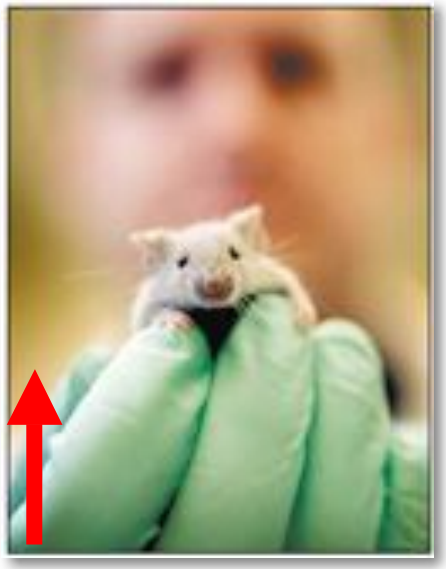
Vývojové souvislosti I: vznik a vývoj zubu jako produkt genetických regulačních kaskád

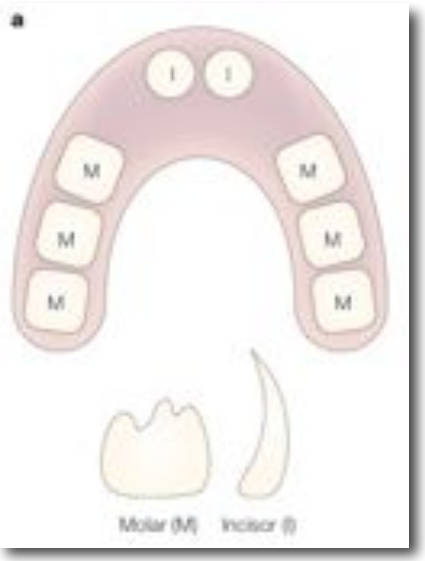
Obecná odontologie DNES: ontogenese tvaru zubu = specifický uspořádaný sled dílčích regulačních modulů

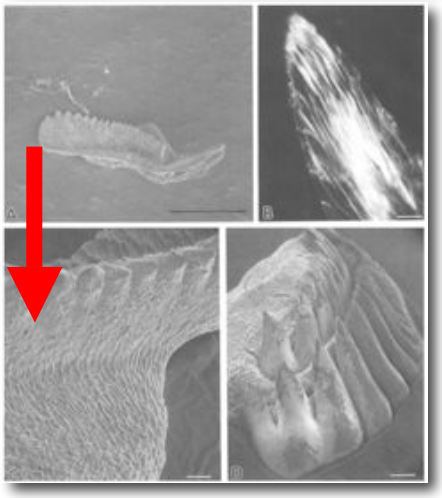
čítanková moudra odontogenese jsou založena na humánní embryologii s komparativním aspektem savců (*Lidská odontologie* + *paleontologie*).

*mf*DNES:
akcent vývojové biologie, molekulární embryologie, kmenových buněk…
(*a co kontext??*)

Biologa však zajímá, co je plesiomorfním stavem znaku a jak dochází ke změnám znaku.
Plesiomorfní stav? žraloci?
Primit. aktinopterygií jako bichir či amia?
Plakodermi? Conodonta?







Nová doba:

-

- obrovské množství dílčích molekulárních studií,

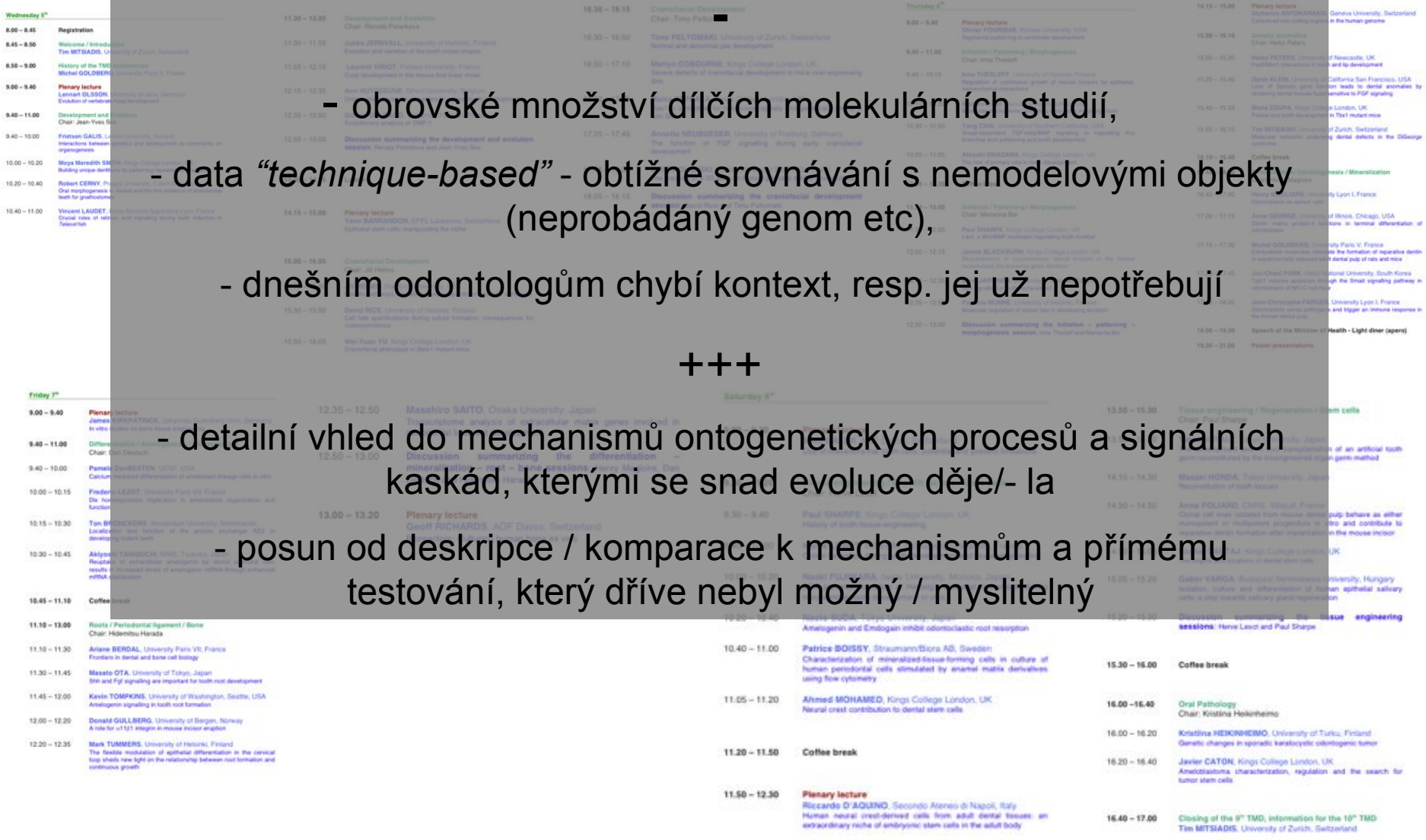
- data *“technique-based”* - obtížné srovnávání s nemodelovými objekty (neprobádáný genom etc),

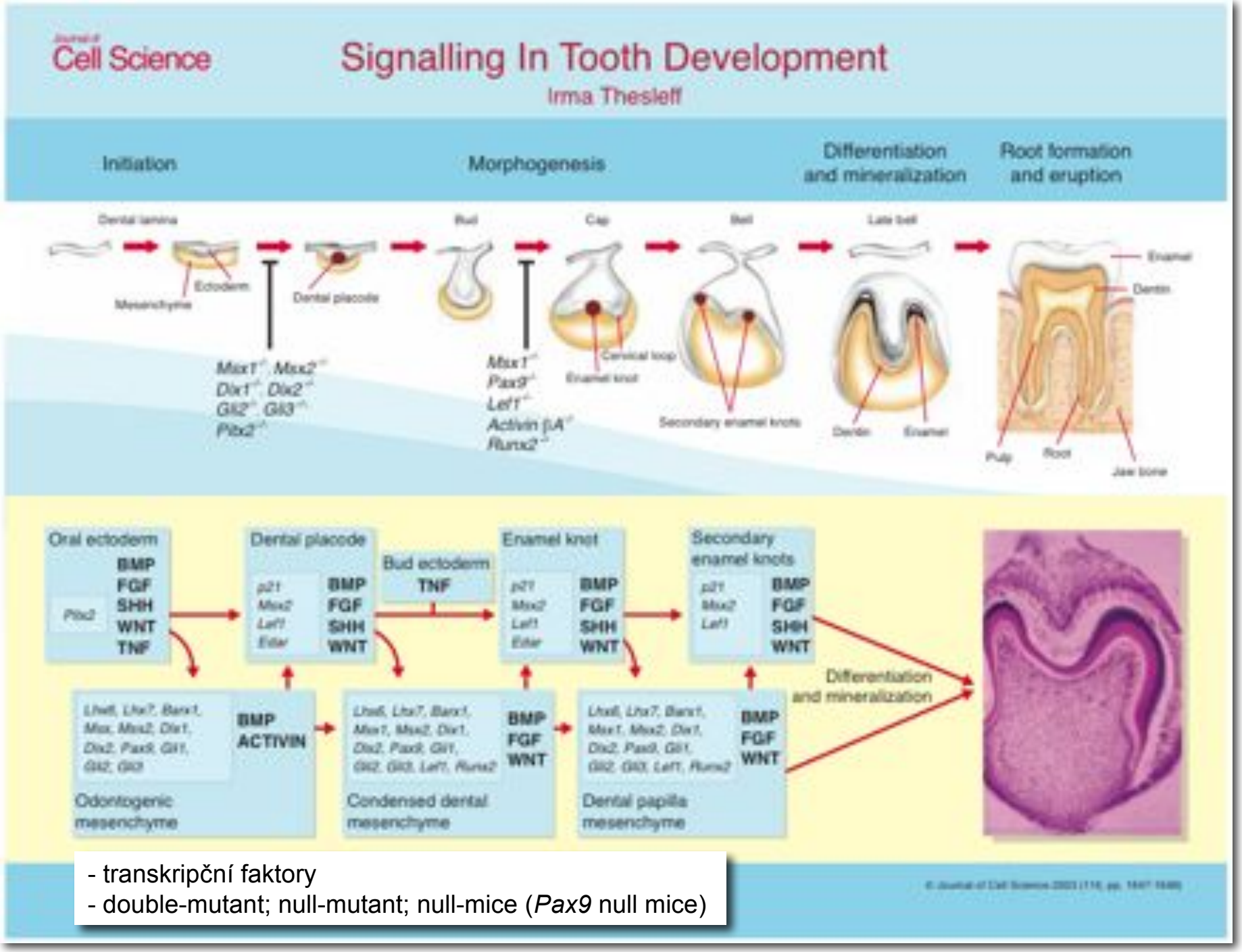
- dnešním odontologům chybí kontext, resp. jej už nepotřebují

+++

- detailní vhled do mechanismů ontogenetických procesů a signálních kaskád, kterými se snad evoluce děje/- la

- posun od deskripce / komparace k mechanismům a přímému testování, který dříve nebyl možný / myslitelný





- transkripční faktory
- double-mutant; null-mutant; null-mice (*Pax9* null mice)

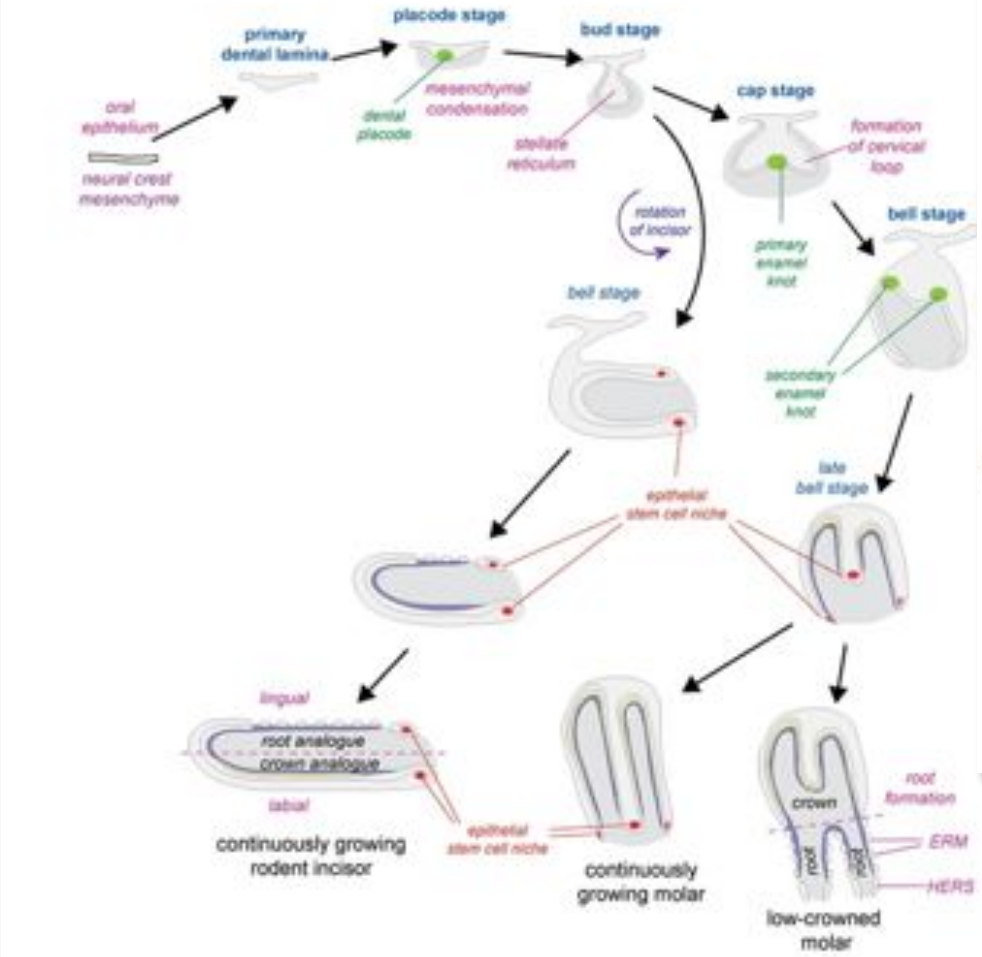


Figure 1.

The developmental anatomy of early tooth morphogenesis and the formation of different tooth types: low-crowned molar, continuously growing molar with a complex cusp pattern, and continuously growing incisor lacking a complex cusp pattern.

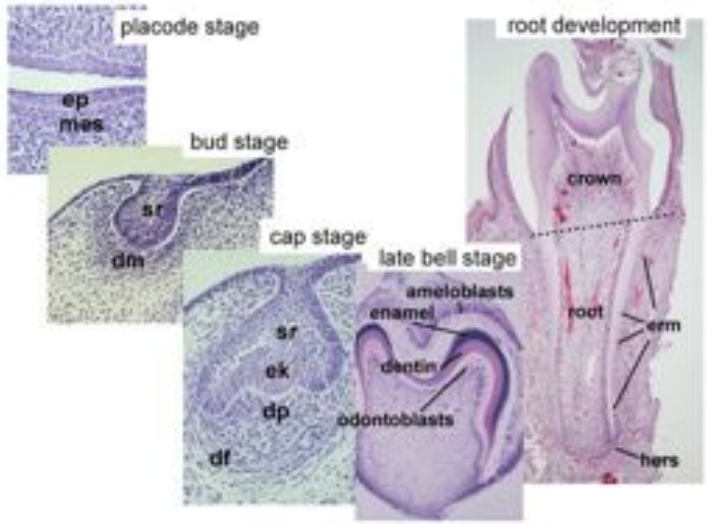


Figure 2.

Histology of important stages of tooth development.

Note that all early development is directed at creating the crown and only then root formation is initiated. Ameloblasts differentiate from the epithelium and odontoblasts from the mesenchyme and they deposit the matrices of enamel and dentin, respectively. Ameloblasts and enamel are missing on the root which is covered by the softer dentin and cementum. Ep, epithelium; mes, mesenchyme; sr, stellate reticulum; dm; dental mesenchyme; dp, dental papilla; df, dental follicle; ek, enamel knot; erm, epithelial cell rests of malassez; hers, hertwig's epithelial root sheath.

TGF beta (super) family: Transforming Growth Factor beta

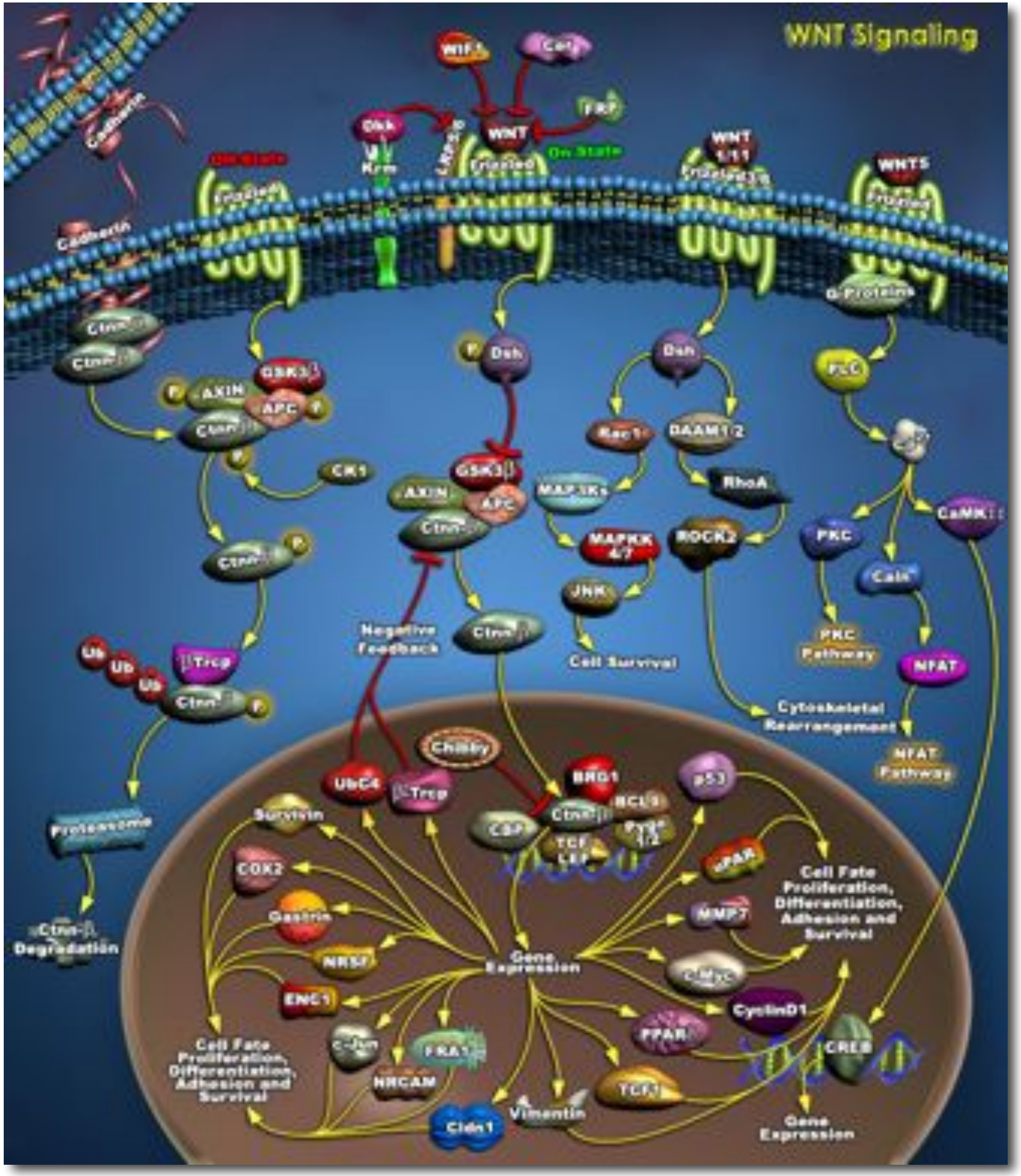
Hedgehog family: (SHH) sonic hedgehog; IHH,

BMPs: Bone Morphogenetic Proteins

FGF: Fibroblast Growth Factor

Wnt: Wg (wingless); Int: (integration sites…)

… jeden z nejpozoruhodnějších objevů posledních let je to, že malé množství signálních molekul je využíváno znova, znova a znova ve všemožných typech tkáních a v nejrůznějších kontextech u všech živočichů - viz Shh, BMPs, FGFs, Wnts etc.

