Obecná a srovnávací odontologie

And now something completely different

Vývojové souvislosti 1:

vznik a vývoj zubu jako produkt genetických regulačních kaskád, odontogenní regulační kód

Vývojové souvislosti 1:

vznik a vývoj zubu jako produkt genetických regulačních kaskád, odontogenní regulační kód

plakody jako signalizační centrum odontogeneze, evoluční ztráty a případné znovuzískání zubů

dentální lamina a paternování zubů

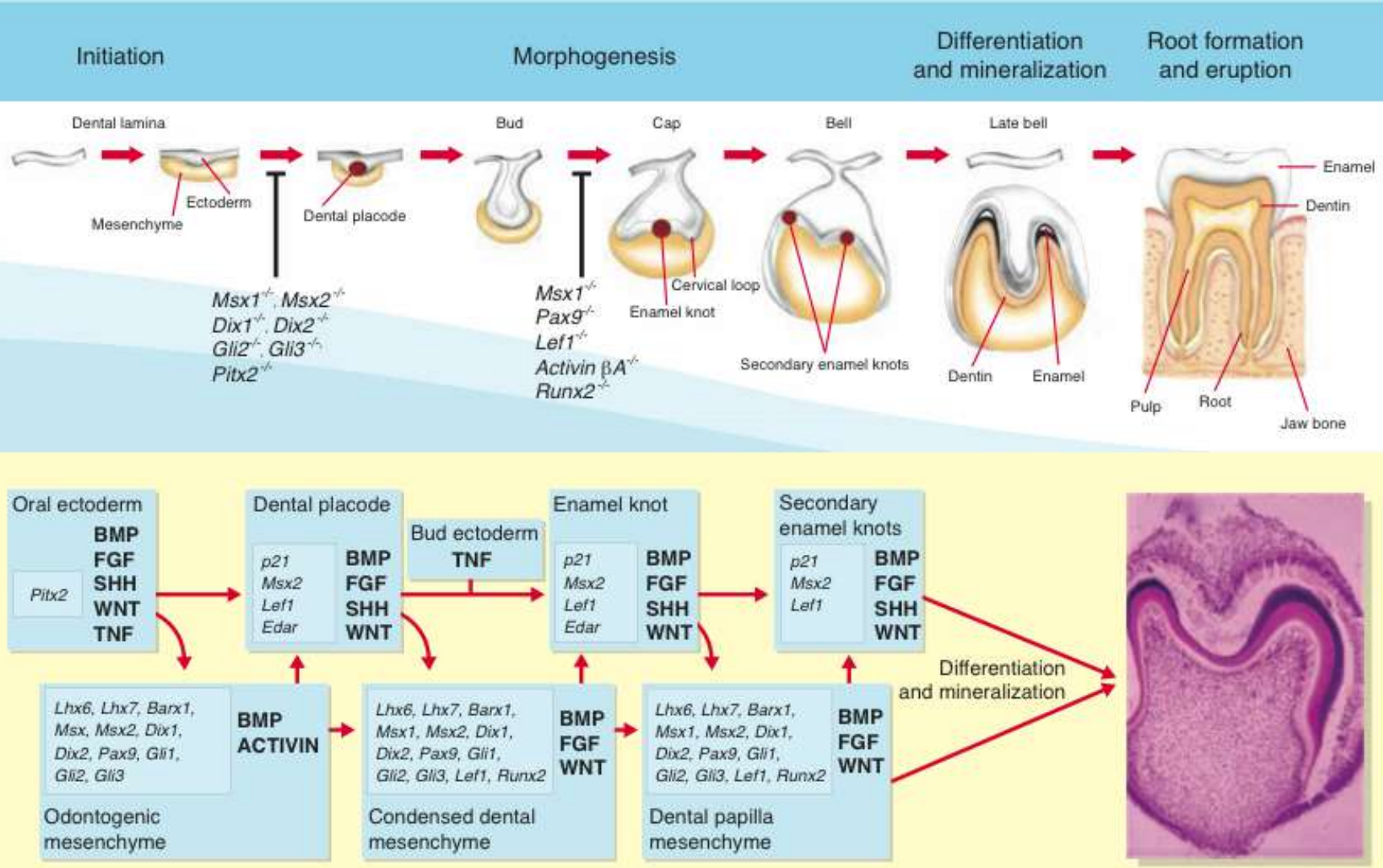
zubní epitel vs. mesenchym v zubním vývoje i evoluci

