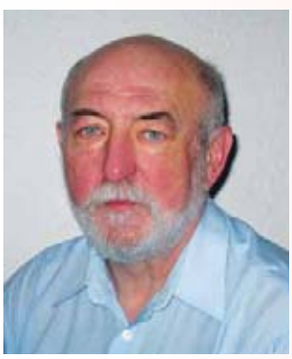
DEPARTMENT OF TERATOLOGY

Head: Assoc. Prof. Miroslav Peterka, MD, DSc
E-mail: peterka@biomed.cas.cz
Phone: +420 241 062 604



LABORATORY OF EMBRYOGENESIS

Assoc. Prof. Miroslav Peterka, MD, DSc | Head of Laboratory
E-mail: peterka@biomed.cas.cz
Phone: +420 241 062 604

Miroslav Peterka, MD, DSc | Research Scientist
Zbyněk Likovský, PhD | Research Scientist
Petra Herlová, MSc | PhD Student
Natalie Hrozinková, MSc | PhD Student
Bronislava Rokytová | Technician
Ivana Koppová | Technician

LABORATORY OF ODONTOGENESIS

Renata Peterková, MD, PhD | Head of Laboratory
E-mail: repete@biomed.cas.cz
Phone: +420 241 062 232

Renata Peterková, MD, PhD | Research Scientist
Maria Hovořáková, PhD | Research Scientist
Svatava Churavá, MSc | PhD Student
Jan Procházka, MSc | PhD Student
Michaela Rothová, MSc | PhD Student
Zdenka Lisá | Technician
Lucie Smrčková | Undergraduate Student

RESEARCH TOPICS

The Department of Teratology focuses on experimental and clinical teratology with the aim of contributing to our knowledge of normal and pathological development, the ethiopathogenesis of developmental anomalies, and possibilities for their prevention. Only a small portion of inborn defects in man can be explained either by prenatal exposure to a harmful external factor (15 % of cases) or by genetic reasons (20 % of cases). Most developmental defects (65 %) are thought to result from prenatal exposure to the combined effect of several sub-threshold doses of external factors that act either simultaneously or sequentially; a genetic predisposition is presumed in some of these cases. In the Department, the causes and mechanisms that are responsible for the origin of developmental defects induced by environmental and/or genetic factors are investigated. In these studies, two experimental models are used (developing chick embryo and developing mouse dentition), as well as a clinical/epidemiological approach. The origin of external malformations, especially of orofacial clefts, is a pivotal research topic of the Laboratory of Embryogenesis (M. Peterka). The Laboratory of Odontogenesis (R. Peterkova) focuses on tooth development under normal, pathological, and experimental conditions.

Laboratory of Embryogenesis

RESEARCH TOPICS

– Investigation of orofacial clefts
– investigation of other developmental defects
– investigation of experimental and clinical/ epidemiological aspects.