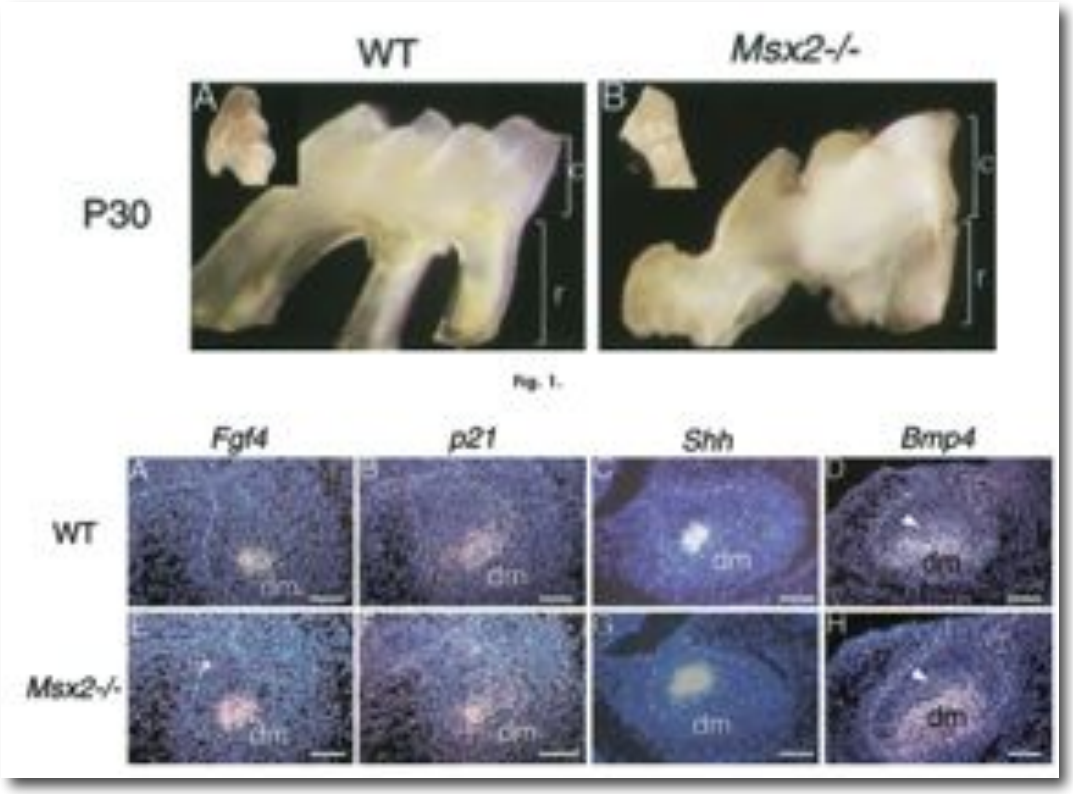


WNT Signaling
WIF1
Cer
Dkk
WNT
FRP
Krm
On State
Frizzled
WNT 1/11
WNT5
Cadherin
G-Proteins
Dsh
PLC
GSK3β
AXIN
APC
CK1
Rac1
DAAM1/2
RhoA
MAP3Ks
MAPKK 4/7
ROCK2
JNK
PKC
CaMKII
CaN
Cell Survival
PKC Pathway
NFAT
Cytoskeletal Rearrangement
NFAT Pathway
Negative Feedback
Ub
βTrcp
Proteasome
Ctnn-β Degradation
Chibby
UbC4
BRG1
BCL9
CBP
TCF LEF
Pygo 1/2
p53
uPAR
Survivin
COX2
Gastrin
NRSF
ENC1
c-Jun
FRA1
NRCAM
Cldn1
Vimentin
TCF1
PPAR
CyclinD1
CREB
c-Myc
MMP7
Gene Expression
Cell Fate Proliferation, Differentiation, Adhesion and Survival

Jak se tato informace získává a proč by nás měla zajímat?

Úrovně informace:

- morfologie
- exprese genu: protein (SHH)
- exprese genu: RNA (*Shh*)
- funkční data: down-regulace (odstřelení) konkrétního genu (*Msx2* null mice = *Msx2*$^{-/-}$)



Gene expression in tooth

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Gene expression in tooth

maintained by
Tooth and Craniofacial Development Group of the Developmental Biology Programme, Institute of Biotechnology, University of Helsinki

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Growth factors
Receptors
Signaling molecules
Transcription factors
Intracellular molecules
Extracellular molecules
Plasma membrane molecules

in situ hybridization
Whole mount in situ hybridization
Immunochemistry
Other methods

Epithelium
Oral epithelium
Dental epithelium
Inner enamel epithelium
Enamel knot
Outer enamel epithelium
Stellate reticulum
Stratum intermedium
Ameloblasts and enamel
Mesenchyme
Dental papilla
Dental sac
Odontoblasts and dentin
Cementum and periodontal ligament
Basement membrane

Initiation stage
Bud stage
Cap stage
Bell stage
Differentiation stage
Secretory stage
Root development

Mouse
Rat
Human
Other species

Molar tooth
Incisor tooth
Other type of tooth

Gene expression in epithelium

	init. stage	bud stage	cap stage	bell stage	diff. stage	secr. stage
activin beta A (rat, mRNA)	-		-			
activin beta A (mouse, mRNA)	-	-	-	-	-	-
activin beta A (mouse, protein)		+	+	-	-	
activin beta A (mouse, mRNA)				+	-	
aggrecan 1 (mouse, mRNA)				-	-	-
Ahr (mouse, mRNA)		+				+
Ahr (mouse, protein)		-		-	+	+
alkaline phosphatase (mouse, protein)		-	-	+		+
amelotilastin (rat,mouse, mRNA)					+	+
amelogenin (mouse, mRNA)				-	-	+
amelogenin (hamster, protein)		-	-	-	+	+
amelogenin (hamster, mRNA)		-	-	+	+	+
amelogenin (mouse, protein)					+	+
amelogenin and enamelin (rat, protein)					+	+
amelopriclease-1 (pig, protein)						+
amlayrna 1 (mouse, protein, mRNA)		+	+	+	+	
appican (mouse, mRNA)				-	-	-
Aquaporin2 (mouse, human, protein)			-	-	-	
Aquaporin3 (mouse, human, protein)			-	-	-	
Aquaporin4 (mouse, human, protein)				+	+	-
Aquaporin5 (mouse, human, protein)				+	+	-
Aquaporin9 (mouse, human, protein)			-	-	-	
Amt (mouse, protein)		+	+			+
Axin1 (mouse, mRNA)	+	+	+	+	+	
Axin2 (mouse, mRNA)	-	+	+	-	-	
Bars1 (mouse, mRNA)	-	-	-	-		
Bax (rat, protein)					+	+
Bcl2 (rat, protein)					+	+
BENOM-ORAL/P/SC1 (mouse, mRNA)	-	-	+	-		
biglycan (mouse, mRNA)					-	-
Bmp2 (bovine, mRNA)				+		
Bmp2 (rats, duration bud, mRNA)						

Gene expression in tooth

http://bite-it.helsinki.fi/

Gene expression in tooth

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Click and search

Growth factors
Receptors
Signaling molecules
Transcription factors
Intracellular molecules
Extracellular molecules
Plasma membrane molecules

In situ hybridization
Whole mount in situ hybridization
Immunochemistry
Other methods

Epithelium
Oral epithelium
Dental epithelium
Inner enamel epithelium
Enamel knot
Outer enamel epithelium
Stellate reticulum
Stratum intermedium
Ameloblasts and enamel
Mesenchyme
Dental papilla
Dental sac
Odontoblasts and dentin
Cementum and periodontal ligament
Basement membrane

Initiation stage
Bud stage
Cap stage
Bell stage
Differentiation stage
Secretory stage
Root development

Mouse
Rat
Human
Other species

Molar tooth
Incisor tooth
Other type of tooth

miRNAs

Expression of Sonic hedgehog in mouse tooth

Shh; Dsh; Hhg1; short digits

Species: mouse
Location in mouse genome: chromosome 5, 28737815 - 28716063 (UCSC, assembly October 2003)
Tooth: lower molar
Method: in situ hybridization (radioactive) probe

Bud stage

Expression: dental epithelium
No expression: oral epithelium, dental mesenchyme

Cap stage

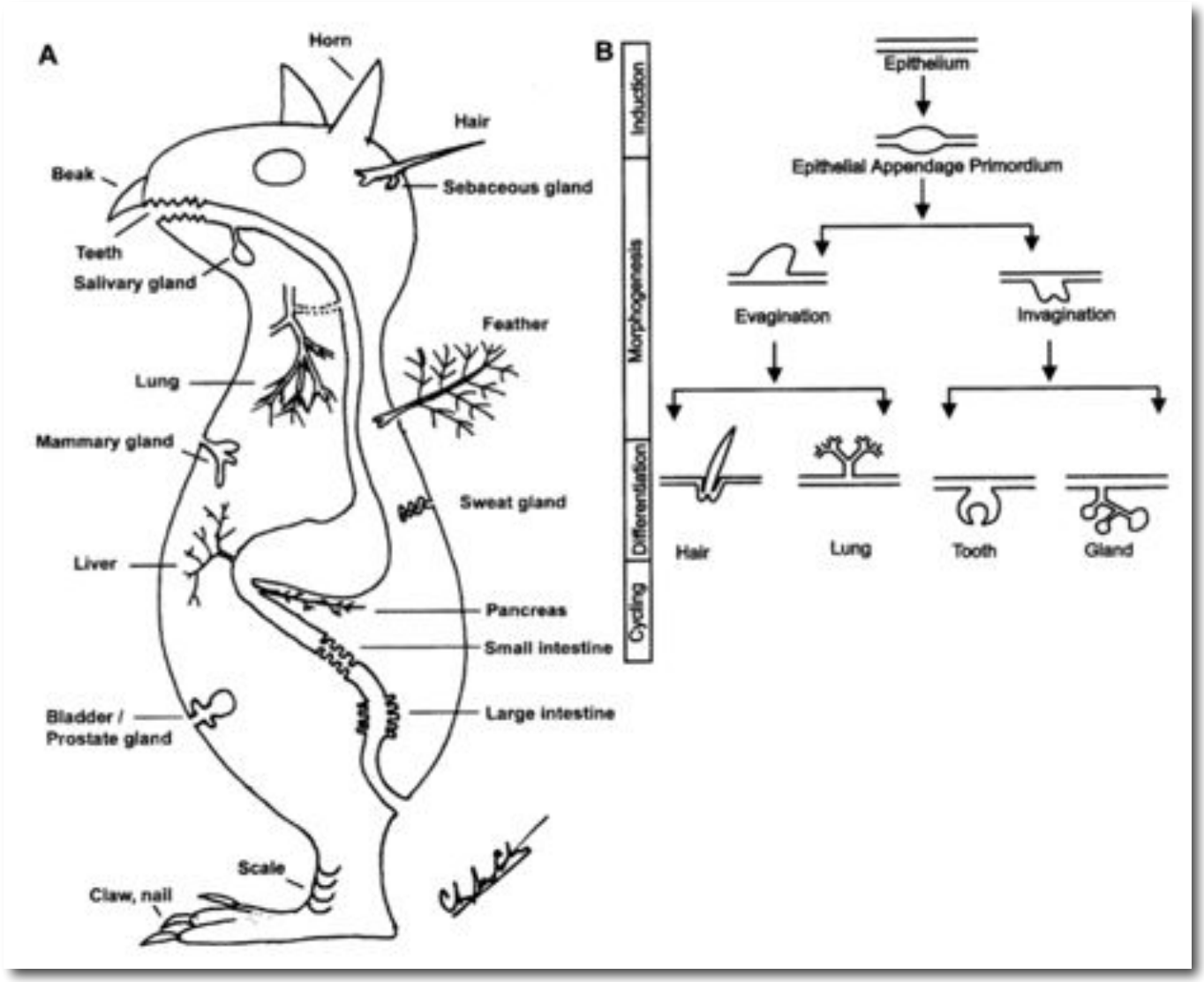
Expression: enamel knot
No expression: oral epithelium, outer enamel epithelium, inner enamel epithelium, stellate reticulum, dental papilla, dental sac

Shh expression is lost in the enamel knot in the *Lef1* null mutant mouse (Kratochwil et al 2002). See expression of *Lef1*.
Shh expression was absent in the enamel knots of lower molars and reduced in the enamel knots of the upper molars in *Runx2* null mutant mice (Åberg et al 2004). See expression of *Runx2*.

Bell stage

Expression: inner enamel epithelium
No expression: oral epithelium, outer enamel epithelium, stratum intermedia, stellate reticulum, dental papilla, dental sac

Ve všech případech morfogenesi (evaginaci epitelu) aktivuje stejný morfogen - **Shh**



CMLS, Cell. Mol. Life Sci. 57 (2000) 1672–1681
1420-682X/00/121672-10 $ 1.50 + 0.20/0

CMLS Cellular and Molecular Life Sciences

Sonic hedgehog signaling pathway in vertebrate epithelial appendage morphogenesis: perspectives in development and evolution

C.-M. Chuong[a,*], N. Patel[a], J. Lin[a], H.-S. Jung[b] and R. B. Widelitz[a]

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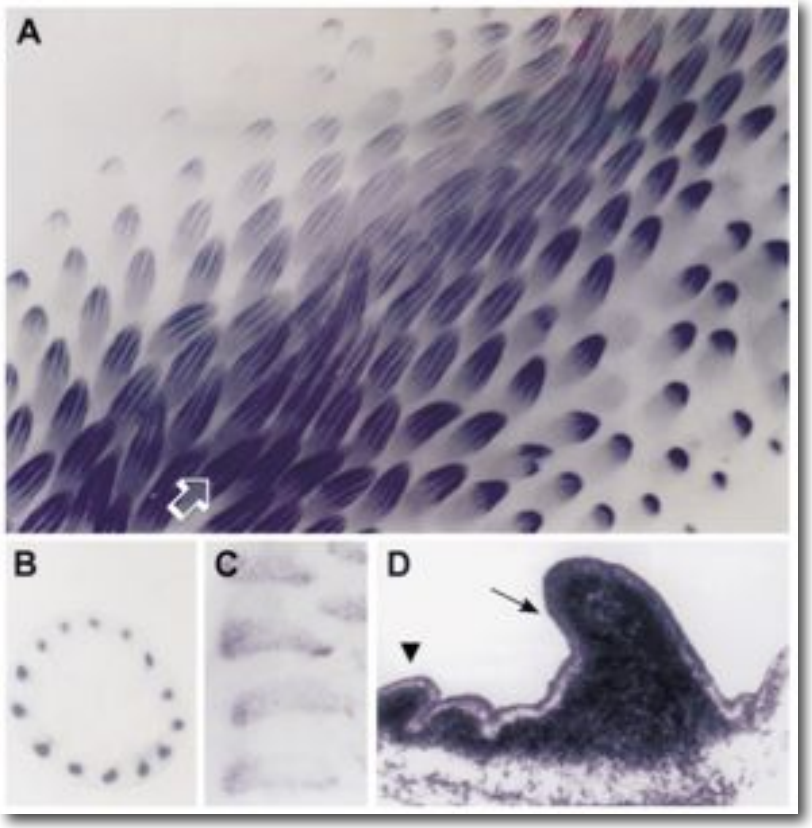
[b]Institute of Biotechnology, University of Helsinki and CBRC, MGH-East, Harvard Medical School and Dept. of Oral Biology, College of Dentistry, Yonsei University, Seoul (Korea)

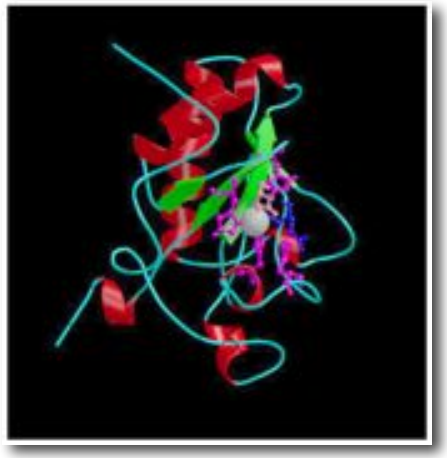
Abstract. Vertebrate epithelial appendages are elaborate topological transformations of flat epithelia into complex organs that either protrude out of external (integument) and internal (oral cavity, gut) epithelia, or invaginate into the surrounding mesenchyme. Although they have specific structures and diverse functions, most epithelial appendages share similar developmental stages, including induction, morphogenesis, differentiation and cycling. The roles of the SHH pathway are analyzed in exemplary organs including feather, hair, tooth, tongue papilla, lung and foregut. SHH is not essential for induction and differentiation, but is involved heavily in morphogenetic processes including cell proliferation (size regulation), branching morphogenesis, mesenchymal condensation, fate determination (segmentation), polarizing activities and so on. Through differential activation of these processes by SHH in a spatiotemporal-specific fashion, organs of different shape and size are laid down. During evolution, new links of developmental pathways may occur and novel forms of epithelial appendages may emerge, upon which evolutionary selections can act. Sites of major variations have progressed from the body plan to the limb plan to the epithelial appendage plan. With its powerful morphogenetic activities, the SHH pathway would likely continue to play a major role in the evolution of novel epithelial appendages.

Key words. Evolution; development; skin appendages; morphogenesis; size.