odontoda; zuby 1. a 2. typu; systematická část

Journal of Cell Science

Signalling In Tooth Development

Irma Thesleff

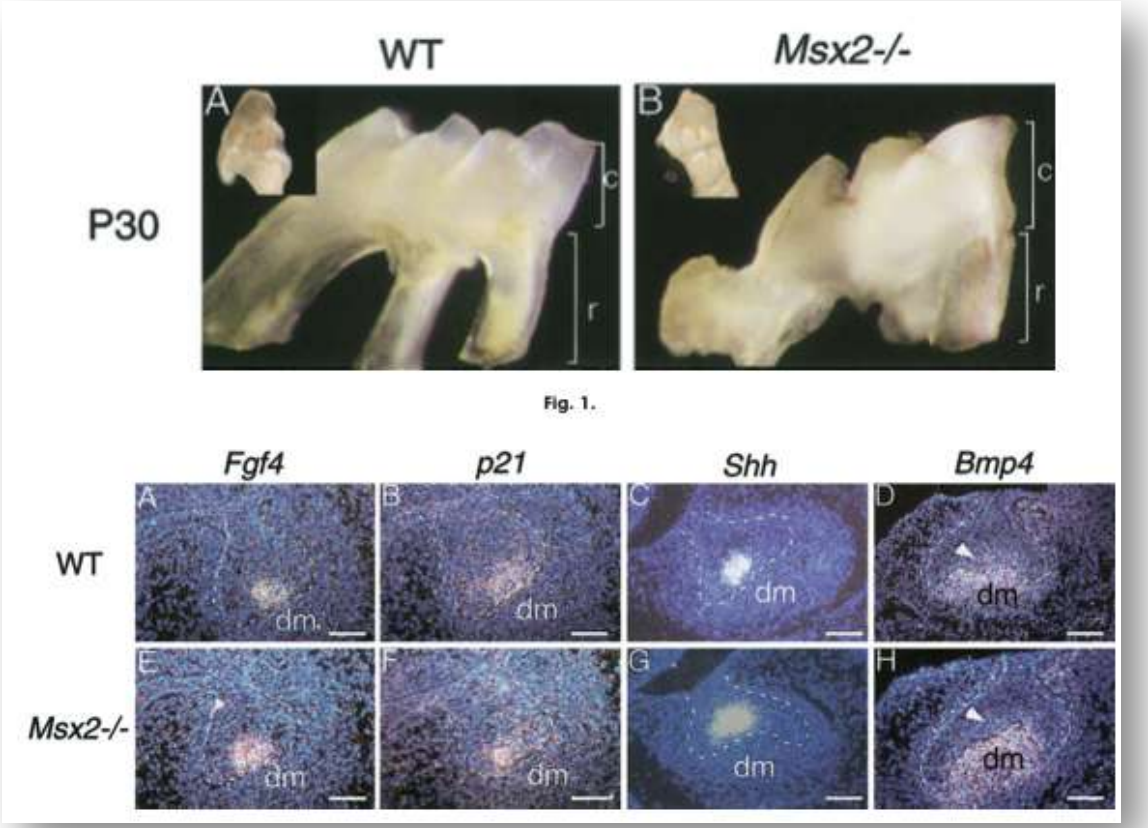


- transkripční faktory
- double-mutant; null-mutant; null-mice (*Pax9* null mice)

molekulární informace:

- exprese (přítomnost) proteinu – **BMP2**
- exprese (aktivita) genu, resp. mRNA - ***Shh***
- funkční data: down-regulace (odstřelení) konkrétní signalizace
  (*Msx2*$^{-/-}$ = *Msx2* null mice)

obr. myší farma ☺



Genes and pathways involved in regulation of tooth development

Four major signaling pathways and their inhibitors control tooth formation: a fine balance that determines number and patterning

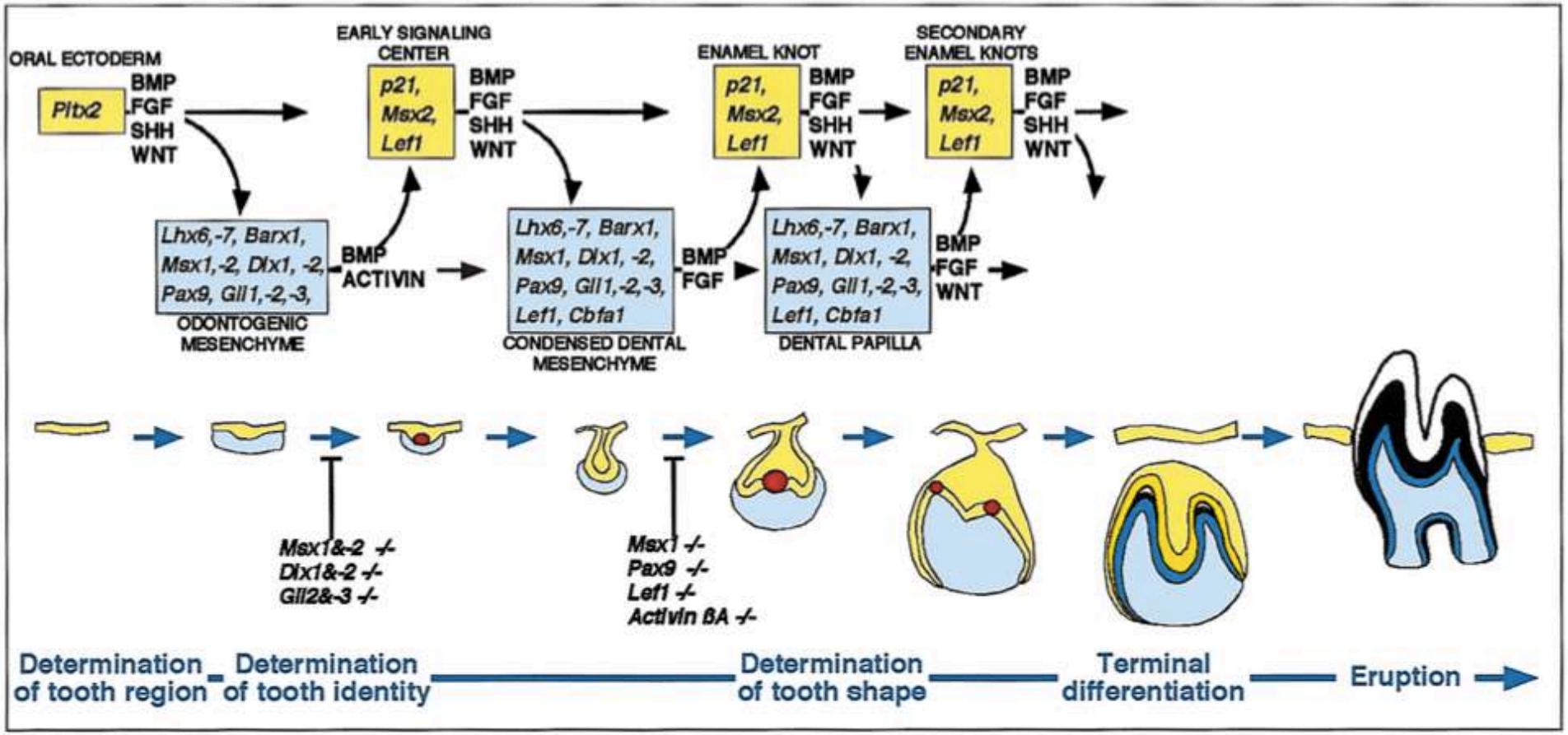


Fig. 2. Schematic representation of the signals and transcription factors mediating the reciprocal signaling between epithelium and mesenchyme during advancing tooth development. The molecular cascades are shown above and the corresponding morphological stages below. The transcription factors and signals considered to be important for particular developmental stages are indicated in the squares and above the arrows, respectively. Note how the same signaling pathways are used reiteratively during advancing tooth development, and how tooth development arrests in the knockout mouse experiments to the early signaling center or the enamel knot stage. Yellow, tooth epithelium; red, enamel knots; blue, tooth mesenchyme.