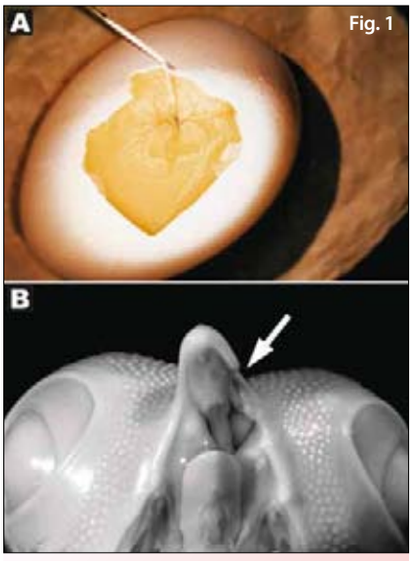
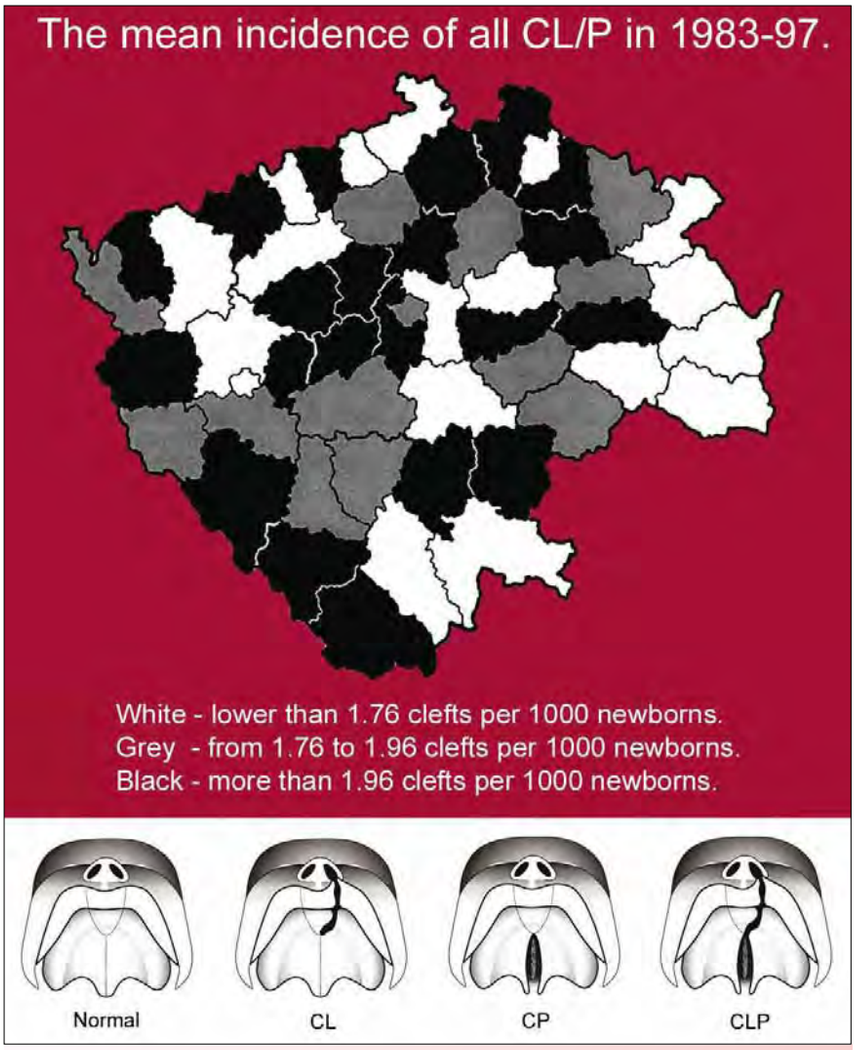


Fig. 1

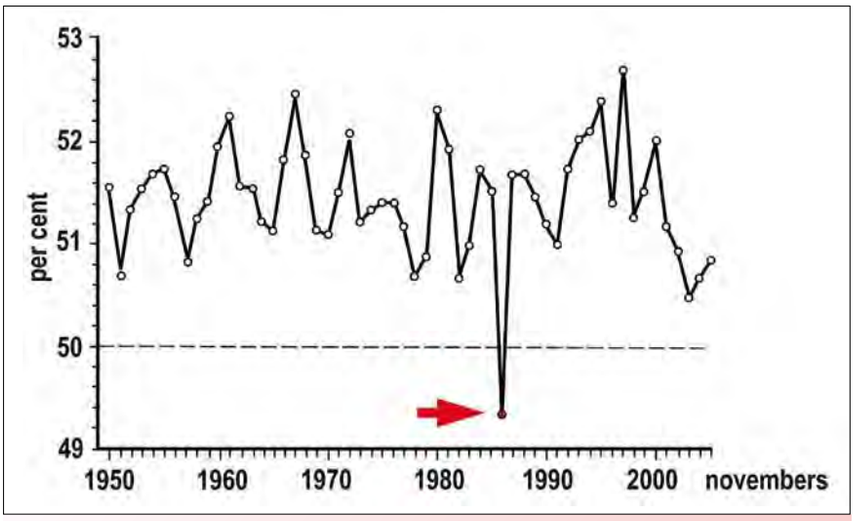
Experimental model – developing chick embryo.
(A) The injection of a test substance into the amniotic sac of a day 3 chick embryo in ovo. (B) Unilateral cleft beak in a day 9 chick embryo induced by the intra-amniotic injection of hydrocortisone on day 4 of incubation.