Ektodermální morfogeneze:

Shh

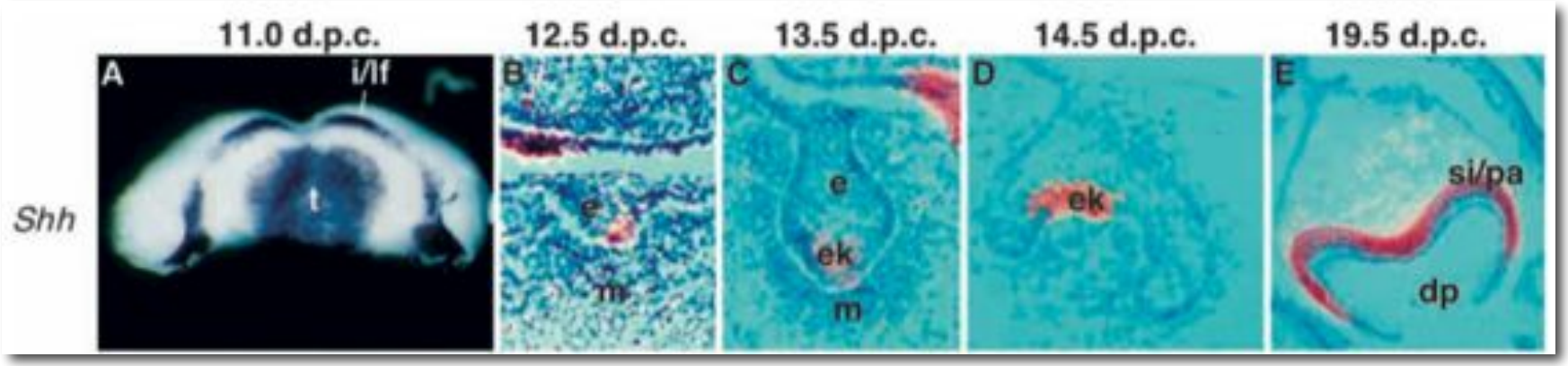


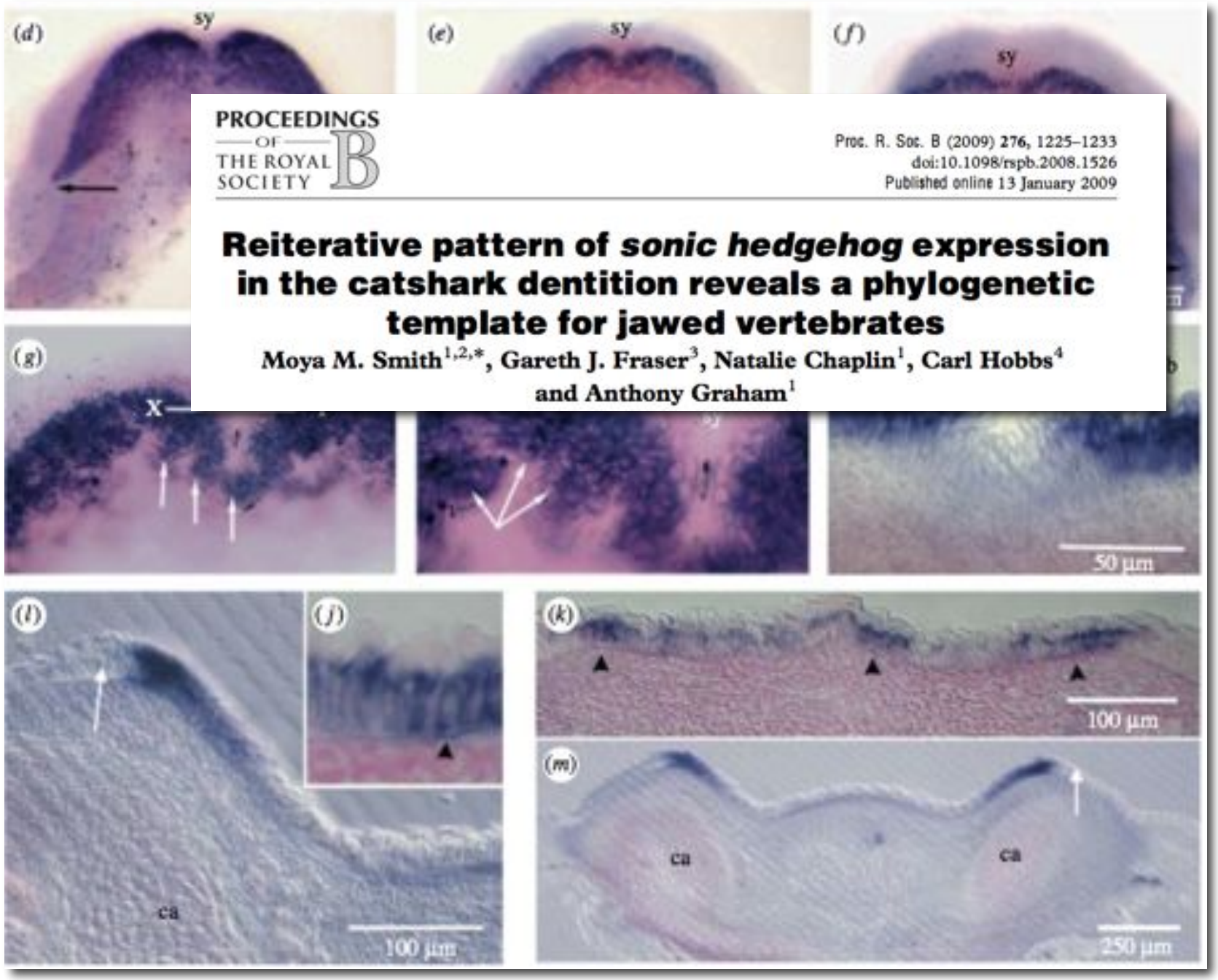
hedgehog - Drosofila: mutantní embrya byla pokrytá trnitými výrůstky, takže embrya připomínala ježka (*hedgehog*).

U obratlovců jsou 3 homology (*paralogy*): **shh**, **lhh** a **dhh**.

Shh: transkripční regulační protein; tzn ovlivnuje transkripci dalších proteinů; morfogen, vytváří tedy koncentrický gradient od svého centra.

ZUB: raná fáze - růst a vývoj zubního základu; později: buněčná diferenciace a polarizace vývoje ep. části zubu.





PROCEEDINGS OF THE ROYAL SOCIETY B

Proc. R. Soc. B (2009) 276, 1225–1233
doi:10.1098/rspb.2008.1526
Published online 13 January 2009

Reiterative pattern of *sonic hedgehog* expression in the catshark dentition reveals a phylogenetic template for jawed vertebrates

Moya M. Smith[1,2,*], Gareth J. Fraser[3], Natalie Chaplin[1], Carl Hobbs[4] and Anthony Graham[1]

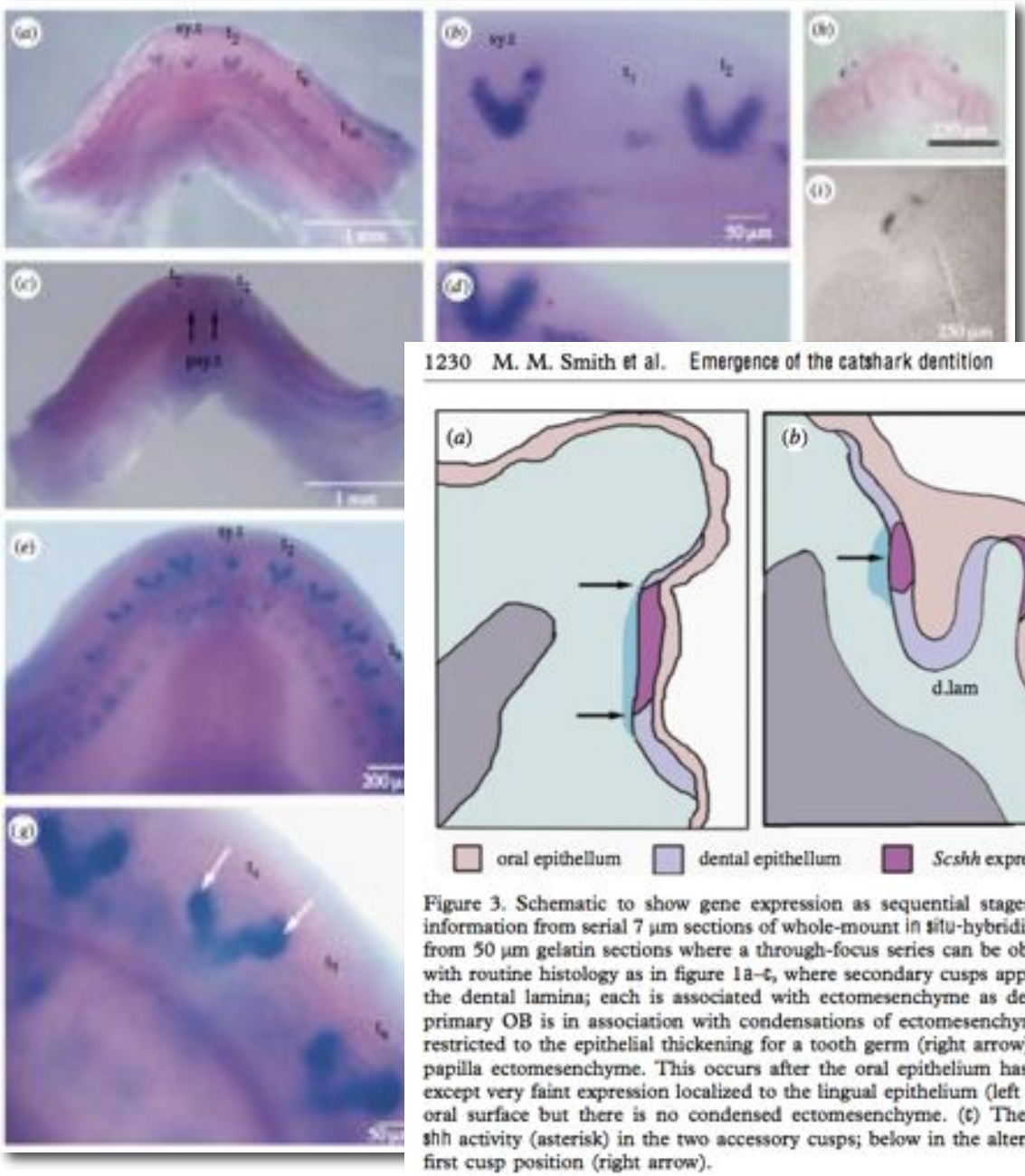
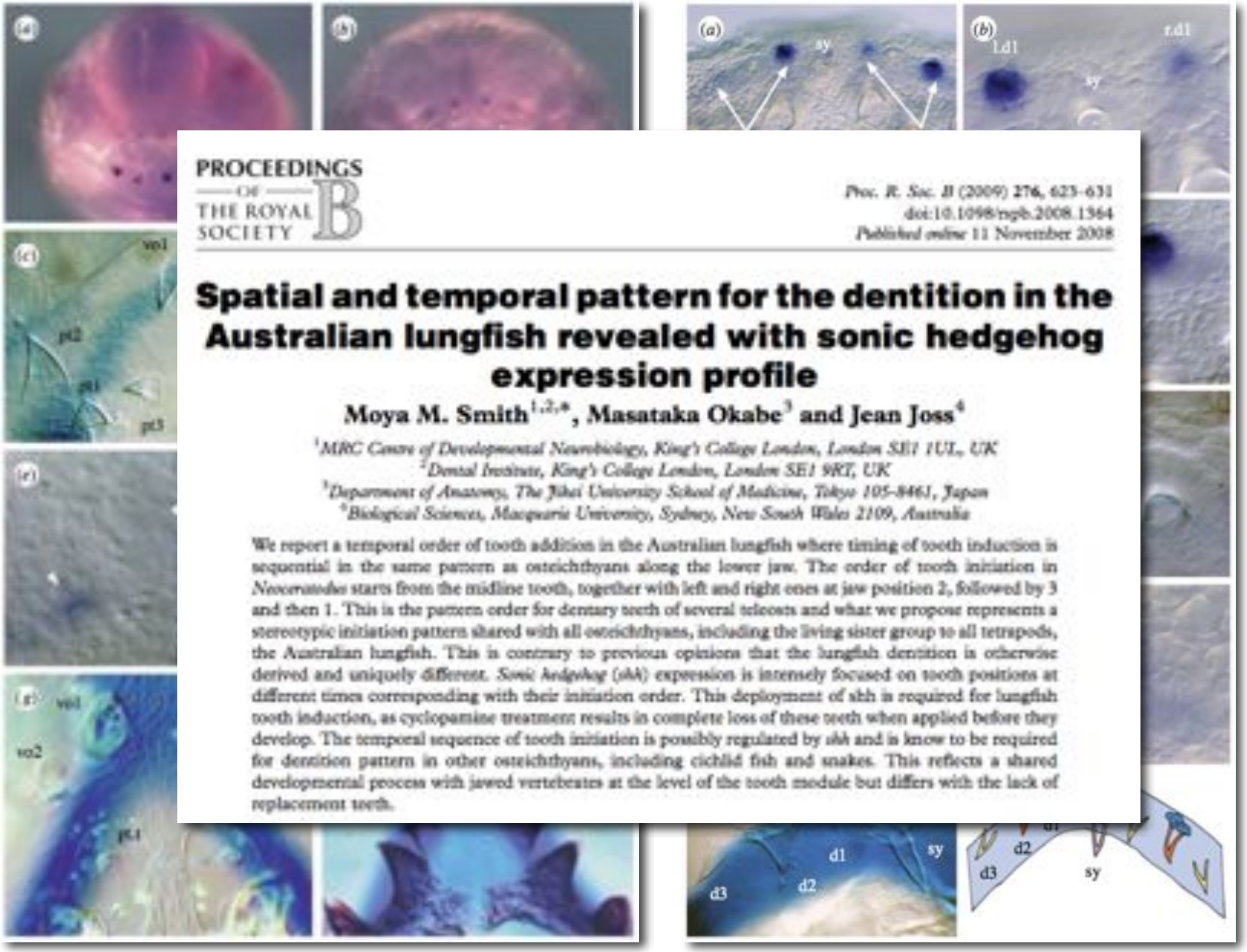


Figure 3. Schematic to show gene expression as sequential stages of odontogenesis. These are derived from composite information from serial 7 μm sections of whole-mount in situ-hybridized shh expression at several tooth sites along the jaw and from 50 μm gelatin sections where a through-focus series can be observed. Information is also obtained from a comparison with routine histology as in figure 1a–c, where secondary cusps appear and new tooth germs form on the deep extension of the dental lamina; each is associated with ectomesenchyme as dental papillae. (a) Restriction of gene expression to the primary OB is in association with condensations of ectomesenchyme cells (arrows). (b) Focused intense shh expression is restricted to the epithelial thickening for a tooth germ (right arrow) on the epithelial dental lamina (d.lam) associated with papilla ectomesenchyme. This occurs after the oral epithelium has infolded: no expression is seen in the oral epithelium, except very faint expression localized to the lingual epithelium (left arrow) where the lamina epithelium is reflected onto the oral surface but there is no condensed ectomesenchyme. (c) The first tooth is at the morphogenesis stage with intense shh activity (asterisk) in the two accessory cusps; below in the alternate series tooth germ intense shh activity locates to the first cusp position (right arrow).



PROCEEDINGS OF THE ROYAL SOCIETY B

Proc. R. Soc. B (2009) **276**, 623–631
doi:10.1098/rspb.2008.1364
Published online 11 November 2008

Spatial and temporal pattern for the dentition in the Australian lungfish revealed with sonic hedgehog expression profile

Moya M. Smith[1,2,*], Masataka Okabe[3] and Jean Joss[4]

[1]*MRC Centre of Developmental Neurobiology, King's College London, London SE1 1UL, UK*
[2]*Dental Institute, King's College London, London SE1 9RT, UK*
[3]*Department of Anatomy, The Jikei University School of Medicine, Tokyo 105-8461, Japan*
[4]*Biological Sciences, Macquarie University, Sydney, New South Wales 2109, Australia*

We report a temporal order of tooth addition in the Australian lungfish where timing of tooth induction is sequential in the same pattern as osteichthyans along the lower jaw. The order of tooth initiation in *Neoceratodus* starts from the midline tooth, together with left and right ones at jaw position 2, followed by 3 and then 1. This is the pattern order for dentary teeth of several teleosts and what we propose represents a stereotypic initiation pattern shared with all osteichthyans, including the living sister group to all tetrapods, the Australian lungfish. This is contrary to previous opinions that the lungfish dentition is otherwise derived and uniquely different. *Sonic hedgehog* (*shh*) expression is intensely focused on tooth positions at different times corresponding with their initiation order. This deployment of shh is required for lungfish tooth induction, as cyclopamine treatment results in complete loss of these teeth when applied before they develop. The temporal sequence of tooth initiation is possibly regulated by *shh* and is know to be required for dentition pattern in other osteichthyans, including cichlid fish and snakes. This reflects a shared developmental process with jawed vertebrates at the level of the tooth module but differs with the lack of replacement teeth.