Genes and pathways involved in regulation of tooth development

Four major signaling pathways and their inhibitors control tooth formation: a fine balance that determines number and patterning

- **Hedgehog family:** sonic hedgehog (SHH); IHH, DHH
- **BMPs:** Bone Morphogenetic Proteins
- **FGFs:** Fibroblast Growth Factor
- **Wnts:** Wg (wingless); Int: (integration sites…)

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

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

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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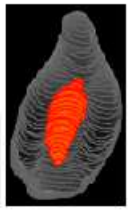

Gene expression in epithelium

	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)		-	-	+		+
ameloblastin (rat,mouse, mRNA)					+	+
amelogenin (mouse, mRNA)				-	-	+
amelogenin (hamster, protein)		-	-	-	+	+
amelogenin (hamster, mRNA)		-	-	+	+	+
amelogenin (mouse, protein)					+	+
amelogenin and enamelin (rat, protein)					+	+
ameloprotease-I (pig, protein)						+
antizyme 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)			-	-	-	
Arnt (mouse, protein)		+	+			+
Axin1 (mouse, mRNA)	+	+	+	+	+	
Axin2 (mouse, mRNA)	-	+	+	-	-	
Barx1 (mouse, mRNA)	-	-	-	-		
Bax (rat, protein)					+	+
Bcl2 (rat, protein)					+	+
BEN/DM-GRASP/SC1 (mouse, mRNA)	-	-	+	-		
biglycan (mouse, mRNA)					-	-
Bmp2 (bovine, mRNA)				+		
Bmp2 (vnln, diastema bud, mRNA)		+				

Gene expression in tooth

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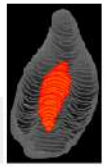
Gene expression in tooth

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



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Outer enamel epithelium
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Dental sac
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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

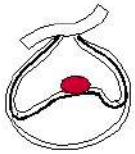
Shh; Dsh; Hhg1; short digits

Species: mouse
Location in mouse genome: chromosome 5, 26707815 - 26718063 (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



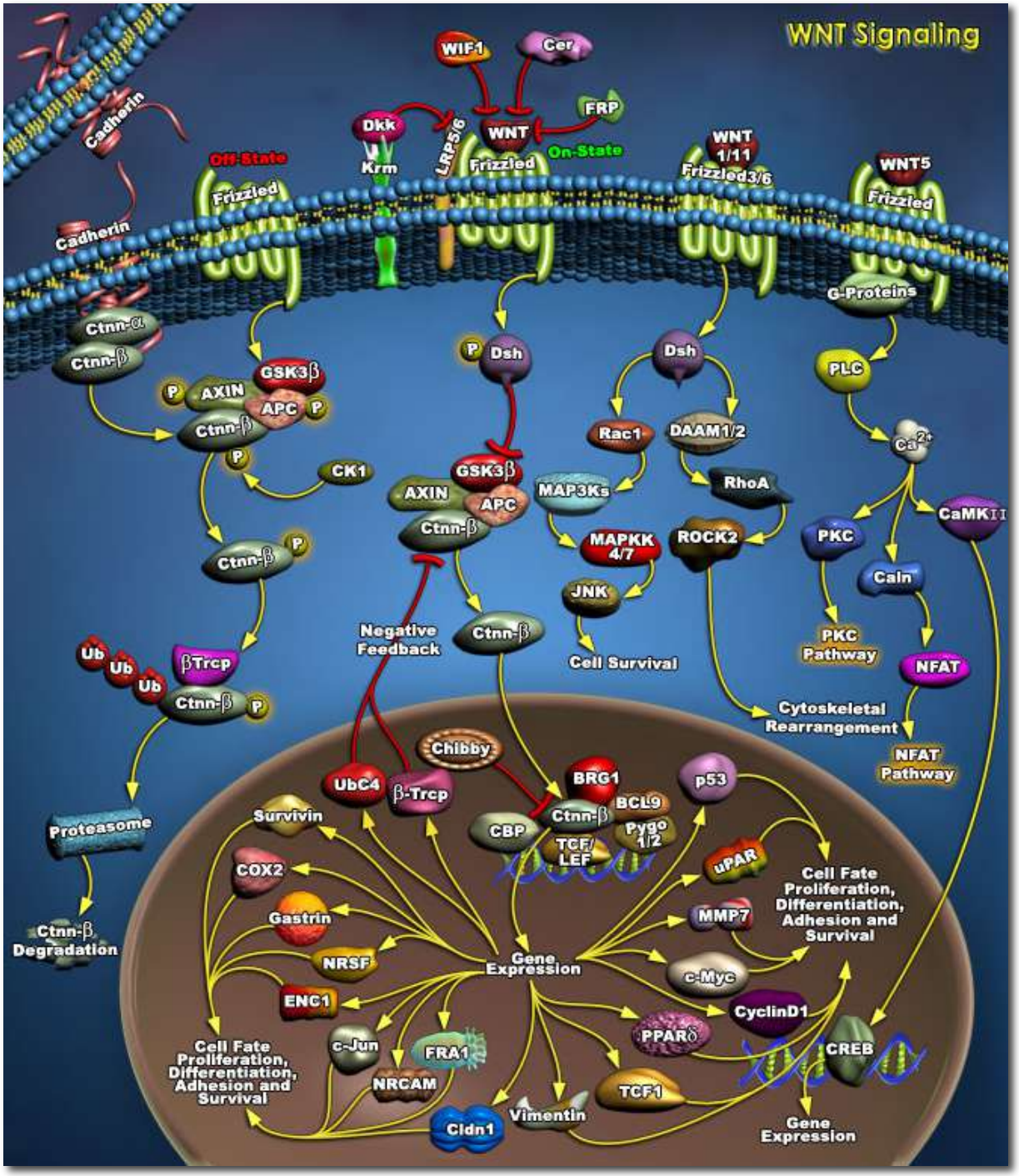
Expression: enamel knot
No expression: oral epithelium, outer enamel epithelium, inner enamel epithelium, stellate reticulum, dental papilla, dental sac