Harmful external factors and a genetic predisposition are sought in clinical/epidemiological studies of developmental defects. Suspected external factors are tested experimentally in an animal model – chick embryogenesis.

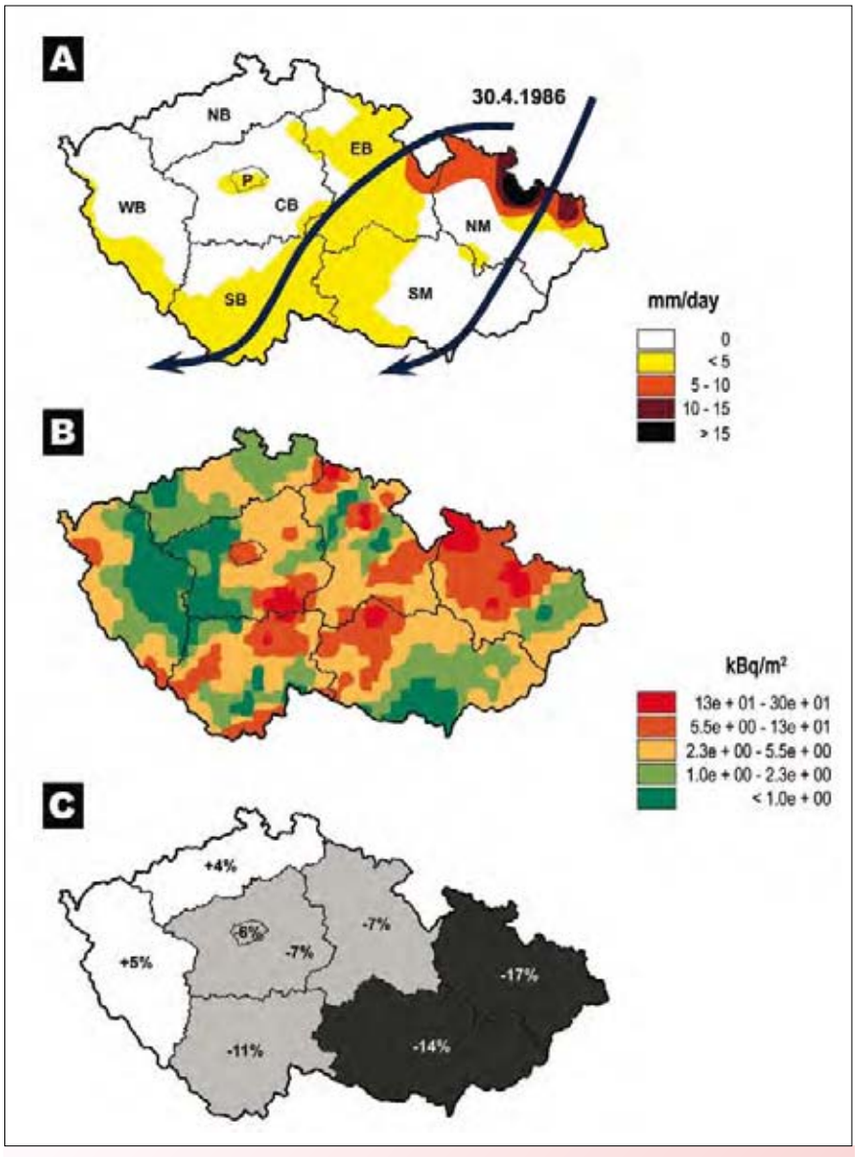
Previous investigations in the Department have detected significant differences in the incidence of orofacial clefts between Czech districts during the last 30 years. The analysis of natality data from the Czech Republic has revealed that the number of newborn boys was higher than that of girls in each month from 1950 to 2005. The only exception was November 1986, when the number of newborn boys was significantly reduced. This has been explained by a selective negative impact of the Chernobyl accident in April 1986 on male fetuses during the 3rd month of their prenatal development. The correlation between the numbers of missing boys with the radioactivity levels has suggested that I-131 probably played the most important role, being taken-up by the fetal thyroid gland during saturation by iodine at the onset of its function in the 3rd month of human prenatal develop-



Orofacial clefts in man.
(A) The mean incidence of orofacial clefts in the districts of the Czech Republic during 1983–1997. (B) Basic types of orofacial clefts in man. CL – cleft lip and jaw unilateral, CLP – cleft lip and palate unilateral, CP – isolated cleft palate. The CL and CLP can also affect both the right and left side - CL bilateral and CLP bilateral, respectively.