Ektodermální morfogeneze: *ectodin*, BMP antagonista

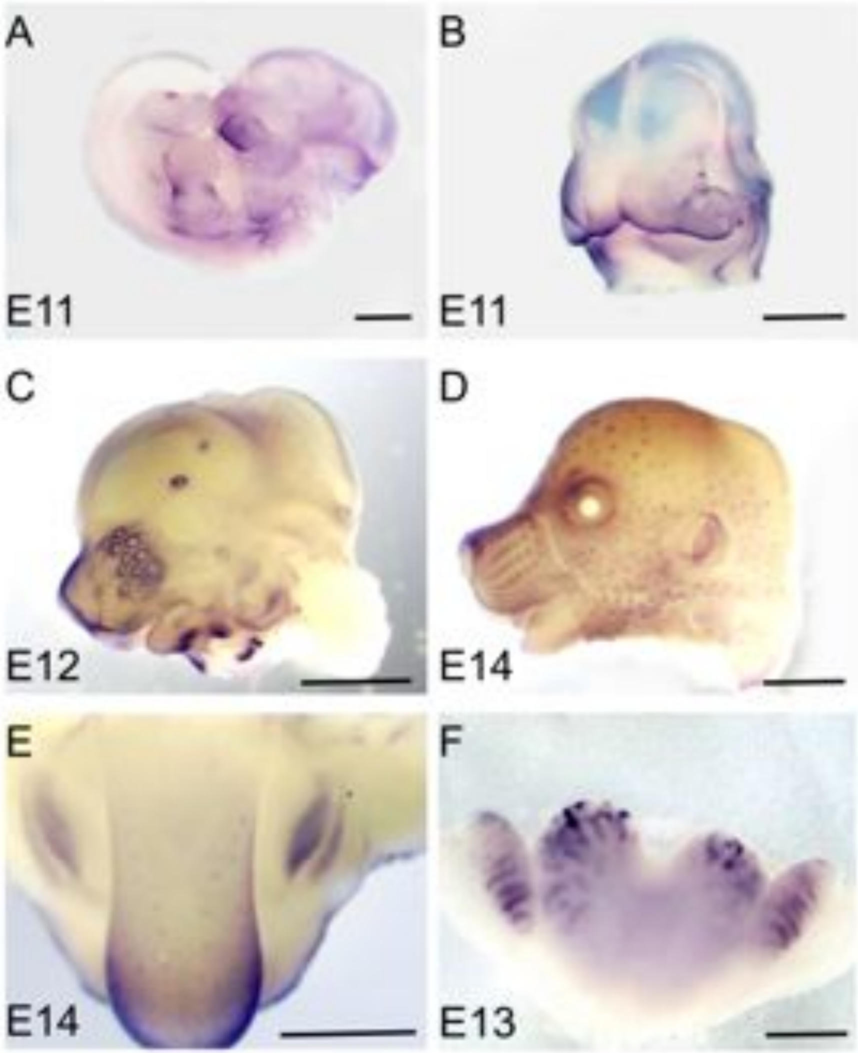
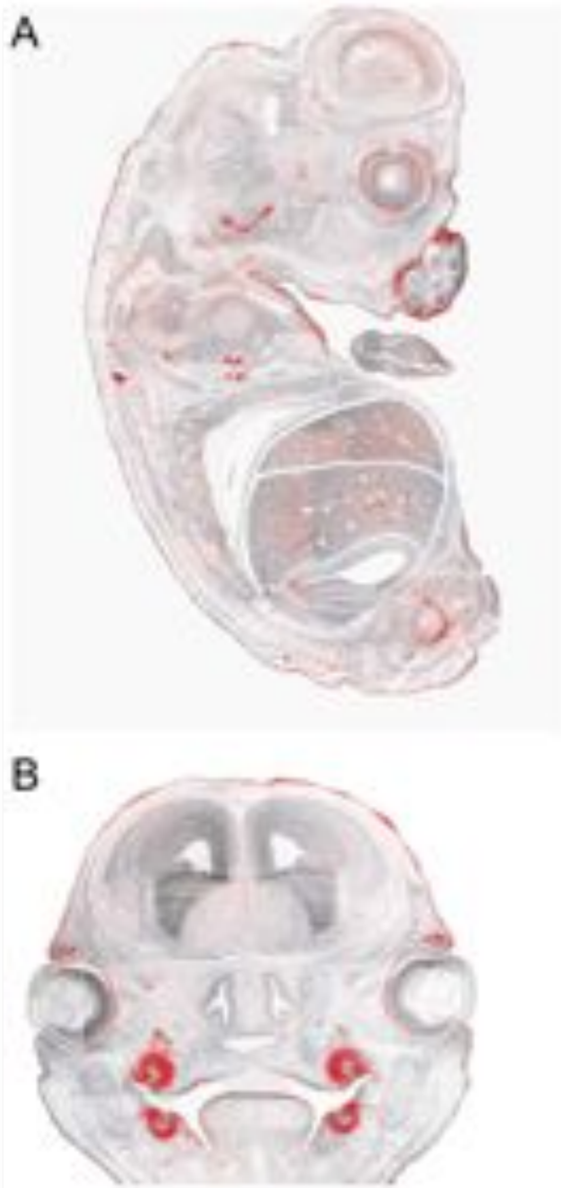


Fig. 5. Whole-mount in situ hybridization analysis of *ectodin* expression (A) E11 mouse embryo showing expression on the surface of the branchial arches and in limb buds. (B) Frontal view of E11 head shows staining at the surface of facial processes. (C) At E12, staining in vibrissae is seen as circles. (D) At E14, the vibrissae, hair follicles, and ear auricle show *ectodin* expression. (E) In the dissected E14 mandible molar tooth germs, tongue papillae and surface ectoderm express *ectodin* intensely. (F) In the dissected urogenital block of E13 embryo, *ectodin* expression is seen in the stalk and tips of ureter in the kidneys. In the testes, expression is intense in the spermatic ducts. Bar, 100 mm.



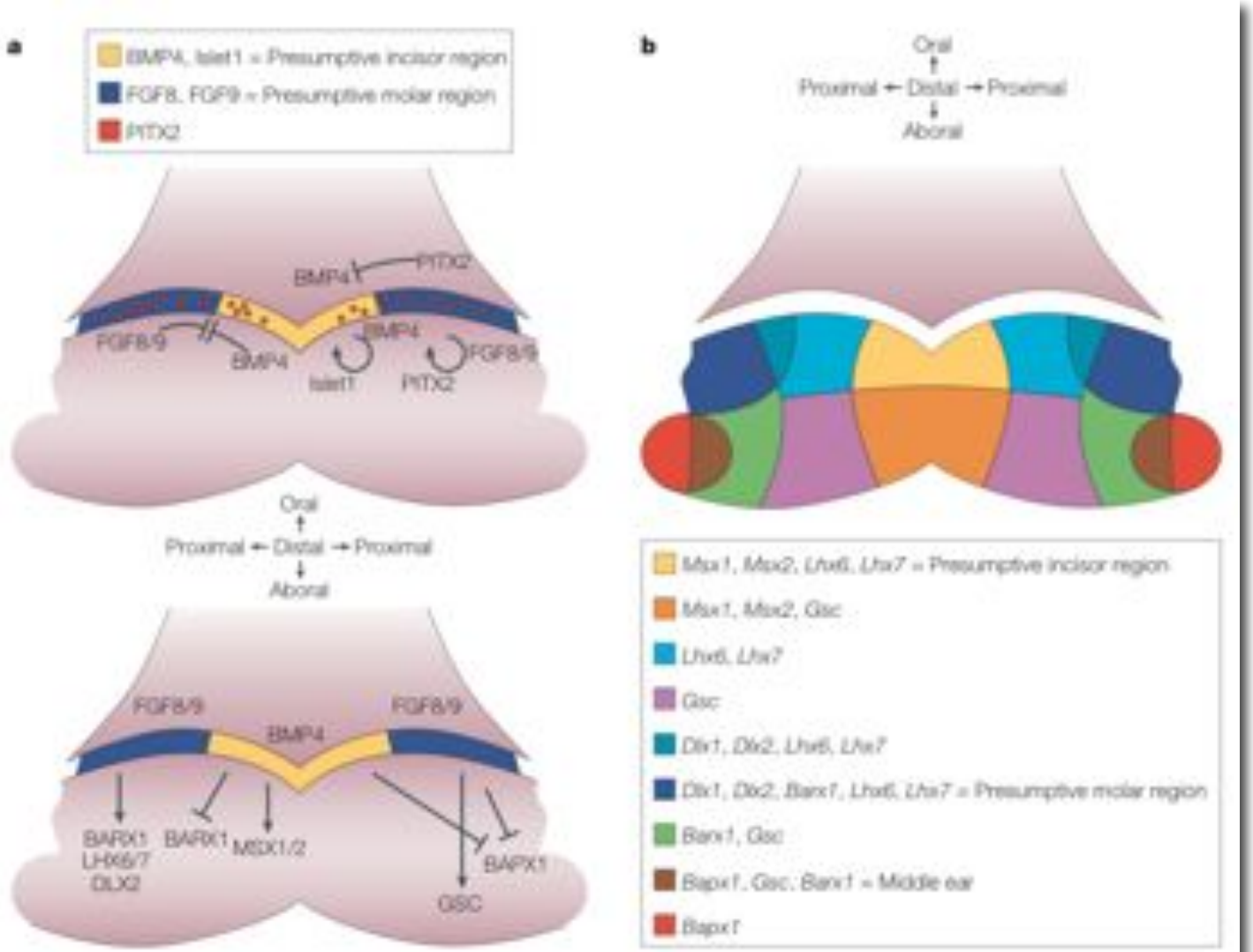
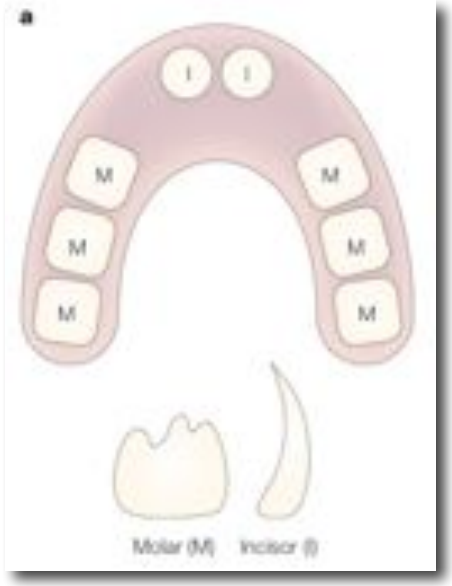


Figure 3 | **Pattern of gene expression in the developing tooth. a** | Signalling within the epithelium and between the epithelium and the mesenchyme at embryonic day (E)10.5. The diagram shows an isolated mandibular arch. Positive auto-regulatory loops and mutual repression within the epithelium leads to the formation of strict boundaries of gene expression, which set up the presumptive incisor and molar fields. Members of the bone morphogenetic protein (BMP) and fibroblast growth factor (FGF) families of protein in the epithelium induce and inhibit the expression of various homeobox genes. This results in a complex pattern of gene expression in the mesenchyme, across both the proximal–distal and oral–aboral/rostral–caudal axes. **b** | The odontogenic homeobox code model of dental patterning. The nested expression pattern of homeobox genes in the MAXILLA produces a homeobox code that defines tooth type. *Bapx1*, bagpipe homeobox gene 1 homologue; *Barx1*, Barh-like homeobox 1; *Dlx*, distal-less homeobox; *Gsc*, goosecoid; *Lhx*, LIM homeodomain genes; *Msx*, homeobox, msh-like; *Pitx*, paired-related homeobox gene.



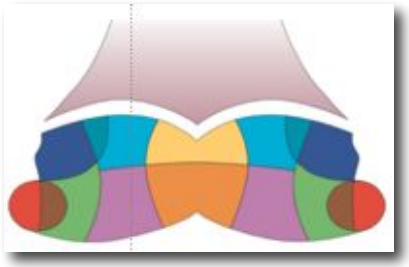
Transformace zubní identity z řezáku na špičák

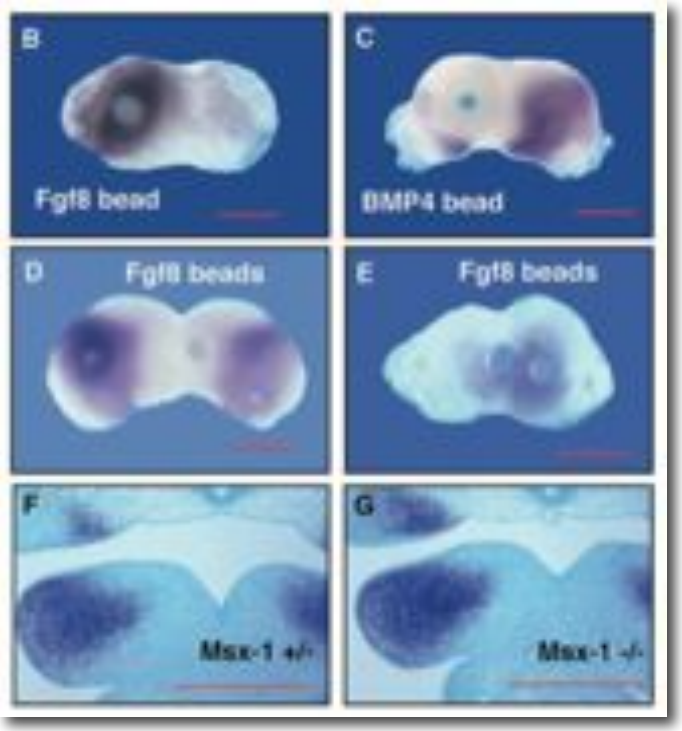
posunem exprese BMP a FGF

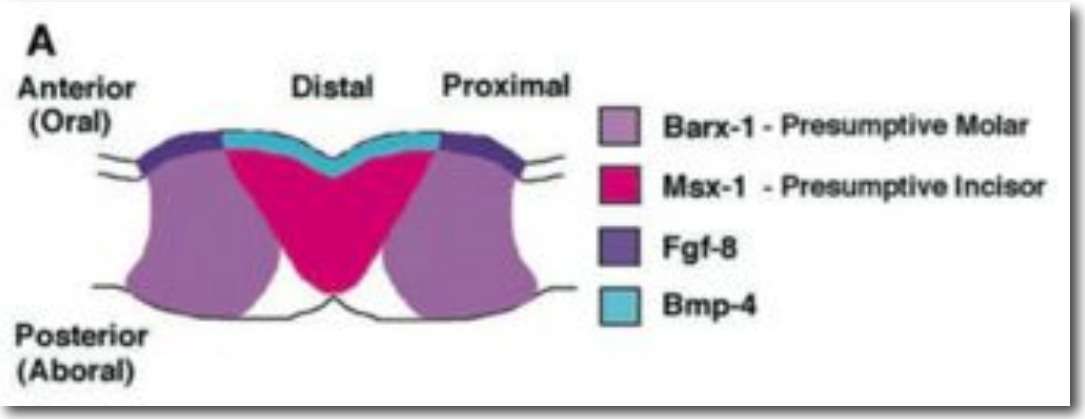
Transformation of Tooth Type Induced by Inhibition of BMP Signaling

Abigail S. Tucker, Karen L. Matthews, Paul T. Sharpe*

Mammalian dentitions are highly patterned, with different types of teeth positioned in different regions of the jaws. BMP4 is an early oral epithelial protein signal that directs odontogenic gene expression in mesenchyme cells of the developing mandibular arch. BMP4 was shown to inhibit expression of the homeobox gene *Barx-1* and to restrict expression to the proximal, presumptive molar mesenchyme of mouse embryos at embryonic day 10. The inhibition of BMP signaling early in mandible development by the action of exogenous Noggin protein resulted in ectopic *Barx-1* expression in the distal, presumptive incisor mesenchyme and a transformation of tooth identity from incisor to molar.

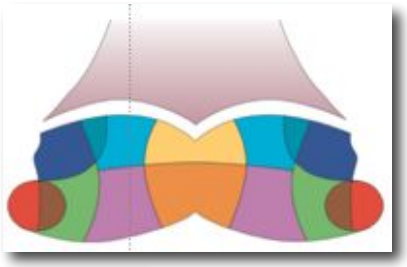






Transformace zubní identity z řezáku na špičák

posunem exprese BMP a FGF



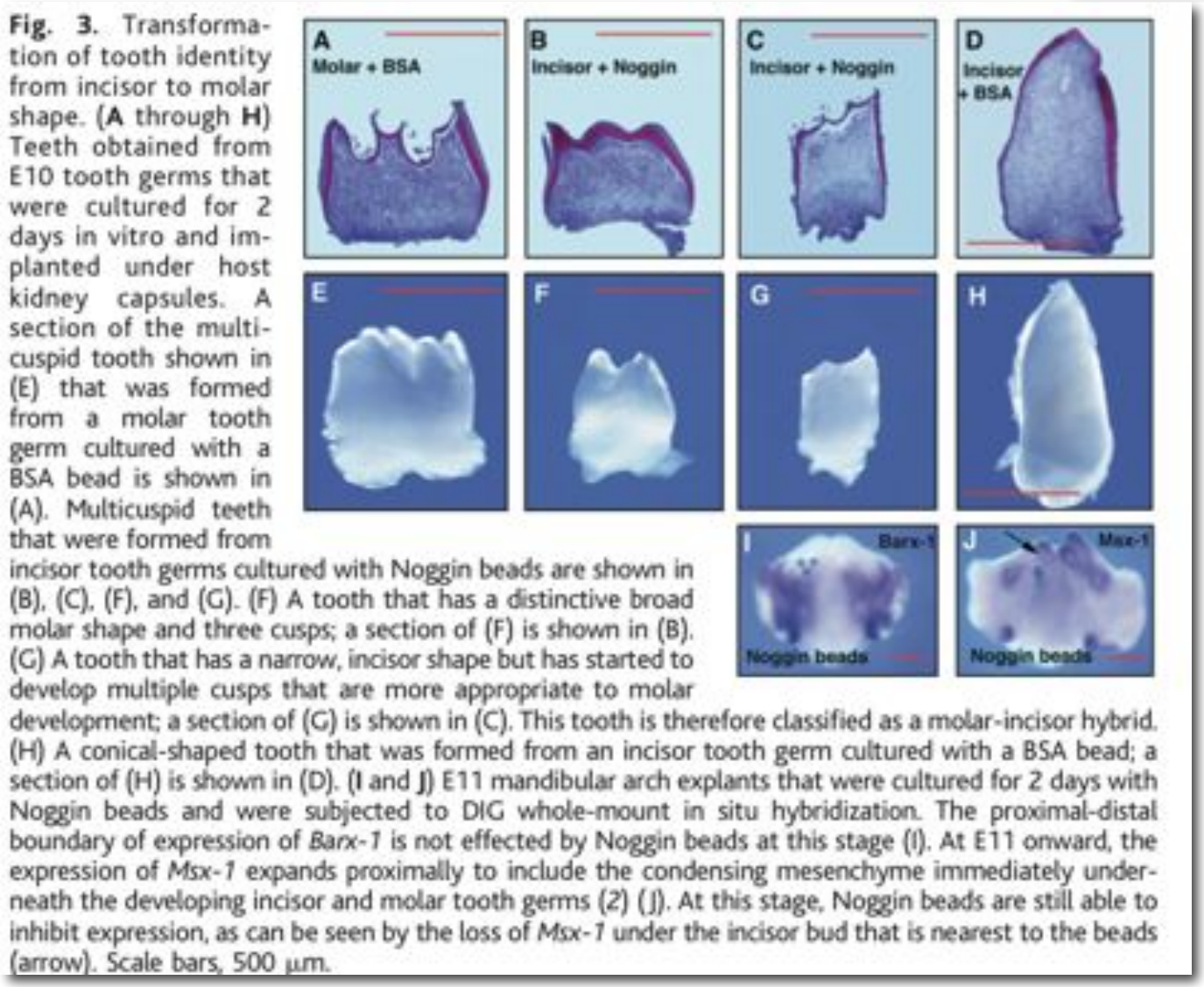


Fig. 3. Transformation of tooth identity from incisor to molar shape. (**A** through **H**) Teeth obtained from E10 tooth germs that were cultured for 2 days in vitro and implanted under host kidney capsules. A section of the multicuspid tooth shown in (E) that was formed from a molar tooth germ cultured with a BSA bead is shown in (A). Multicuspid teeth that were formed from incisor tooth germs cultured with Noggin beads are shown in (B), (C), (F), and (G). (F) A tooth that has a distinctive broad molar shape and three cusps; a section of (F) is shown in (B). (G) A tooth that has a narrow, incisor shape but has started to develop multiple cusps that are more appropriate to molar development; a section of (G) is shown in (C). This tooth is therefore classified as a molar-incisor hybrid. (H) A conical-shaped tooth that was formed from an incisor tooth germ cultured with a BSA bead; a section of (H) is shown in (D). (**I** and **J**) E11 mandibular arch explants that were cultured for 2 days with Noggin beads and were subjected to DIG whole-mount in situ hybridization. The proximal-distal boundary of expression of *Barx-1* is not effected by Noggin beads at this stage (I). At E11 onward, the expression of *Msx-1* expands proximally to include the condensing mesenchyme immediately underneath the developing incisor and molar tooth germs (*J*) (J). At this stage, Noggin beads are still able to inhibit expression, as can be seen by the loss of *Msx-1* under the incisor bud that is nearest to the beads (arrow). Scale bars, 500 μm.

Je tento homeobox-kód specifický pro heterodontní dentici či myši, nebo má obecnou platnost?