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.

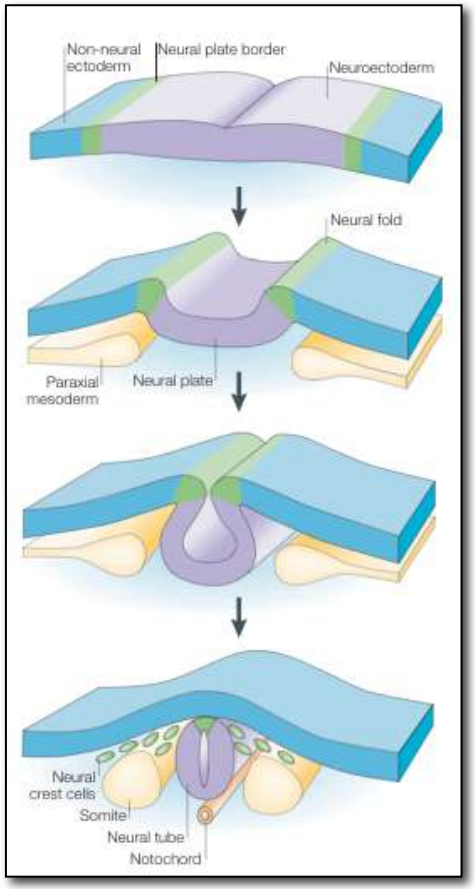
Bell stage

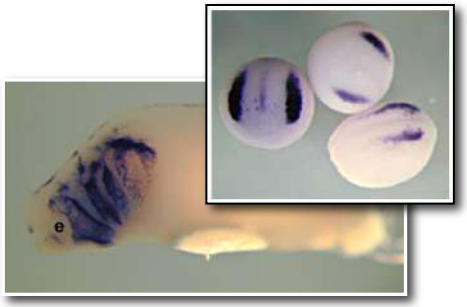
Expression: inner enamel epithelium
No expression: oral epithelium, outer enamel epithelium, stratum intermedia, stellate reticulum, dental papilla, dental sac

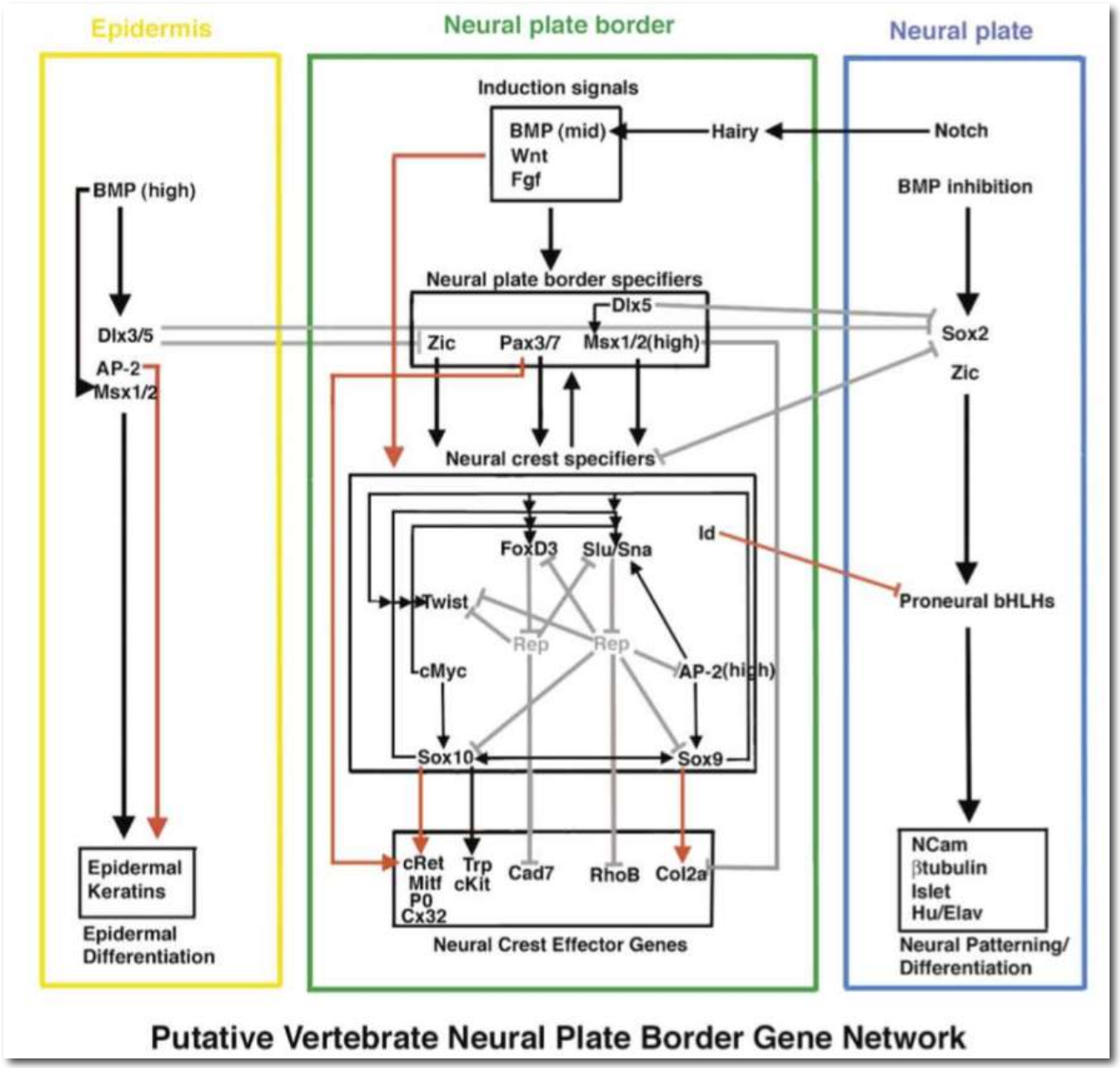
...obrovské množství molekulární signalizace: její "specificita"?


