss, F. (2005) Determinants of specific binding of HMGB1 protein to hemicatenated DNA loops. *Journal of Molecular biology*, **353**, 822-837.
(7) Štros, M., Muselíková-Polanská, E., Pospíšilová, S. and Strauss, F. (2004) High-affinity binding of tumor-suppressor protein p53 and HMGB1 to hemicatenated DNA loops. *Biochemistry*, **43**, 7215-7225.

4.1.9. Discovery of a functional link between HMGB1/2 proteins and pro-apoptotic *Bax* gene

We have for the first time detected interactions of HMGB1/2 proteins with a novel member of p53 family, p73. We have also identified functional consequence of these interactions (like the interactions of HMGB1/2 with p53): modulation of the activity of gene promoters which were under the control of the tumor suppressor proteins p53 or p73. The modulatory effect of HMGB1/2 was most prominent with the pro-apoptotic *Bax* gene promoter and depended on functional status of retinoblastoma tumor suppressor protein pRb in studied human cells (up-regulation in pRb-positive cells and down-regulation in pRb-negative cells).

References:

(9) Štros, M., Ozaki, T., Bačíková, A., Kageyama, H. and Nakagawara, A.(2002) HMGB1 and HMGB2 cell-specifically down-regulate the p53- and p73-dependent sequence-specific transactivation from the human Bax gene promoter. *Journal of Biological Chemistry*, **277**, 7157-7164.

4.2.0. Stimulation of catalytic activity of human topoisomerase IIα

We have found that HMGB1 could stimulate catalytic activity of human topoisomerase IIα (topo IIα is an essential nuclear enzyme implicated in many aspects of chromosome dynamics such as chromosome replication and segregation during mitosis) and interact with the enzyme *in vitro*. The stimulation of catalytic activity of topoisomerase IIα by HMGB1 was explained as a consequence of enhanced DNA cleavage by the enzyme.

References:

(3) Štros, M., Bačíková, A., Polanská, E., Štokrová, J. and Strauss, F. (2007) HMGB1 interacts with human topoisomerase IIα and stimulates its catalytic activity. *Nucleic Acids Research*, **35**, 5001-5013.

4.2.1. Stimulation of cellular expression of human topoisomerase IIα by HMGB1 and HMGB2

We have found that HMGB1 and HMGB2 could up-regulate the activity of the *topoisomerase IIα* gene promoter in human cells lacking functional retinoblastoma protein pRb. Transient over-expression of pRb in pRb-negative cells inhibited the ability of HMGB1 to activate the *topoisomerase IIα* promoter. Silencing of HMGB1/2 expression by shRNA resulted in decreased levels of topoisomerase IIα mRNA and protein. Up-regulation of cellular expression of topoisomerase IIα in pRb-negative cells by HMGB1 was due tostimulation of binding of transcription factor NF-Y to the *topoisomerase IIα* promoter (ChIP experiments, Chromatin Immuno-Precipitation). The observed higher cellular expression (and activity) of topoisomerase IIα by HMGB1/2 proteins in *Rb*-minus cells (together with published data in the literature on frequently reported HMGB1/2 over-expression and *Rb* deletions in tumors) could have clinical relevance in respect to prognosis of patients treated with topoisomerase II poisons.

References:

(2) Štros, M., Polanská, E., Štruncová, S. and Pospíšilová, S. (2009) HMGB1 and HMGB2 proteins up-regulate cellular expression of human topoisomerase II alpha. *Nucleic Acids Research*, **37**, 2070-2086.

5. Importance of results obtained by the applicant for basic and medical research

HMGB1 (like HMGB2) is a highly abundant and ubiquitously expressed non-histone protein, acting as a DNA chaperone influencing multiple processes in chromatin such as transcription, replication, recombination, DNA repair and genomic stability (reviewed in **Refs. 1,4**). HMGB1 is a nuclear protein but it can also be secreted into the extracellular milieu as a signaling molecule when cells are under stress (in particular, when necrosis occurs), and the protein has an extracellular function as a late mediator of inflammation in sepsis. Thus, many of the previous studies on nuclear functioning of HMGB1 (obtained by the applicant as well as by other researchers) gained additional importance by being used by medical laboratories, such as those working on the extracellular roles of HMGB1 (i.e. in inflammation, tumor growth and metastasis).

Results of the DSc. thesis present novel data of basic research on interaction of HMGB proteins with DNA and chromatin, as well as on a role of HMGB1 (or HMGB2) in modulation of activity of a number of nuclear genes. However, some of our findings could have possible applications in developing new techniques in molecular biology (i) or in cancer research (ii-iv):

(i) The ability of HMGB1 to promote (non-covalent) association of DNA helices via their termini (irrespective of their nature) - Section 4.1.6 - (**Refs. 11,13,14**) could have practical output in developing "*Kits for efficient ligation of DNA fragments*" (the applicant has already been contacted in this respect by BioLabs)

(ii) Higher cellular expression (and activity) of topoisomerase IIα by HMGB1/2 proteins in *Rb*-minus, as well as the stimulatory effect of HMGB1 on activity of topoisomerase IIα (Section 4.2.1.(**Ref. 2**) could have clinical relevance in respect to prognosis of patients treated with topoisomerase II poisons. This idea is supported by the fact that HMGB1/2 proteins are frequently reported to be over-expressed in cancer and *Rb* deletions are observed in most of tumors (the project will conducted in collaboration with Šárka Pospíšilová from *Center of Molecular Biology and Gene Therapy, University Hospital Brno*).

(iii) Inhibitory effect of HMGB1 on the p53/p73-dependent activity of the pro-apoptotic *Bax* gene in cells with non-functional tumor suppressor retinoblastoma protein pRb (Section 4.1.9.)(**Ref.9**) has also a possible relevance to cancer research with respect to the fact the reported HMGB1/2 over-expression in cancer and *Rb* deletions observed in most tumors (refs. to be found in **Ref. 2**).

(iv) Our very recent discovery identifying HMGB1 as a novel telomerase-associated protein enhancing cellular activity of telomerase (**Ref. 4** and *unpublished*) could also have a relevance to cancer research (notice that cancer cells have consistently high activity of telomerase, see **Ref. 4**).

Developing experimental strategies blocking extracellular HMGB1 could counteract the anti-apoptotic (and possibly cancer-promoting) effect of HMGB1. Similar "anti-HMGB1 approach" has recently been successfully used for preventing inflammatory processes mediated by extracellular HMGB1 (100).

5. List of research papers submitted for DSc. thesis

Total number of papers: 24

Total number of papers (applicant first author): 20

Total number of papers (applicant corresponding author): 21

Total number of citations (without autocitations): 493

Total number of citations without autocitations (applicant first author): 411

Total impact factor of all papers: 103

Average impact factor per paper: 4.3

(1) Štros, M., (2009) HMGB proteins: interactions with DNA and chromatin. *Biochimica Et Biophysica Acta-Genes Regulatory Mechanisms, in press*

IF = 2.28 **Total citations: 0** (*in press*)

(2) Štros, M., Polanská, E., Štruncová, S. and Pospíšilová, S. (2009) HMGB1 and HMGB2 proteins up-regulate cellular expression of human topoisomerase II alpha. *Nucleic Acids Research*, **37**, 2070-2086.

IF = 6.88 **Total citations: 0** (newly published paper)

(3) Štros, M., Bačíková, A., Polanská, E., Štokrová, J. and Strauss, F. (2007) HMGB1 interacts with human topoisomerase II alpha and stimulates its catalytic activity. *Nucleic Acids Research*, **35**, 5001-5013.

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