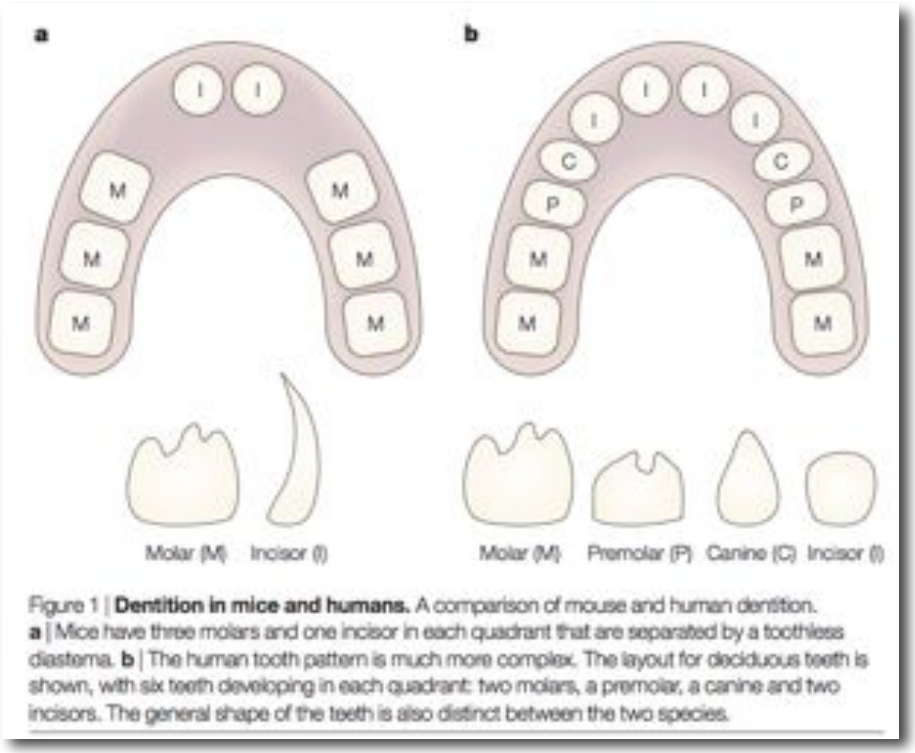
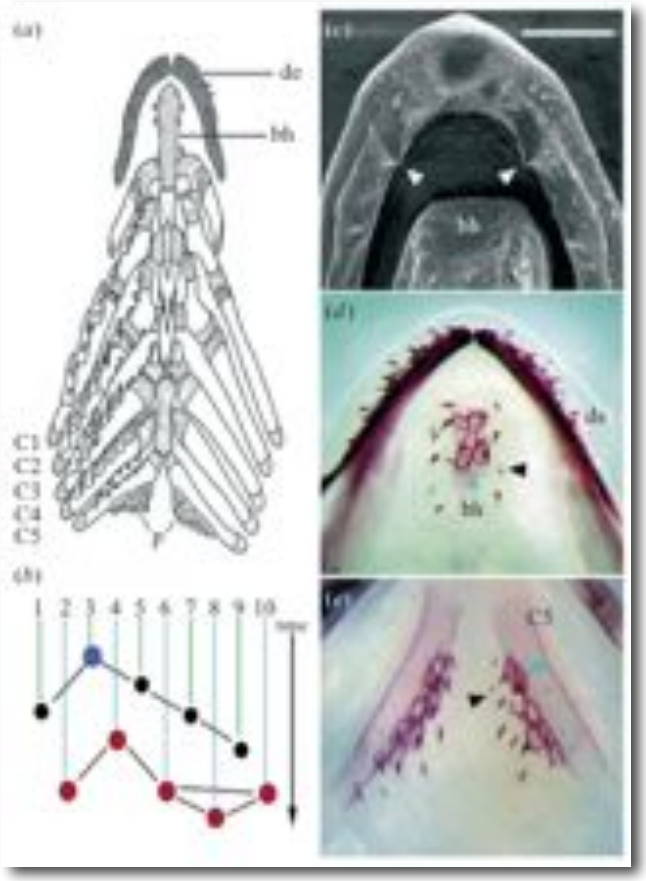
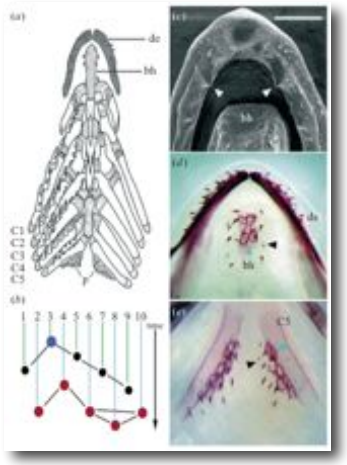


Figure 1 | **Dentition in mice and humans.** A comparison of mouse and human dentition. **a** | Mice have three molars and one incisor in each quadrant that are separated by a toothless diastema. **b** | The human tooth pattern is much more complex. The layout for deciduous teeth is shown, with six teeth developing in each quadrant: two molars, a premolar, a canine and two incisors. The general shape of the teeth is also distinct between the two species.





Je tento homeobox-kód specifický pro heterodontní identici mysi, nebo má obecnou platnost?

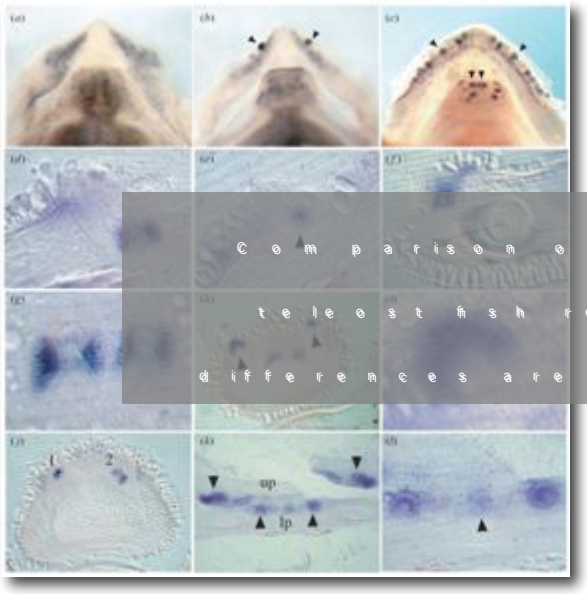
Pstruh *Oncorhynchus mykiss*

(3 druhy cichlid

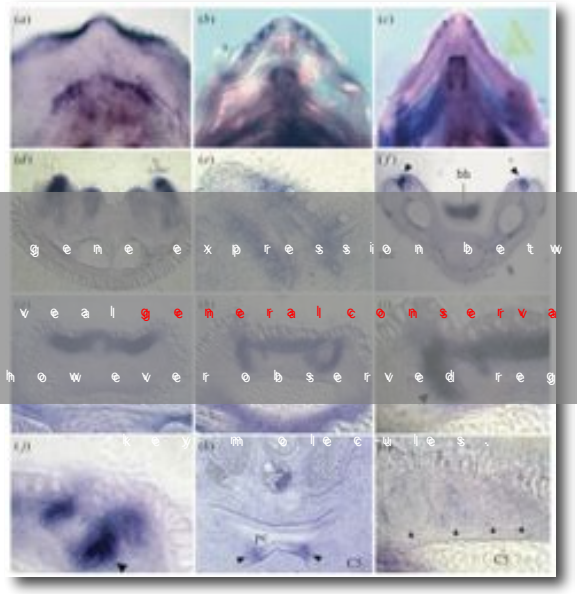
Zebrafish *Danio rerio*

Tetra *Astyanax mexicanus*

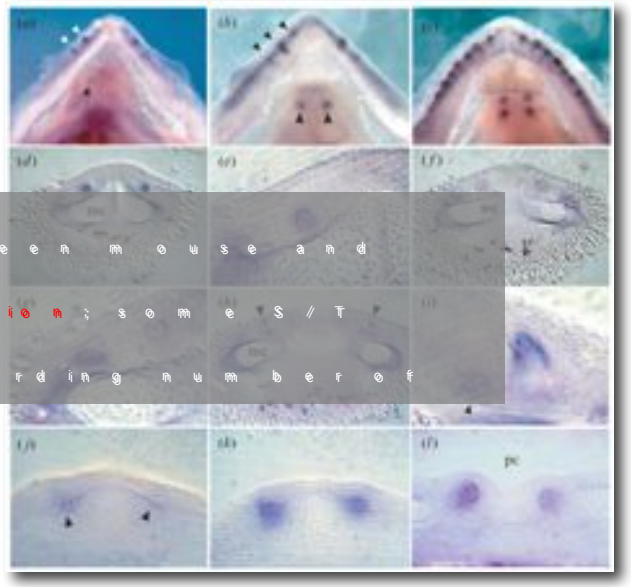
Medaka *Oryzias latipes*)



Shh



Pitx-2



Bmp-4

Comparison of gene expression between mouse and teleost fish reveal general conservation; some S/T differences are however observed regarding number of key molecules.

Comparison of gene expression between mouse and teleost fish reveal general conservation; some S/T differences are however observed regarding number of

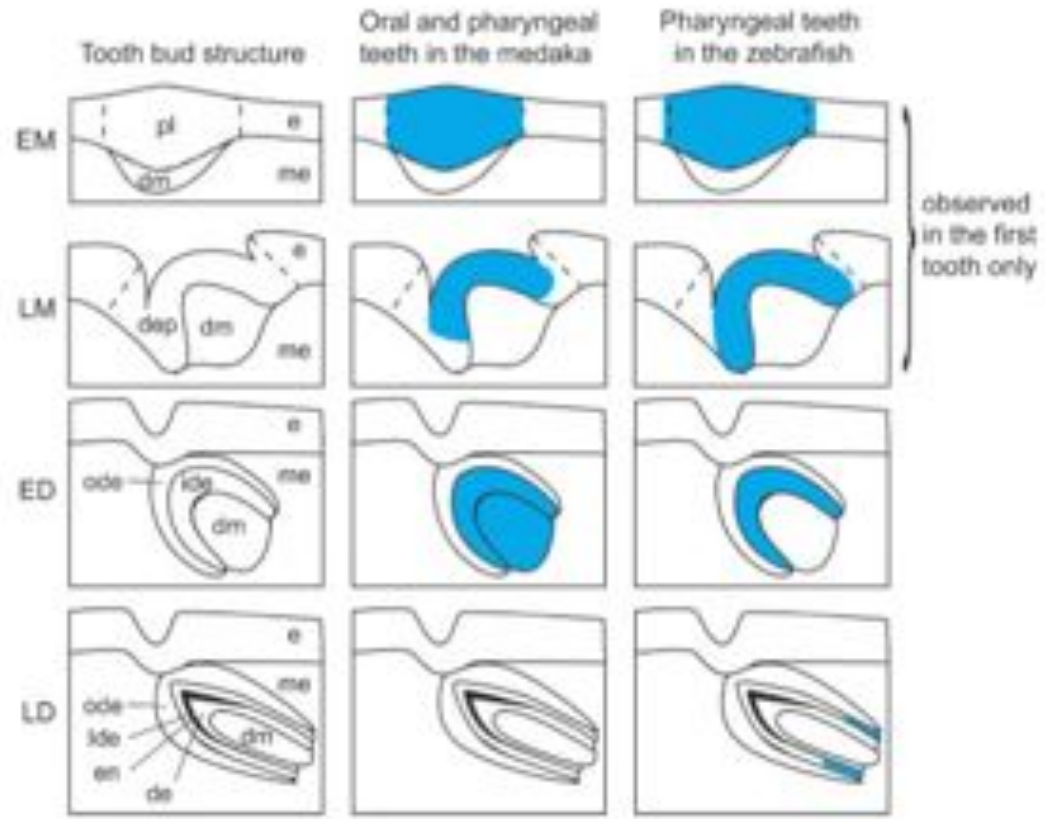


Fig. 8. Comparative schematic representation of *eve1* expression pattern (grey) during odontogenesis in the medaka and zebrafish (where the EM stage does not exist in teeth subsequent to the first tooth). EM, early morphogenesis; LM, late morphogenesis; ED, early differentiation; LD, late differentiation; de, dentine; dep, dental epithelium; dm, dental mesenchyme; e, epithelium (oral) or endothelium (pharyngeal); en, enameloid cap; ide, inner dental epithelium; m, mesenchyme; ode, outer dental epithelium; pl, placode.

Základ ektodermálním morfogeneze:

signalizace epidermální placody

aktivátory vs. inhibitory

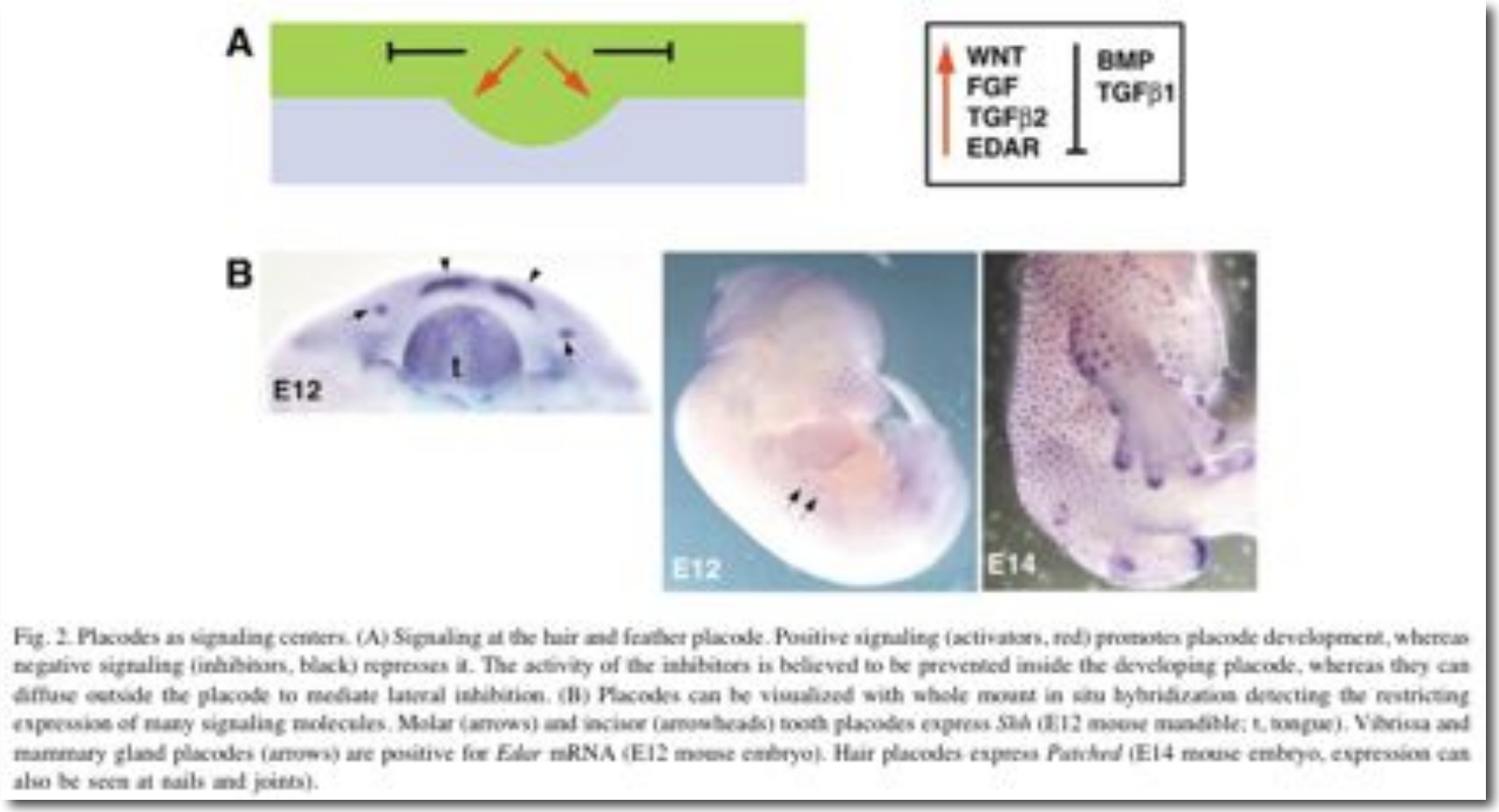


Fig. 2. Placodes as signaling centers. (A) Signaling at the hair and feather placode. Positive signaling (activators, red) promotes placode development, whereas negative signaling (inhibitors, black) represses it. The activity of the inhibitors is believed to be prevented inside the developing placode, whereas they can diffuse outside the placode to mediate lateral inhibition. (B) Placodes can be visualized with whole mount in situ hybridization detecting the restricting expression of many signaling molecules. Molar (arrows) and incisor (arrowheads) tooth placodes express *Shh* (E12 mouse mandible; t, tongue). Vibrissa and mammary gland placodes (arrows) are positive for *Edar* mRNA (E12 mouse embryo). Hair placodes express *Patched* (E14 mouse embryo, expression can also be seen at nails and joints).

Morfologie zubních hrbolů je odvislá od činnosti sklovinotvorných hrbolů - enamel knots

Enamel knot:
přímo řídí tvar a pozici z. hrbolů
(prim., sek. i terciální)

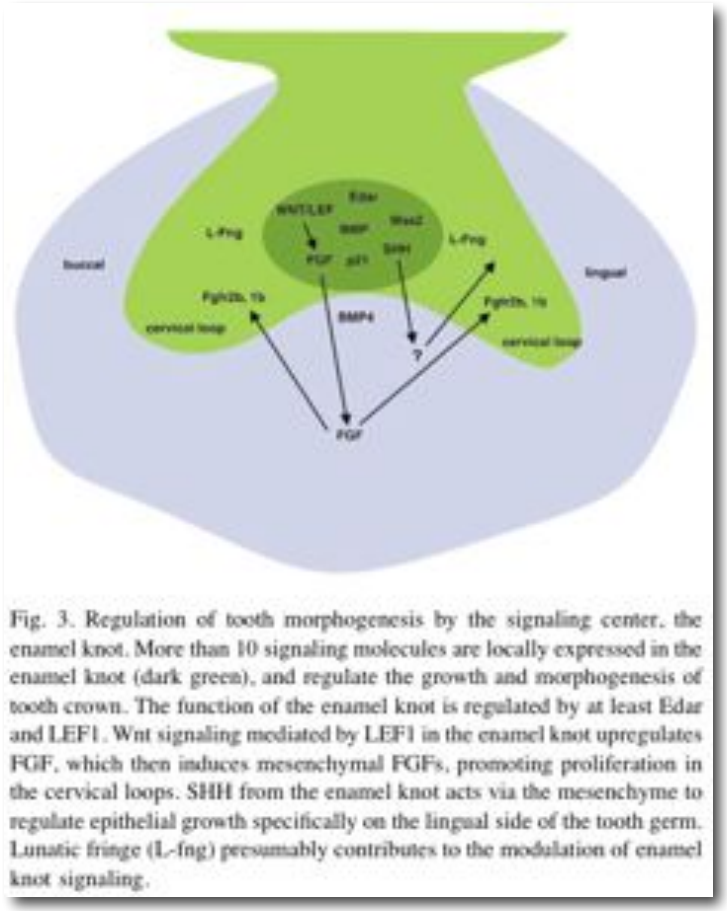


Fig. 3. Regulation of tooth morphogenesis by the signaling center, the enamel knot. More than 10 signaling molecules are locally expressed in the enamel knot (dark green), and regulate the growth and morphogenesis of tooth crown. The function of the enamel knot is regulated by at least Edar and LEF1. Wnt signaling mediated by LEF1 in the enamel knot upregulates FGF, which then induces mesenchymal FGFs, promoting proliferation in the cervical loops. SHH from the enamel knot acts via the mesenchyme to regulate epithelial growth specifically on the lingual side of the tooth germ. Lunatic fringe (L-fng) presumably contributes to the modulation of enamel knot signaling.