WNT Signaling
WIF1
Cer
FRP
Dkk
Krm
LRP5/6
WNT
On-State
Off-State
Frizzled
WNT 1/11
Frizzled3/6
WNT5
Frizzled
Cadherin
Cadherin
G-Proteins
Ctnn-α
Ctnn-β
GSK3β
AXIN
APC
Ctnn-β
CK1
Ctnn-β
Ub
Ub
Ub
βTrcp
Ctnn-β
Proteasome
Ctnn-β Degradation
P
Dsh
GSK3β
AXIN
APC
Ctnn-β
Negative Feedback
Ctnn-β
Dsh
Rac1
DAAM1/2
MAP3Ks
RhoA
MAPKK 4/7
ROCK2
JNK
Cell Survival
Cytoskeletal Rearrangement
PLC
Ca2+
PKC
CaMKII
Caln
PKC Pathway
NFAT
NFAT Pathway
Chibby
UbC4
β-Trcp
BRG1
BCL9
Ctnn-β
CBP
Pygo 1/2
TCF/ LEF
p53
Survivin
COX2
Gastrin
NRSF
ENC1
c-Jun
FRA1
NRCAM
Cldn1
Vimentin
Gene Expression
uPAR
MMP7
c-Myc
CyclinD1
PPARδ
TCF1
CREB
Cell Fate Proliferation, Differentiation, Adhesion and Survival
Cell Fate Proliferation, Differentiation, Adhesion and Survival
Gene Expression

Geny "nefungují" samostatně, ale v zapojení do genetických regulačních sítí/kaskád (GRNs); **není "gen pro"!**







O hlubinné kontinuitě informace, patrnosti a nastavení modulů vývoje a evoluce: DPM (dynamical patterning modules)

DPM	Characteristic molecules	Physical principle	Morphogenetic Role
ADH	cadherins	adhesion	multicellularity
DAD	cadherins	differential adhesion	tissue multilayering
LAT	Notch	lateral inhibition	coexistence of alternative cell types
POLa	Wnt	cell surface anisotropy	lumen formation
POLp	Wnt	cell shape anisotropy	tissue elongation
OSC	Wnt + Notch	synchronized biochemical oscillation	morphogenetic fields; segmentation
MOR	TGF-β/BMP; Hh	diffusion	pattern formation
ASM	FGFs	diffusion	induction
TUR	MOR + Wnt + Notch	chemical waves	periodic patterning
ECM	collagen; chitin; fibronectin	stiffness; dispersal + cohesion	epithelial elasticity; skeletogenesis; epithelial-mesenchymal transformation

Table 1: Names, components and roles of major Dynamical Patterning Modules (DPMs)