The percentage of boys among infants born in the Czech Republic in each November during 1950–2005.
Note the only exception – the percentage of newborn boys was less than 50 % in November 1986, indicating that fewer boys were born than girls.



Schematic maps of the Czech Republic showing the situation after the Chernobyl accident.

(A) Country regions are delineated: CB – Central Bohemia; EB - East Bohemia; NB - North Bohemia; NM - North Moravia; P - Prague; SB - South Bohemia; SM - South Moravia; WB - West Bohemia. The black arrows show the passage of the first radioactive cloud over the country on April 30, 1986. The colors indicate the intensity of the rainfall measured from 07: 00 hours on April 30 until 07: 00 hours on May 1.

(B) Distribution and levels of radiation represented by Cs-137; note that the highest radiation levels were in North and South Moravia, which reflects the areas of rainfall at the time the radioactive cloud passed over the country. The lowest radiation levels were recorded in the areas outside the passage of the radioactive cloud - in North and West Bohemia, where rain was absent or minimal.

(C) The percentage of missing boys in each region during November 1986.

ment. Experimental testing (see Fig. 1) of embryotoxic factors on the developing chick embryo) has determined the embryotoxicity ranges of more than 150 chemical substances and allowed for the estimation of embryotoxicity ranges for humans. We have shown that the upper second incisor originates from the fusion of two components in human embryos. These two components presumably do not fuse in patients with a jaw cleft; consequently, their upper lateral incisor can be duplicated, hypoplastic or missing.

PRESENT STUDIES

– Testing of harmful chemical and physical factors and estimation of their minimum embryotoxic doses using a chick embryotoxicity screening test;

– Mechanism of development of the cleft beak in chick embryos and its possible prevention and reparation;

– Clinical/epidemiological studies searching for the causes underlying the origin of orofacial clefts in humans, based on a critical analysis of case- and family-history data;

– Monitoring of the newborn sex ratio as a tool for detecting ecological accidents.

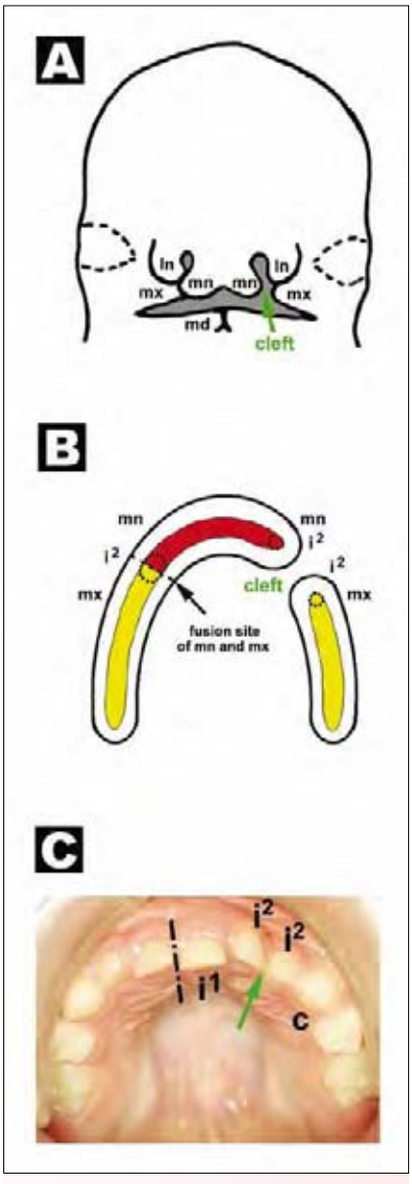
The studies bring new data about the ethiopathogenesis of developmental defects that help in the prevention of inborn anomalies in humans.