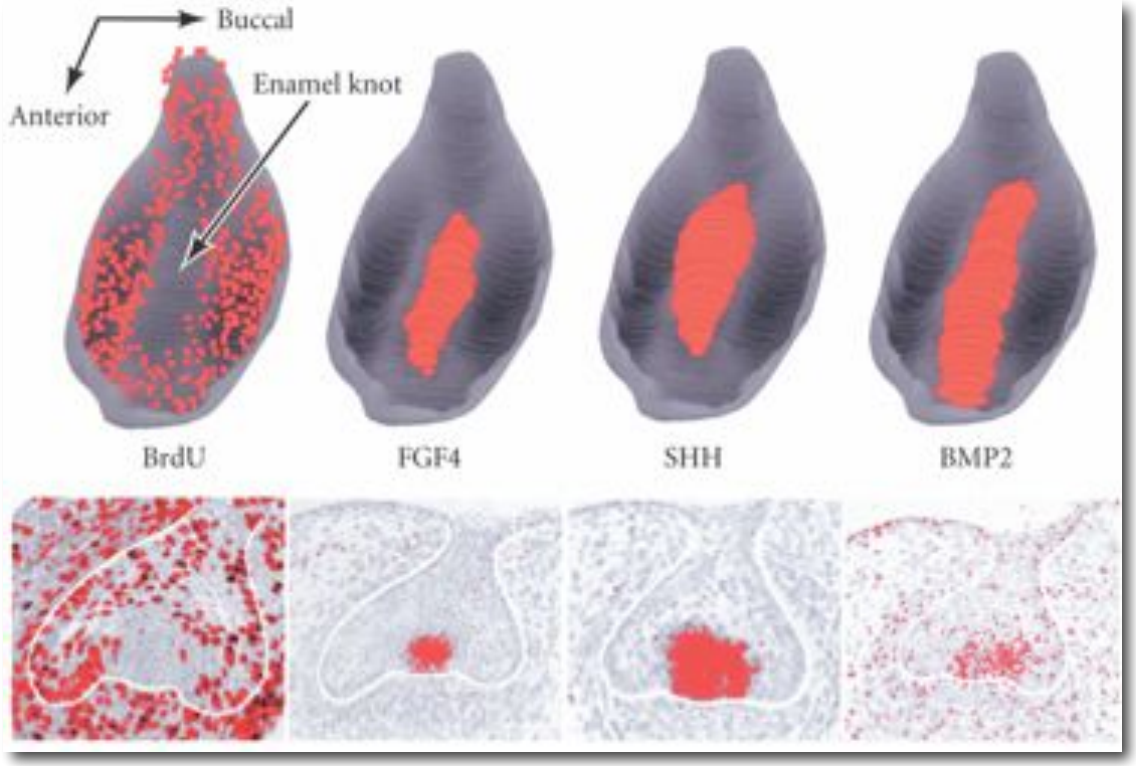
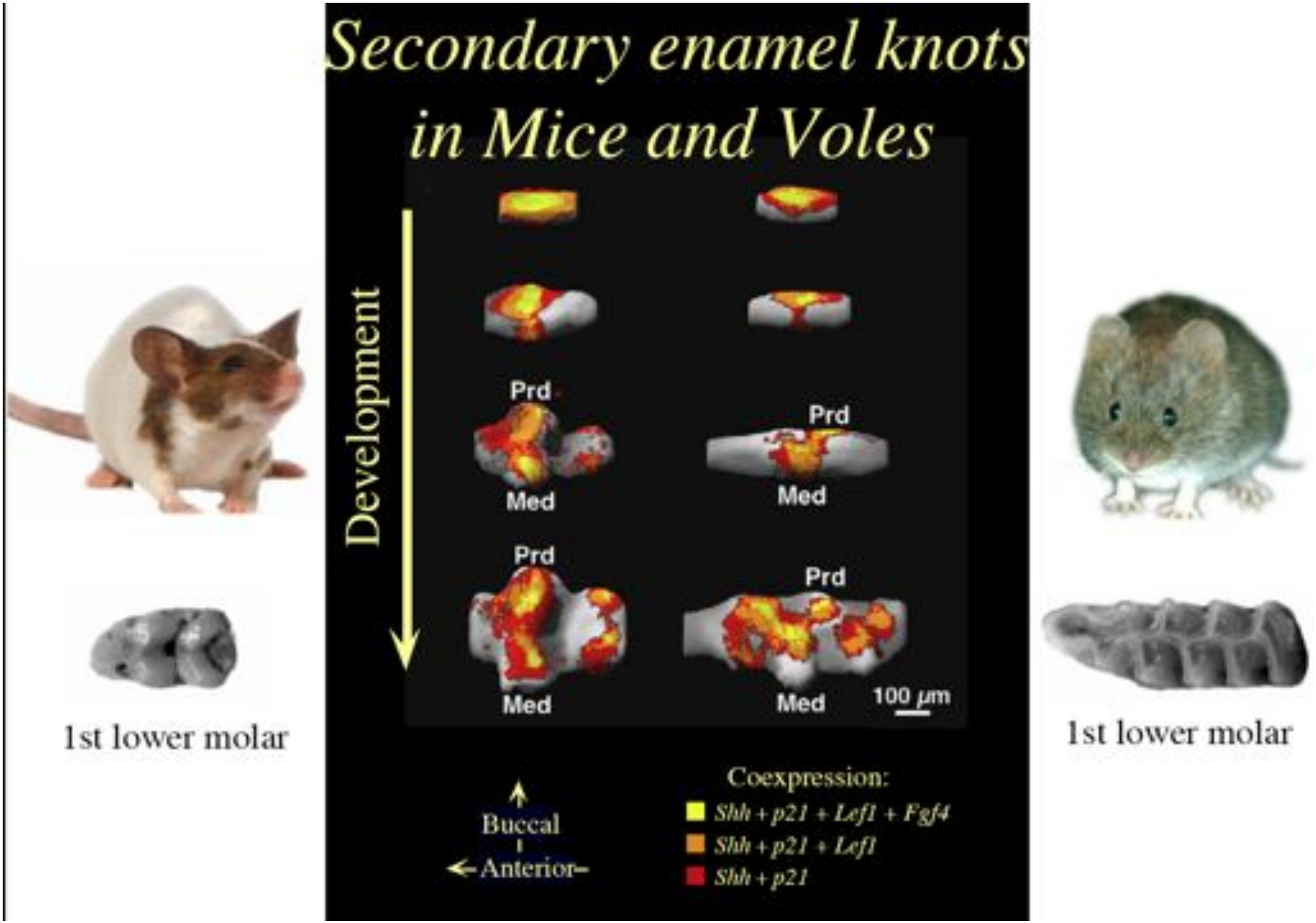
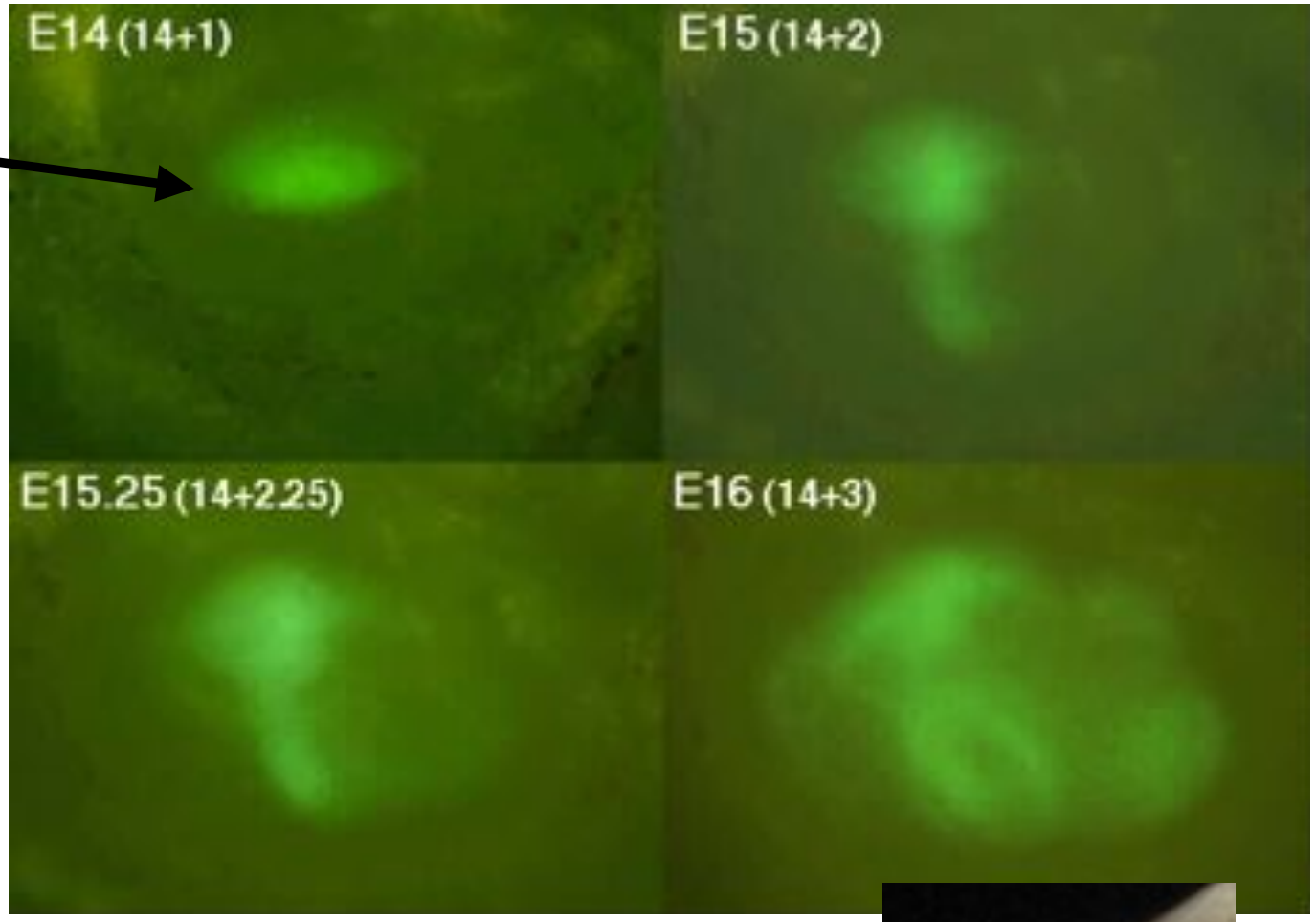


***Fig 6** A. The primary enamel knot is visualized in a frontal section through the cap stage tooth germ (expression of Edar, the receptor for ectodysplasin). B. Secondary enamel knots of the bell stage first molar (left) prefigure cusps. The second molar (right) is at cap stage and the primary enamel knot is seen. (p21 expression, occlusal view of whole mount in situ hybridization).*


Secondary enamel knots
in Mice and Voles
Development
Prd
Med
Prd
Med
Prd
Med
Prd
Med
100 μm
Buccal
Anterior
Coexpression:
Shh + p21 + Lef1 + Fgf4
Shh + p21 + Lef1
Shh + p21
1st lower molar
1st lower molar

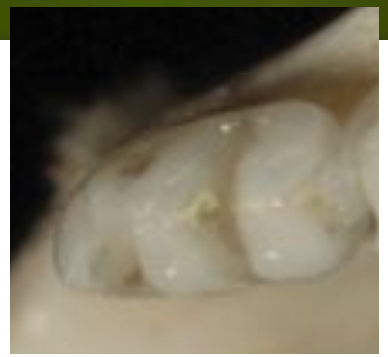
GFP-SHHcre mouse

Enamel Knot signaling center



Sonic Hedgehog, SHH, is a developmental regulatory gene that marks the position of the tooth and cusps.

Adult M1



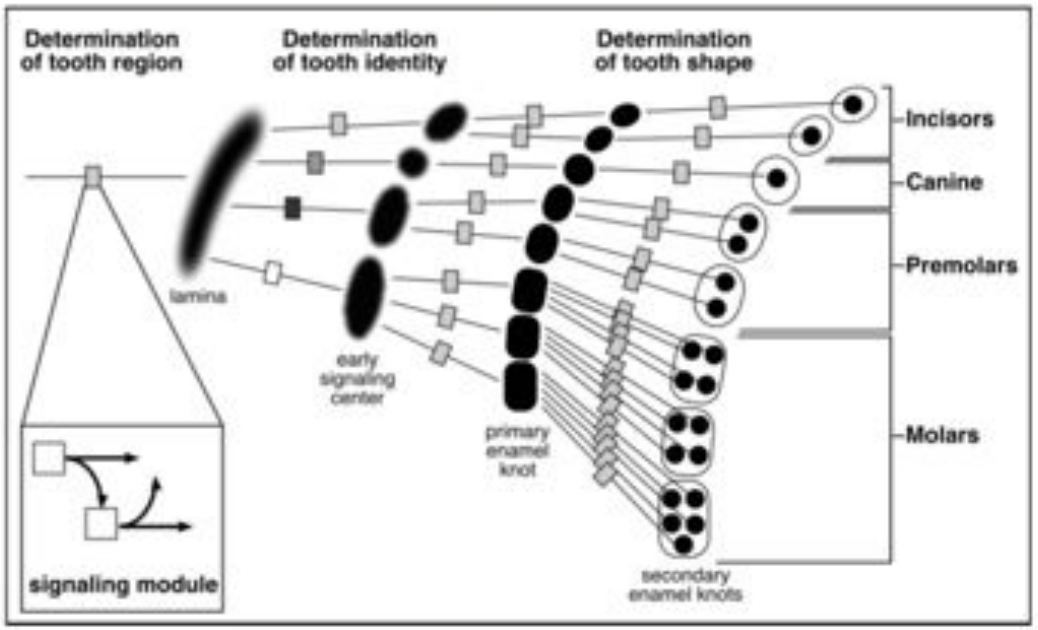
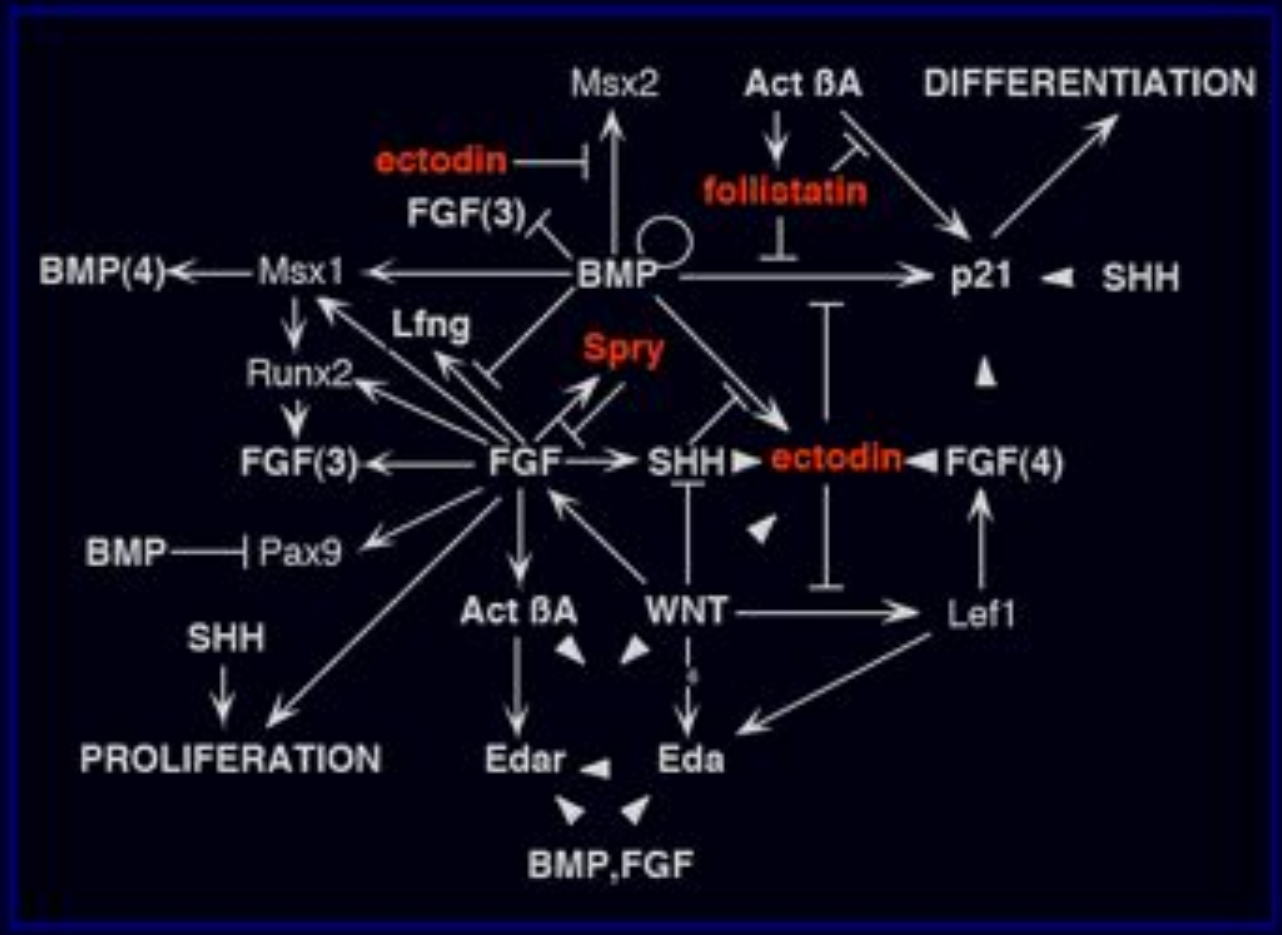


Fig. 6. Largely the same signaling modules (see Fig. 2) are reiterated from the tooth initiation to the formation of cusps. In each iteration, the dental region is partitioned into new compartments and a progressively larger number of the signaling domains are induced. The first partitioning involves the formation of tooth identity (incisor, canine, premolar, or molar identity) and may be regulated by differences in signaling (represented as different shadings in the signaling boxes) after the determination of dental lamina or already prior to lamina formation (see for discussion Weiss et al., 1998a,b). Generally, the premolar and molar teeth have several cusps but they can also be unicusped (e.g. many seals); incisors can also have many cusps (e.g. flying lemurs, Dermoptera). Deciduous teeth (milk teeth) are generally equal or more complex in morphology than their replacement teeth (teeth not shown). As the same genes are repeatedly used in tooth development, knockout experiments affecting signaling will mostly result in early disruption of tooth development and also affect other organs sharing the same signaling pathways (e.g. Kratochwil et al., 1996; Hardcastle et al., 1998; De Moerlooze et al., 2000).