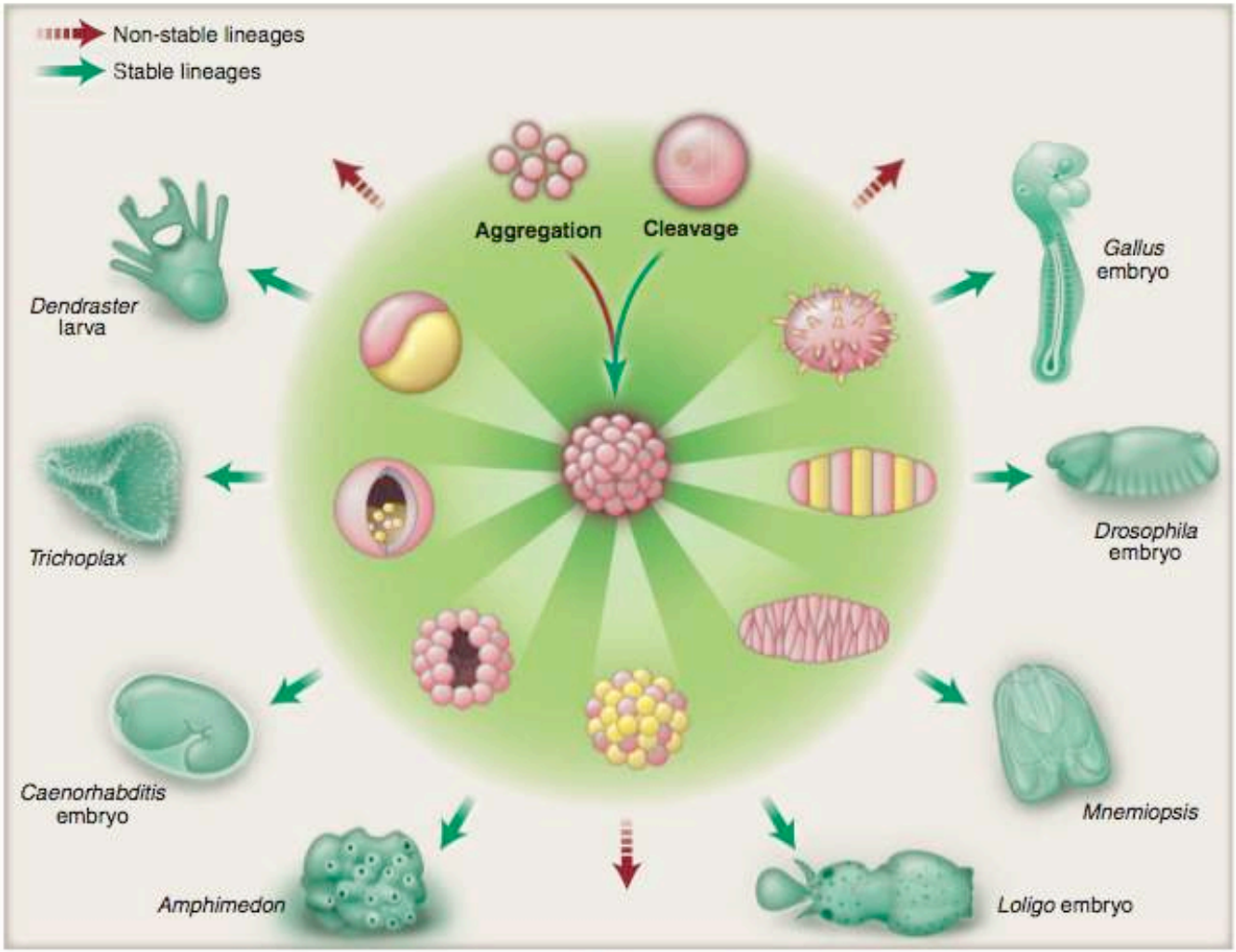


Fig. 1. A core set of physico-genetic modules underlies the morphological evolution of animals. Multicellular entities (center image) were formed by the aggregation of unicellular organisms (red curved arrow) or the cleavage of enlaged cells ["proto-eggs" (*26*) or eventually fertilized eggs] (green curved arrow). The green inner circle shows morphological motifs generated by some of the key DPMs: physical forces and effects relevant to the multicellular scale, mobilized by certain ancient single-cell gene products and pathways. Emergent motifs include (clockwise from top of inner circle) appendages, segments, elongated bodies and primordia, coexisting alternative cell types, interior cavities, dispersed cells, and multiple layers. Genetically uniform clusters produced stable lineages (straight green arrows), whereas chimeric clusters did not (broken red arrows). Contemporary organisms containing some or all of these motifs are shown in the outer circle. Clockwise from top right: vertebrate (*Gallus*) embryo, arthropod (*Drosophila*) embryo, ctenophore (*Mnemiopsis*), cephalopod (*Loligo*) embryo, demosponge (*Amphimedon*), nematode (*Caenorhabditis*) embryo, placozoan (*Trichoplax*), and echinoderm (*Dendraster*) larva.

Shh: marker epidermální morfogeneze

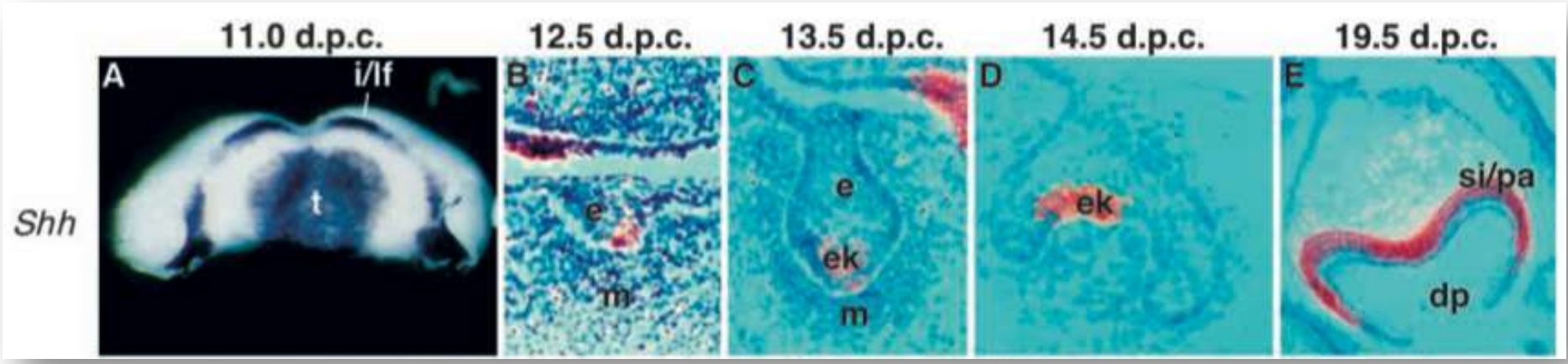
(a odtud *sonic* ☺)

hedgehog: mutantní embrya drosofil byla pokrytá trnitými výrůstky až připomínala ježka (odtud *hedgehog*).