Laboratory of Odontogenesis

RESEARCH TOPICS

– investigation of tooth development under normal, pathological and experimental conditions

Findings on tooth development (odontogenesis) help in understanding the molecular control of organogenesis, the origin of tooth anomalies, and the evolution of an animal species. Recently, odontogenesis investigations have also focused on the possibilities for biological tooth replacements. To design such replacements, an understanding of the factors that promote or inhibit tooth development is essential. Previous studies of the Laboratory have revealed that the embryonic mouse dentition provides an ideal system for studying such factors, since it contains not only the germs of functional teeth, but also several types of rudimentary (vestigial) tooth primordia. These vestigial primordia are either incorporated into developing functional

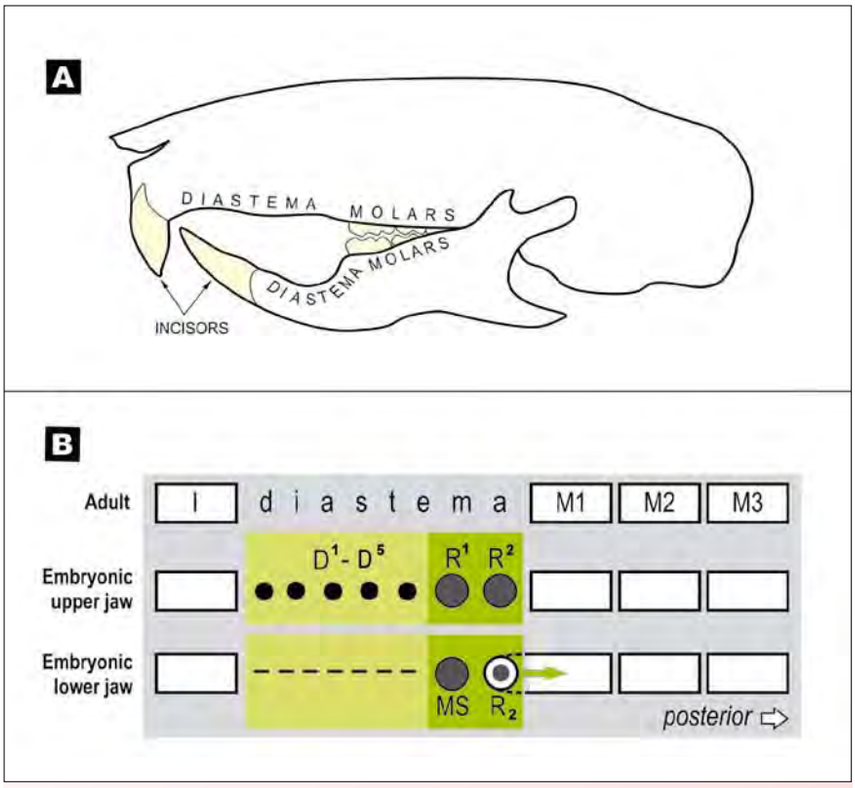


Origin of the double upper lateral incisor in humans.

(A) Scheme of the embryonic human face with a unilateral left-sided cleft of the lip and jaw (green arrow). The medial nasal (mn) and the maxillary (mx) facial processes are fused on the right and not fused on the left side. ln – lateral nasal process, md – mandibular process.

(B) Scheme of the human upper jaw arch viewed from the oral cavity. On the right site, the mn (red) and mx (yellow) fuse. At the fusion site, the lateral deciduous incisor (i^2) develops (dotted line), containing material from both facial processes. On the left side, non-fusion of the mn and mx results in a jaw cleft and the non-fusion of the dental epithelia, which leads to the formation of two i^2.

(C) Double deciduous lateral incisors i^2 (arrow) in a patient with a left-sided alveolar cleft after surgical treatment (from the archive of the Clinic of Plastic Surgery, Prague). The midline is shaded. i^1 – deciduous central incisor; c – deciduous canine.



Schematic of the tooth pattern of adult and embryonic mice.

(A) Adult mice have one incisor and three molars separated by a toothless diastema in each jaw quadrant.