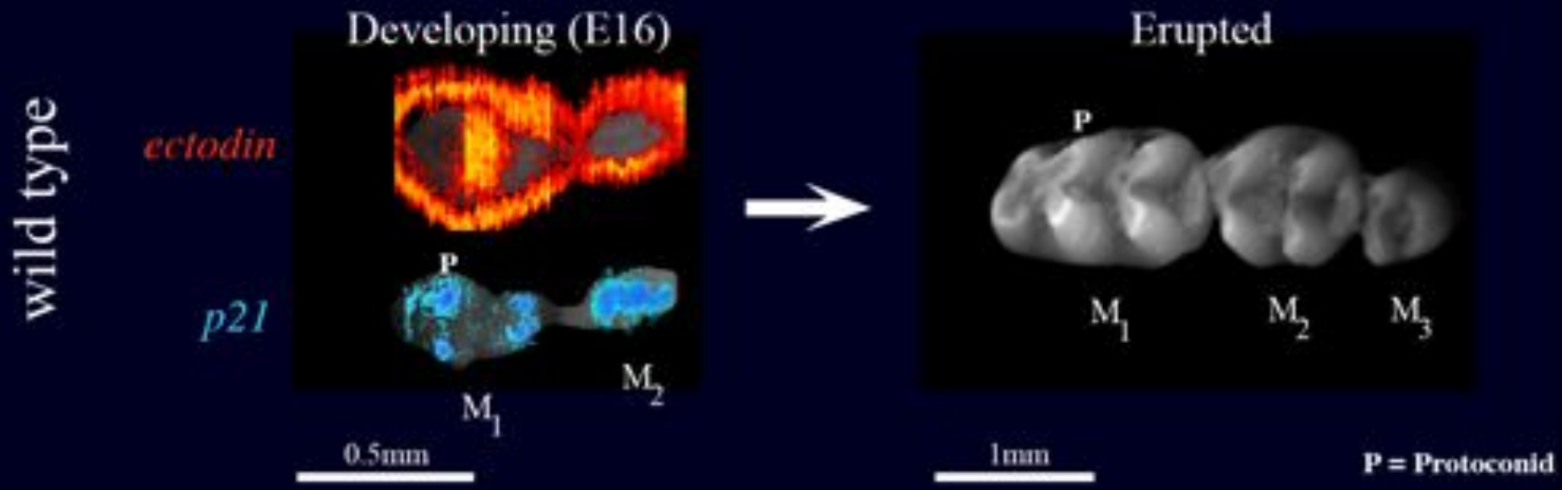
An emerging pattern from experiments and mathematical modeling: inhibition of the enamel knots



Activator-Inhibitor gene network of the developing tooth

Inhibiting enamel knots

ectodin (a.k.a.: *Sostdc1, USAG1, wise*), a BMP antagonist, member of DAN/Cerberus family



Science 309. 2067 (2005)

Inhibiting enamel knots

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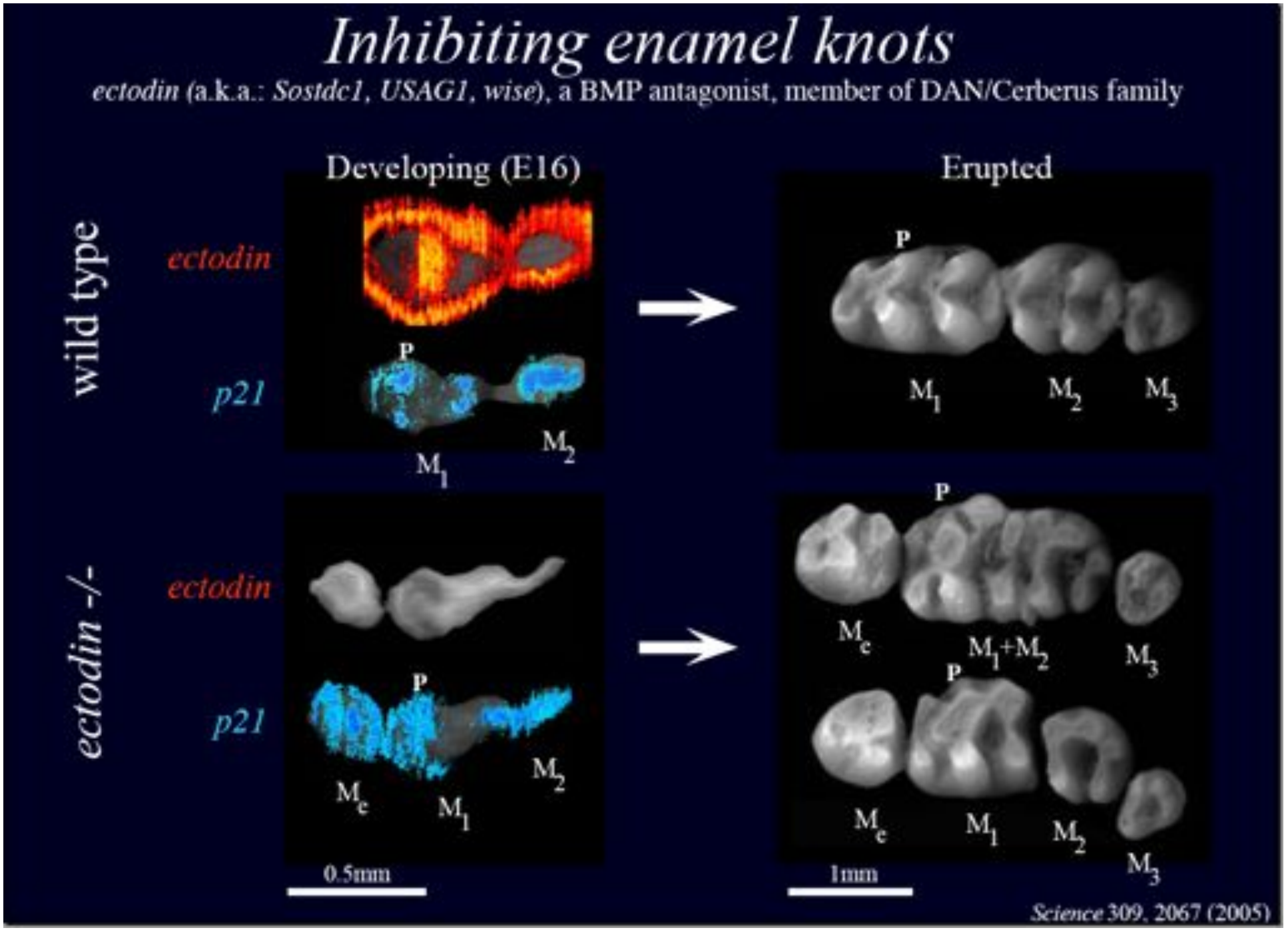
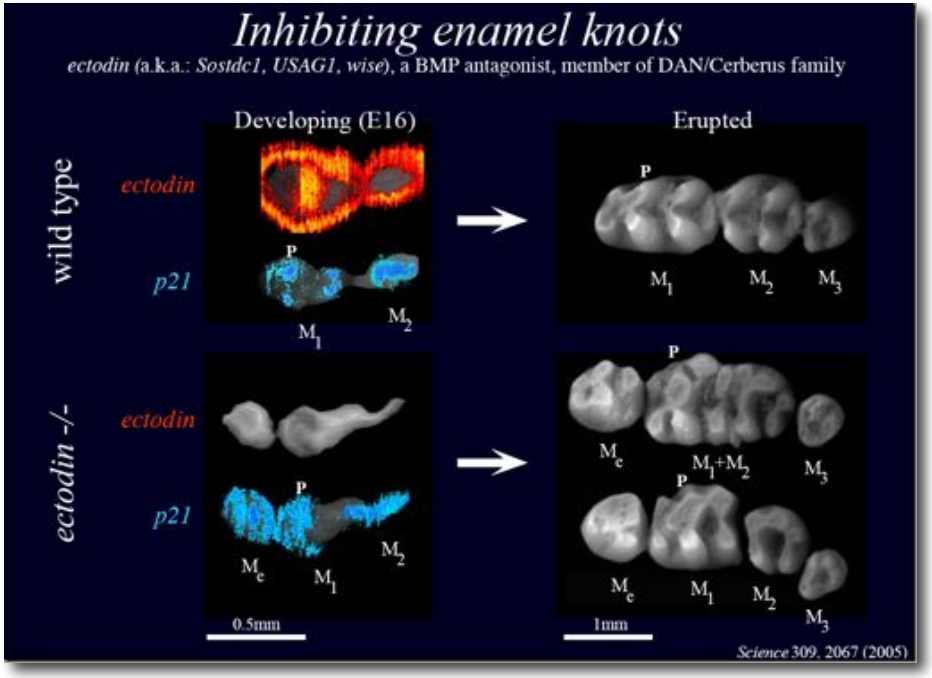


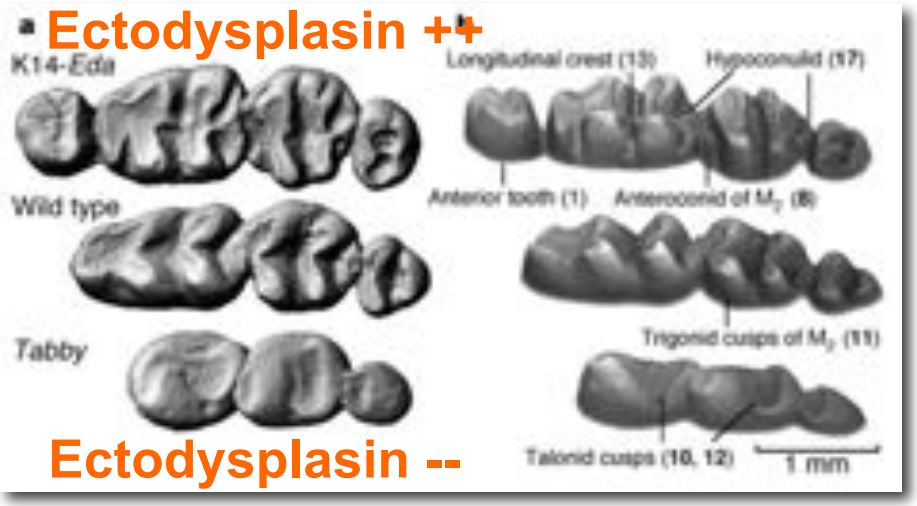
Science 309, 2067 (2005)

-Zubní povrch je generován záhyby epithelo-mesenchymového rozhraní

-Kaspy jsou generovány enamelovými uzly;

- Kaspy nemají specifický genetický kod - to, co je důležité, je celkovostní tvar



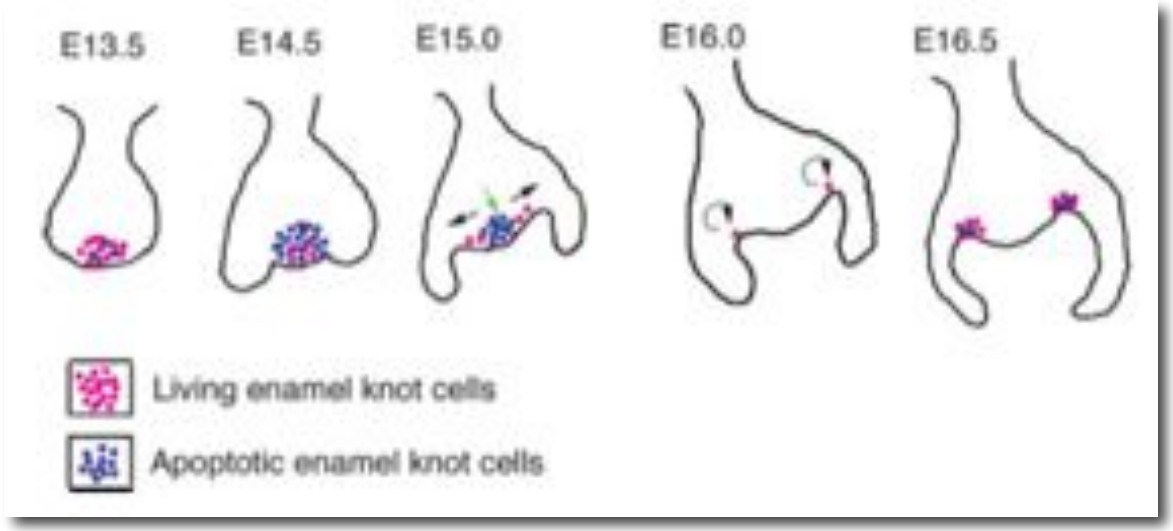


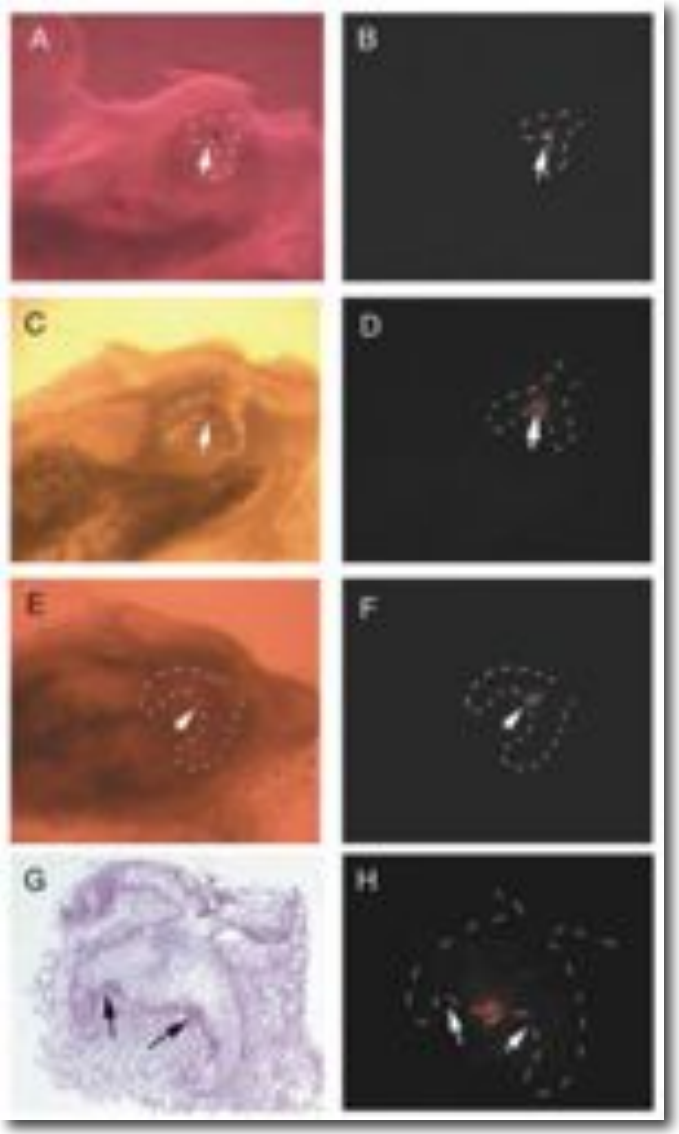
Může tak složité signalizační centrum (v rámci zubu) vzniknout de novo?

Cell Lineage of Primary and Secondary Enamel Knots

E. Matalova,[1] G.S. Antonarakis,[2] P.T. Sharpe,[2] and A.S. Tucker[1,2]*

Recent research indicates that control of cusp morphology involves a signalling center at the heart of the developing tooth germ, known as the enamel knot. The primary enamel knot forms in both incisors and molar tooth germs at the cap stage of tooth development. Secondary and tertiary enamel knots only develop in molar tooth germs. These sit at the sites of future cusp tips from the early bell stage of tooth development. In studies describing the relationship between the primary and secondary enamel knots, it is often assumed that there is a cellular continuity between these structures, such that cells from the primary enamel knot physically contribute to the secondary enamel knots. We have devised a method whereby the developing tooth germ can be cultured in frontal slices with the enamel knot visible. The fate of the primary enamel knot cells can then be followed by 1,1′, di-octadecyl-3,3,3′,3′,-tetramethylindo-carbocyanine perchlorate (DiI) labeling. Using this method, no cells of the primary enamel knot were seen to move toward the developing secondary enamel knots. Thus, although the primary and secondary enamel knots have a close molecular and functional relationship in molar development, they are not actually derived from the same cells. *Developmental Dynamics* 233:754–759, 2005. © 2005 Wiley-Liss, Inc.

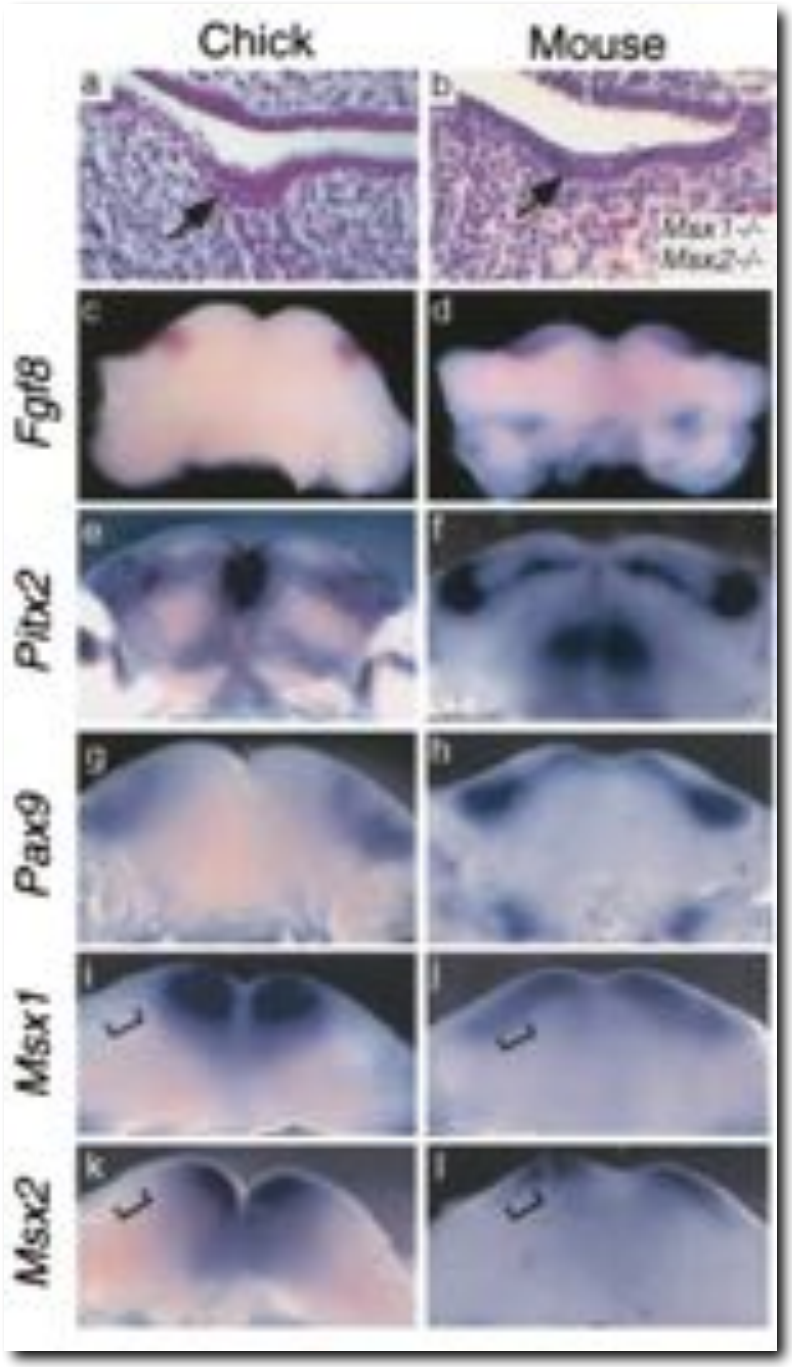




Conservation of early odontogenic signaling pathways in *Aves*

YiPing Chen*†, Yanding Zhang*†, Ting-Xing Jiang‡, Amanda J. Barlow§, Tara R. St. Amand†, Yueping Hu†, Shaun Heaney*, Philippa Francis-West§, Cheng-Ming Chuong‡, and Richard Maas*¶

Teeth have been missing from birds (*Aves*) for at least 60 million years. However, in the chick oral cavity a rudiment forms that resembles the lamina stage of the mammalian molar tooth germ. We have addressed the molecular basis for this secondary loss of tooth formation in *Aves* by analyzing in chick embryos the status of molecular pathways known to regulate mouse tooth development. Similar to the mouse dental lamina, expression of *Fgf8*, *Pitx2*, *Barx1*, and *Pax9* defines a potential chick odontogenic region. However, the expression of three molecules involved in tooth initiation, *Bmp4*, *Msx1*, and *Msx2*, are absent from the presumptive chick dental lamina. In chick mandibles, exogenous bone morphogenetic protein (BMP) induces *Msx* expression and together with fibroblast growth factor promotes the development of *Sonic hedgehog* expressing epithelial structures. Distinct epithelial appendages also were induced when chick mandibular epithelium was recombined with a tissue source of BMPs and fibroblast growth factors, chick skin mesenchyme. These results show that, although latent, the early signaling pathways involved in odontogenesis remain inducible in *Aves* and suggest that loss of odontogenic *Bmp4* expression may be responsible for the early arrest of tooth development in living birds.