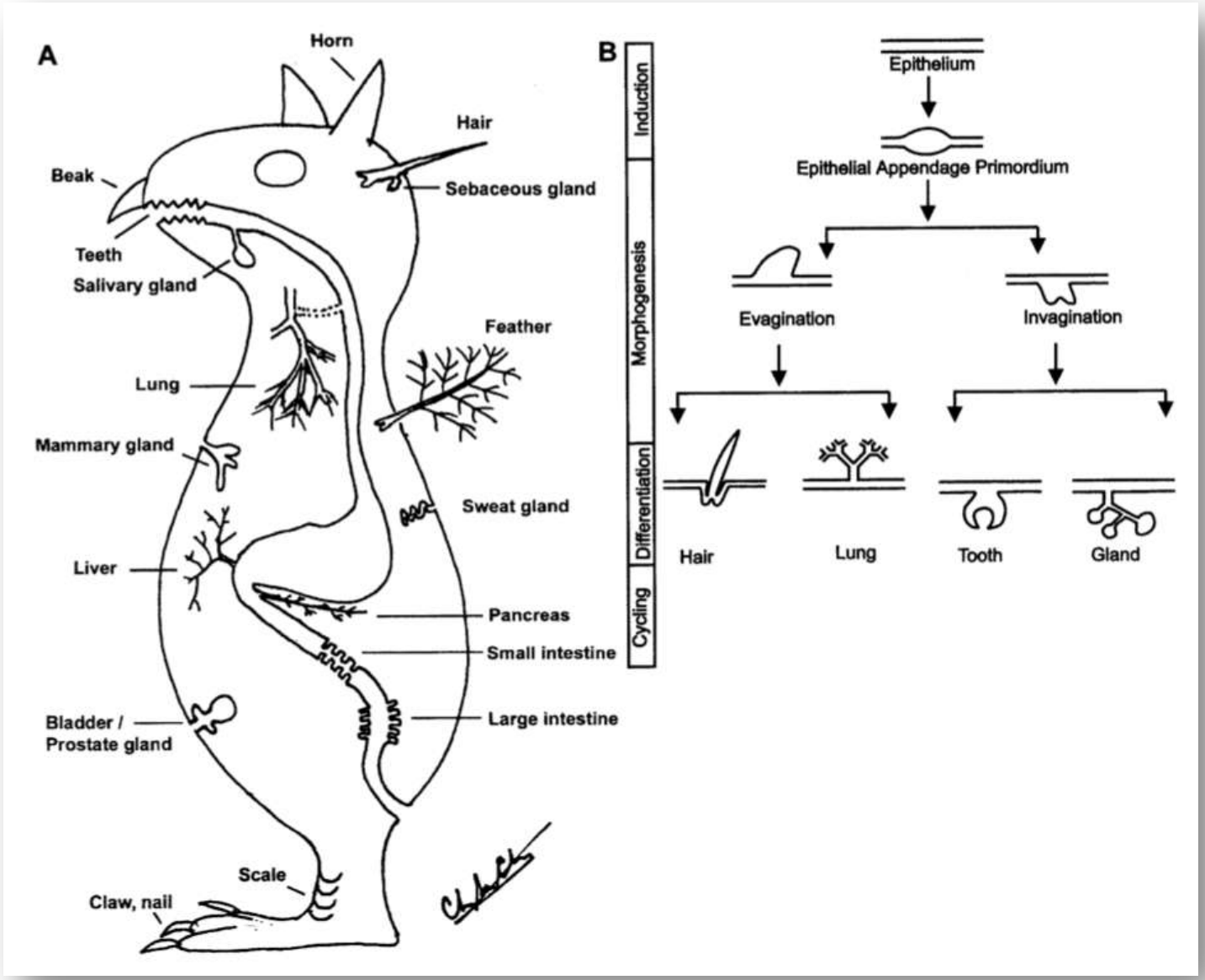
U obratlovců jsou 3 homology (*paralogy*):
Shh, **Ihh** a **Dhh**

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; pozdější: buněčná diferenciace a polarizace vývoje epiteliální části zubu.



Epidermální morfogeneze: ve všech případech morfogenesi/ evaginaci epitelu aktivuje stejný morfogen - *Shh*