(B) A schematic comparison of the tooth pattern in a jaw quadrant of adult and embryonic mice. In contrast to adult mice, we found that mouse embryos have rudimentary tooth primordia in the prospective diastema (green). In the anterior part of the diastema (light green), either rudimentary small placodes/buds (D^1-D^5) or an epithelial thickening (dashed line) develop in the maxilla or mandible, respectively. In the posterior part of diastema (dark green), two rudimentary buds are the most prominent primordia in the cheek region at early stages. Later on, D^1-D^5 disappear, R^1, R^2 and MS regress, while R^2 is incorporated into the first molar (M1). I - incisor; M2 and M3 – the second and third molars, respectively.

teeth or suppressed by epithelial apoptosis. We have interpreted some supernumerary teeth in mouse mutants as atavisms based on the revitalization of rudimental tooth anlagen. Vestigial odontogenous structures are also present in humans (see Fig. 8, page 25) and in other mammals. The inhibited tooth-forming capacity at specific loci of the mammalian dentition suggests that there might be a natural substrate responsive to the controlled stimulation of tooth regeneration.

PRESENT STUDIES

– Odontogenesis in wild type mice – model of the normal development of mammalian dentition;

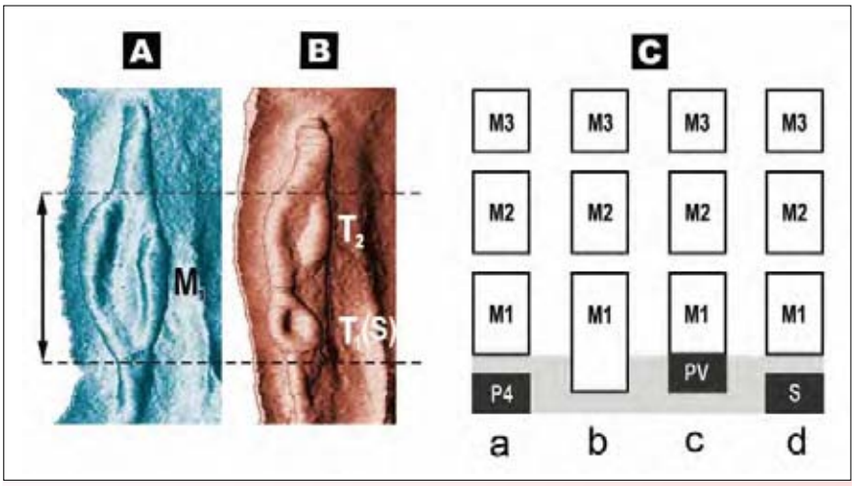
– Comparative odontogenesis studies;

– Development of tooth anomalies in mice with genetic alterations;

– Experimental odontogenesis studies – role of growth activating or inhibiting factors in primordial tooth organ cultures *in vitro*.

– Developmental dynamics of tooth development. Fluorescence transgenic mouse embryos and time lapse microscopy are used to study morphological and molecular events during tooth development in real time.

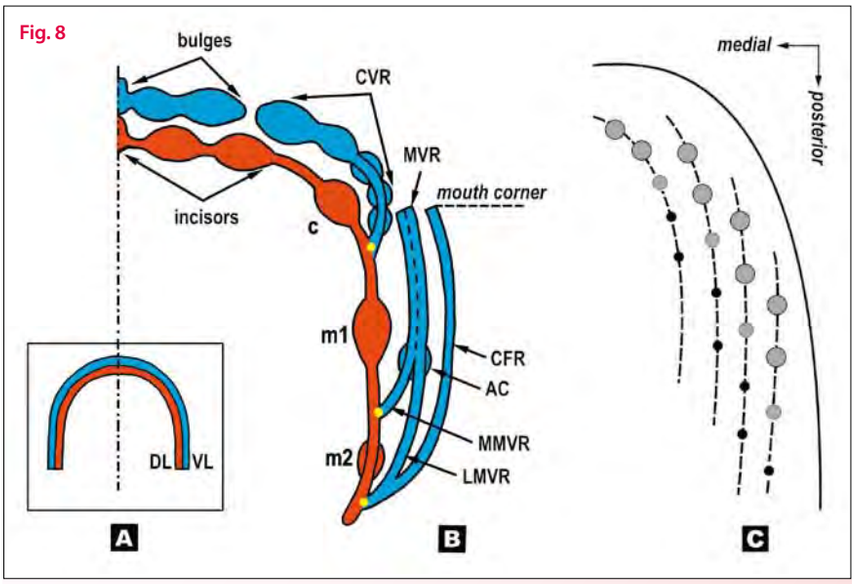
These studies are made in collaboration with H. Lesot (INSERM U-595, Strasbourg, France) and O. D. Klein (Departments of Orofacial Sciences and Pediatrics, UC, San Francisco, USA).