Current Biology 16, 371–377, February 21, 2006 ©2006 Elsevier Ltd All rights reserved DOI 10.1016/j.cub.2005.12.047

Report

The Development of Archosaurian First-Generation Teeth in a Chicken Mutant

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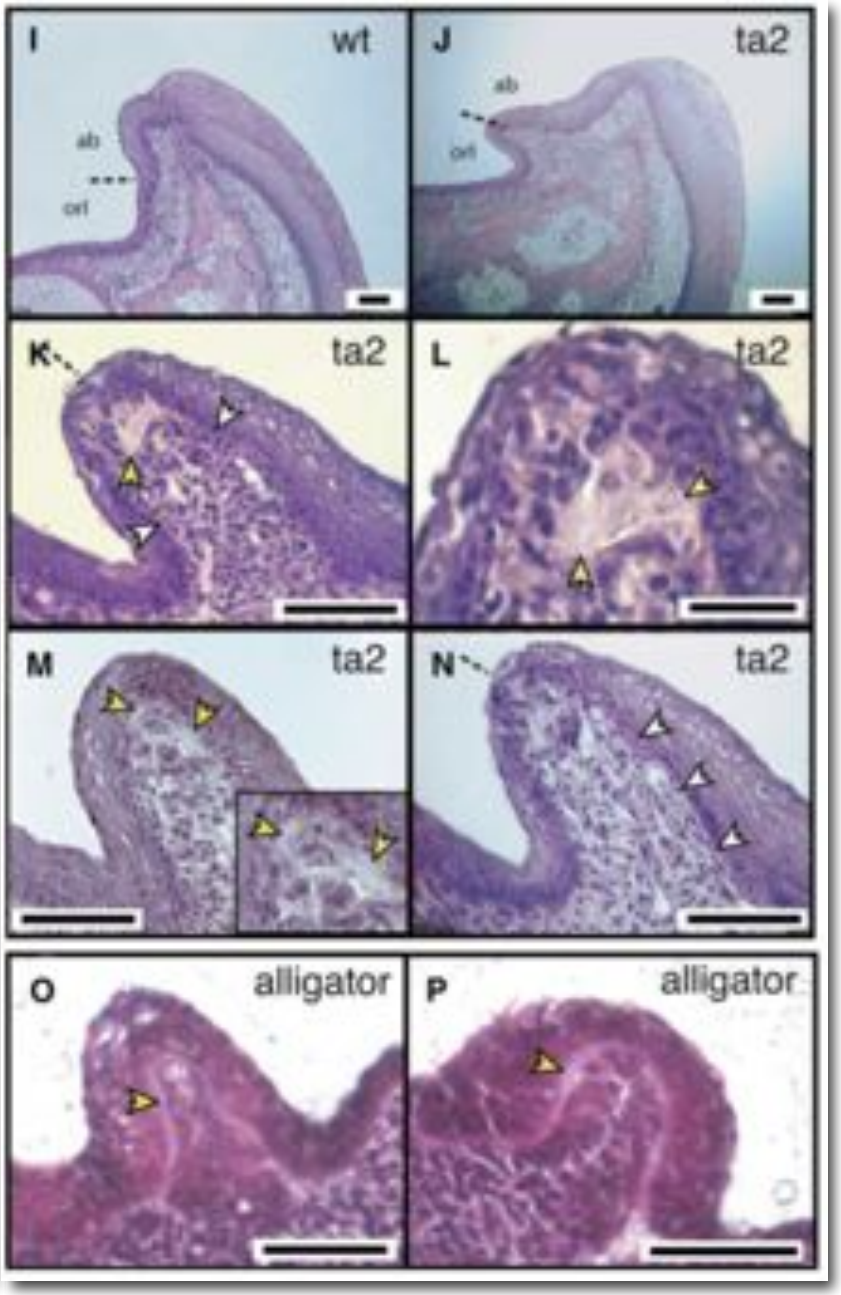
University of Manchester
Manchester M13 9PT
United Kingdom

Summary

Modern birds do not have teeth. Rather, they develop a specialized keratinized structure, called the rhamphotheca, that covers the mandible, maxillae, and premaxillae. Although recombination studies have shown that the avian epidermis can respond to tooth-inductive cues from mouse or lizard oral mesenchyme and participate in tooth formation [1, 2], attempts to initiate tooth development de novo in birds have failed. Here, we describe the formation of teeth in the *talpid*^{2} chicken mutant, including the developmental processes and early molecular changes associated with the formation of teeth. Additionally, we show recapitulation of the early events seen in *talpid*^{2} after in vivo activation of *β-catenin* in wild-type embryos. We compare the formation of teeth in the *talpid*^{2} mutant with that in the alligator and show the formation of decidedly archosaurian (crocodilian) first-generation teeth in an avian embryo. The formation of teeth in the mutant is coupled with alterations in the specification of the oral/aboral boundary of the jaw. We propose an epigenetic model of the developmental modification of dentition in avian evolution; in this model, changes in the relative position of a lateral signaling center over competent odontogenic mesenchyme led to loss of teeth in avians while maintaining tooth developmental potential.



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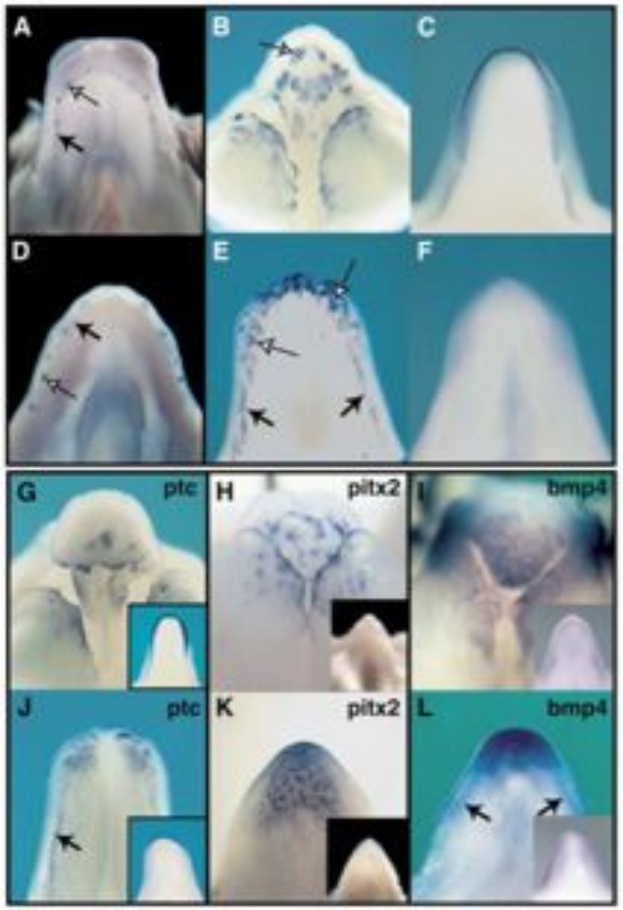

Figure 2. Tooth Developmental Pathways Are Initiated in *ta*^{2}

(A–C and G–I) Ventral view of the upper jaw.

(D–F and J–L) Dorsal view of the associated lower jaw.

(A and D) *shh* expression in developing first-generation teeth of a s20 [40] alligator embryo (white arrows). *shh* expression also marks a linear domain between forming tooth primordia thought to be the location of dental lamina formation (black arrows).

(B, C, E, and F) *shh* expression in the oral cavity of E10 *ta*^{2} mutant (B and E) and its absence in wild-type siblings (C and F) are shown. *ta*^{2} mutants show punctate, circular placodes on the maxillae and mandible (white arrows, [B and E]), and a similar linear expression domain along the aboral boundary is seen as in the alligator ([A and D], black arrows).

(G–L) WMISH analysis of *ptc* (E10, [G and J]), *pitx2* (E8, [H and K]), and *bmp4* (E8, [I and L]) in the *ta*^{2} mutant compared with age-matched wild-type siblings (inserts).

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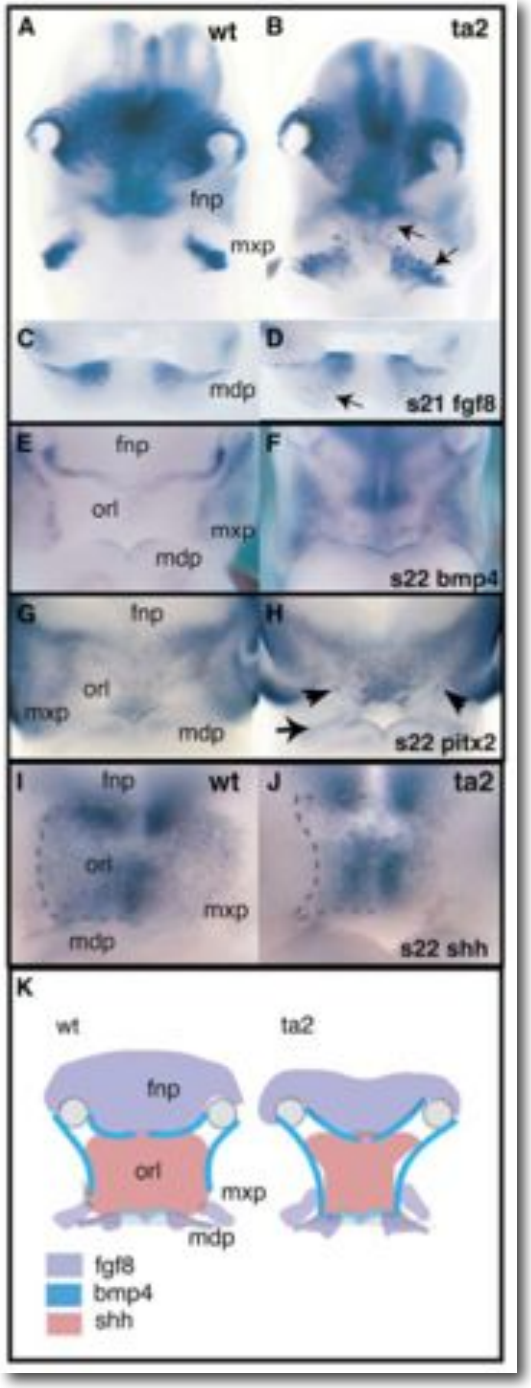
Manchester M13 9PT
United Kingdom

Developmental Potential of the Oral/Aboral Epidermis

As shown in recombination studies, the avian ectoderm and mesenchyme both have potential to participate in tooth development. Given the association of the observed outgrowths and the novel position of the oral/aboral boundary in the mutant, we postulated that initiation of tooth programs in the *ta*^{2} chick was due to the developmental repositioning of an epithelium with signaling potential to overlie mesenchyme competent to form teeth.



Development 133, 3127-3137 (2006) doi:10.1242/dev.02459

Developmental genetic mechanisms of evolutionary tooth loss in cypriniform fishes

David W. Stock*, William R. Jackman and Josh Trapani†

The fossil record i… …ion years ago. Despite subsequent divers… …h as a model for studying the deve… …form tooth loss, we compared the ora… …the zebrafish and the Mexican tetra, *As*… …found was an absence in zebrafish oral e… …*Astyanax* odontogenic epithelium. Analy… …*multipunctatus*) suggests that exp… …n an inhibitor of Fibroblast growth… …l teeth, and expression of *dlx2*… …sh oral epithelium, were unaffected. …rm tooth loss.

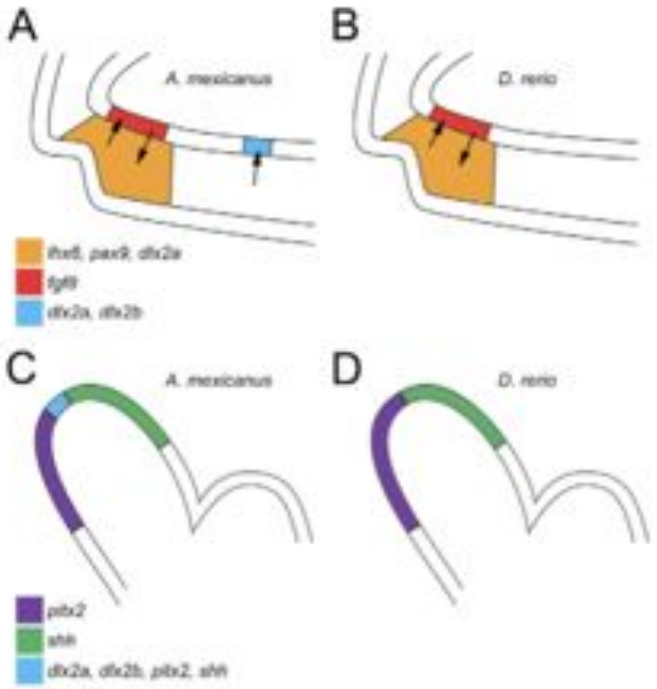
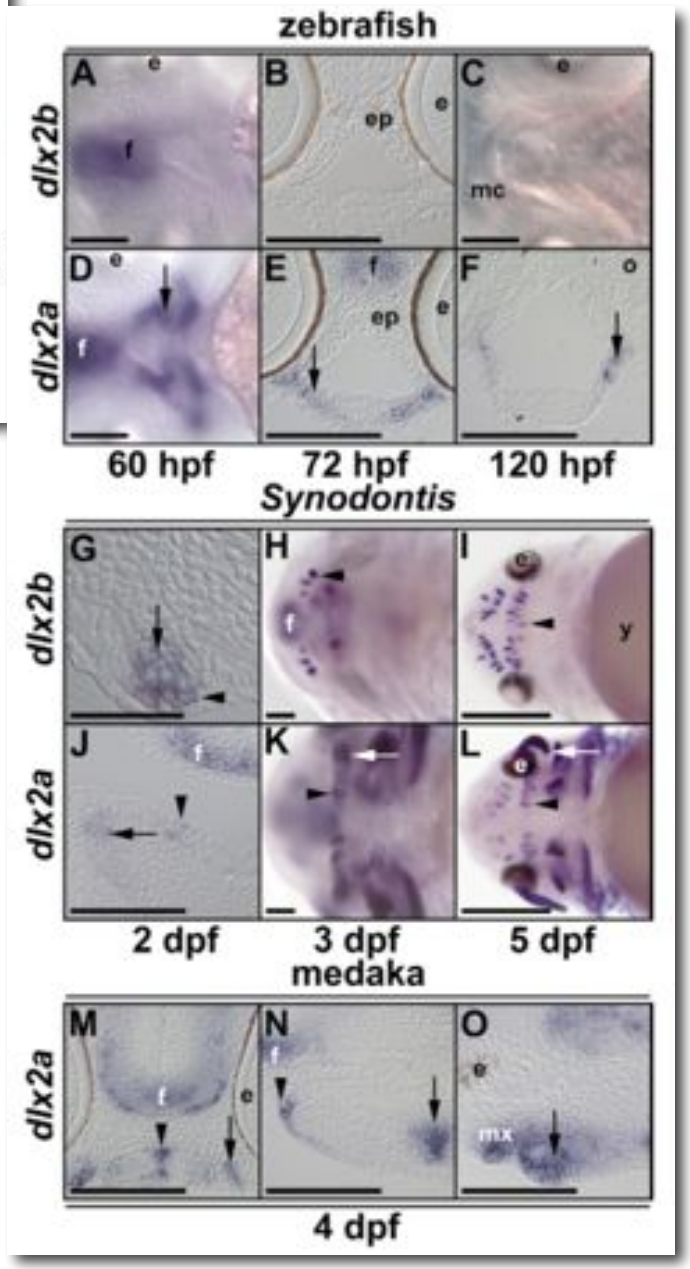
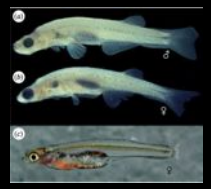


Fig. 8. Comparison of gene expression and hypothesized Fgf signals (arrows) between *Astyanax* and the zebrafish. (**A**,**B**) Transverse views of the left side of the mandible. Lateral epithelial and mesenchymal gene expression common to both species is Fgf dependent. Loss of a medial Fgf signal to the epithelium is hypothesized to have caused cypriniform tooth loss. See text for basis of hypothesized ligand sources. (**C**,**D**) Lateral views of selected features of mandibular epithelial expression. *pitx2* and *shh* expression common to both species is Fgf independent. The zebrafish may lack a domain of overlapping *pitx2* and *shh* expression corresponding to a tooth germ (marked by *dlx2a* and *dlx2b* expression in *Astyanax*).



Modularita, „ontogenetická paměť“ a re-evoluce komplexních znaků



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Spectacular morphological novelty in a miniature cyprinid fish, *Danionella dracula* n. sp.

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Danionella dracula is a new species of sexually dimorphic, miniature and highly developmentally truncated cyprinid fish. Compared with its close relative, the zebrafish *Danio rerio*, it lacks 44 bones or parts thereof and represents one of the most developmentally truncated vertebrates. Absence of the majority of bones appears to be due to developmental truncation via terminal deletion. In contrast to these larval-like features, *D. dracula* also shows several hyperossifications. Uniquely, among carp-like fishes, male *D. dracula* have a series of long, pointed odontoid processes on the jaws greatly resembling the jaw dentition of teleosts with true teeth. The anterior-most process in each jaw is extended as a canine-like fang projecting through the epithelium. True jaw teeth are absent from all 3700 species of cypriniforms and were lost at least in the Upper Eocene. It remains to be investigated, however, whether the conserved pathways to regulate tooth development in cypriniforms have been used in *D. dracula* to form and pattern the odontoid processes. This new species represents a remarkable example linking progenetic paedomorphosis via heterochronic change in developmental timing to the evolution of morphological novelties.

Keywords: *Danionella*; Cypriniformes; jaw teeth; miniaturization; developmental truncation; evolutionary novelty