Tentative explanation of the supernumerary tooth in mouse mutants as an atavistic premolar.

The posterior part of the mouth cavity is at the top of each picture. 3D reconstructions show a similar antero-posterior length of the dental epithelium in wild type (A) and Tabby homo/hemizygous embryos (B) at ED 15. 5. However, the segmentation of the dental epithelium along the antero-posterior axis is different. At the level of one cap of the first molar (M_1) in the wild type embryo, we found two small caps (T_1, T_2) in the mutant. T_1 gives rise to the so-called supernumerary tooth (S), which thus corresponds to the anterior part of the M_1 in wild type mice. (C) We have suggested a developmental relationship between (a) the last premolar (P_4) of non-muroid rodents, (b) the anterior part of the adult M1, (c) the embryonic diastemal vestigial bud (PV) in normal mice, and (d) the supernumerary tooth (S) in mutants. The S in mutants can be considered as an atavism – the revitalization of a premolar suppressed during evolution.

Fig. 8



Schemes of the pattern of the dental and vestibular epithelium in human embryos and in the teeth of fishes.

(A) A textbook concept presenting two parallel U-shaped ridges in human embryos (e. g. Bhaskar, 1980): DL – dental lamina (giving rise to teeth) and VL – vestibular lamina or labio-gingival band (where the oral vestibule will form). (B) Our 3D reconstructions have documented that no continuous vestibular lamina exists, but rather a set of discontinuous epithelial structures (ridges and bulges) transiently occurs externally to the dental lamina. Red – dental epithelium; blue – vestibular epithelium. c, m1 and m2 – the deciduous canine, first and second molars. The yellow spot indicates the site of fusion between the dental lamina and the vestibular ridges. (For further explanations, see Hovorakova et al., 2005). (C) The schematic pattern of tooth rows ("Zahnreihen") in fish (according to data by Edmund, 1960). The empty rings and black spots indicate the older and younger teeth, respectively. New teeth are formed at the posterior end of each tooth row.

The results can help to elucidate the origin of tooth anomalies and to develop methods of tooth regeneration and engineering.

CURRENT GRANT SUPPORT

GA CR, 304/07/0223, Developmental anomalies of dentition in a phylogenetic context, 2007–2012.

GA CR, 304/09/1579, Development of incisor malformations in a mouse model, 2009–2013.

SELECTED RECENT PUBLICATIONS

1. Peterka M, Peterková R, Likovský Z. (2004) Chernobyl: prenatal loss of four hundred male fetuses in the Czech Republic. Reprod Toxicol 18: 75–79.

2. Peterková R, Lesot H, Viriot L, Peterka M. (2005) The „supernumerary" cheek tooth in the tabby/EDA mice – a reminiscence of the premolar in mouse ancestors. Arch Oral Biol 50: 219–225.

3. Hovořáková M, Lesot H, Peterková R, Peterka M. (2006) Origin of the deciduous upper lateral incisor and its clinical aspects. J Dent Res 85: 167–171.

4. Peterková R, Lesot H, Peterka M. (2006) Phylogenetic memory of developing mammalian dentition. J Exp Zoolog B 306: 234–250.

5. Hovořáková M, Lesot H, Vonesch J-L, Peterka M, Peterková R. (2007) Early development of the lower deciduous dentition and oral vestibule in human embryo. Eur J Oral Sci 115: 280–287.

6. Peterka M, Peterková R, Likovský Z. (2007) Chernobyl: Relationship between Number of Missing Newborn Boys and the Level of Radiation in the Czech Regions. Environ Health Perspect 115: 1801–1806.

7. Peterková R, Churavá S, Lesot H, Rothová M, Procházka J, Peterka M, Klein OD. (2009) Revitalization of a diastemal tooth primordium in Spry2 null mice results from increased proliferation and decreased apoptosis. J Exp Zoolog B 312: 292–308.