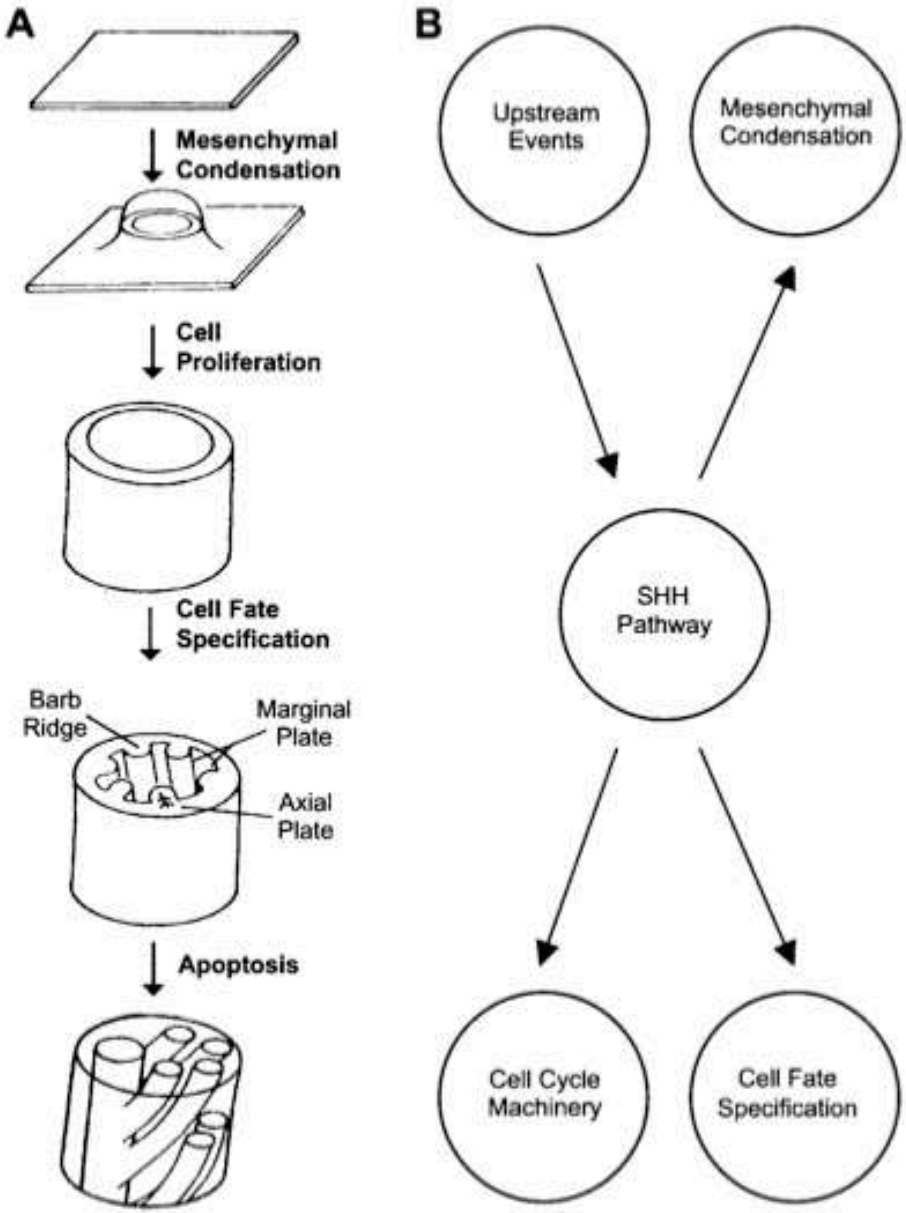
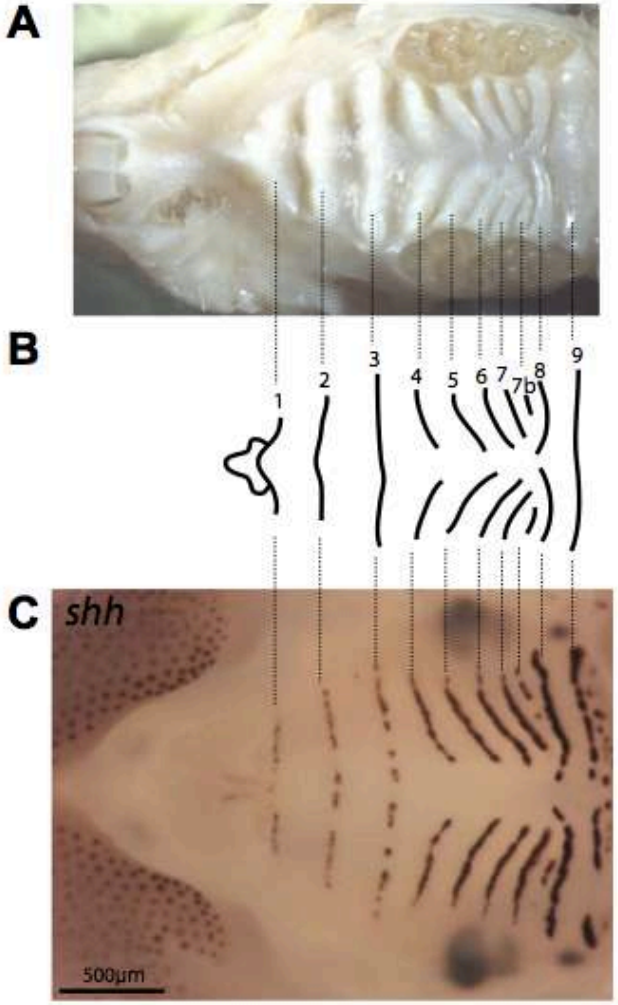
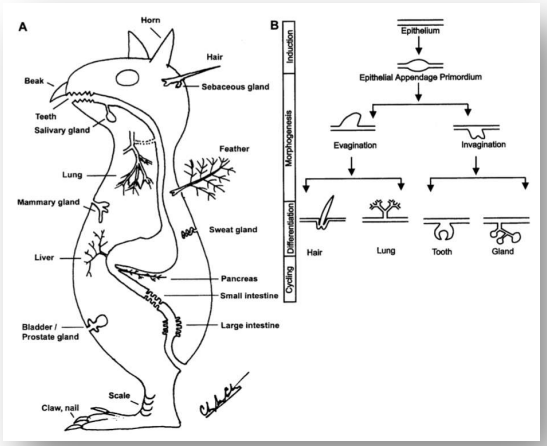


Figure 2. (*A*) Topological transformation of a flat epithelium into three-dimensional feathers. Planar epidermis, short feather buds, elongated feather buds, invaginated feather filament epithelia and the mature branched structure are depicted. Between these stages are morphogenetic processes that transform their morphology. SHH may be involved in mesenchymal condensation, cell proliferation and apoptosis. Another round of apoptosis led to the formation of barbules (not shown). Panel A is adopted from Chuong and Edelman [16, 17]. (*B*) Connection of the SHH pathway with other molecular machineries endow novel morphogenetic activities. SHH is involved in many morphogenetic processes such as size regulation, branching morphogenesis, mesenchymal condensation, fate determination and so on. These are achieved through linking to molecular machineries involved in cell proliferation, apoptosis, migration, differentiation and so on.





Epidermální morfogeneze: Shh je aktivní v zubech i epidermálních patrových lištách

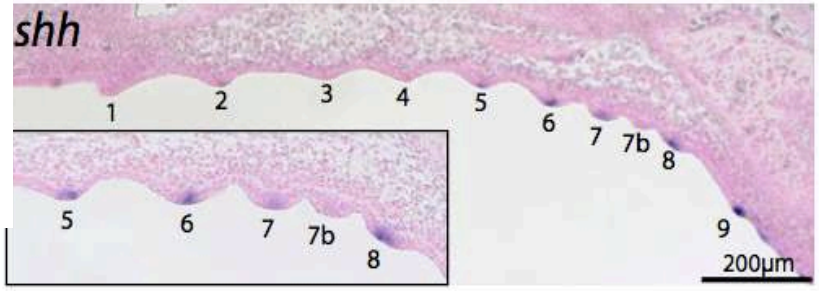
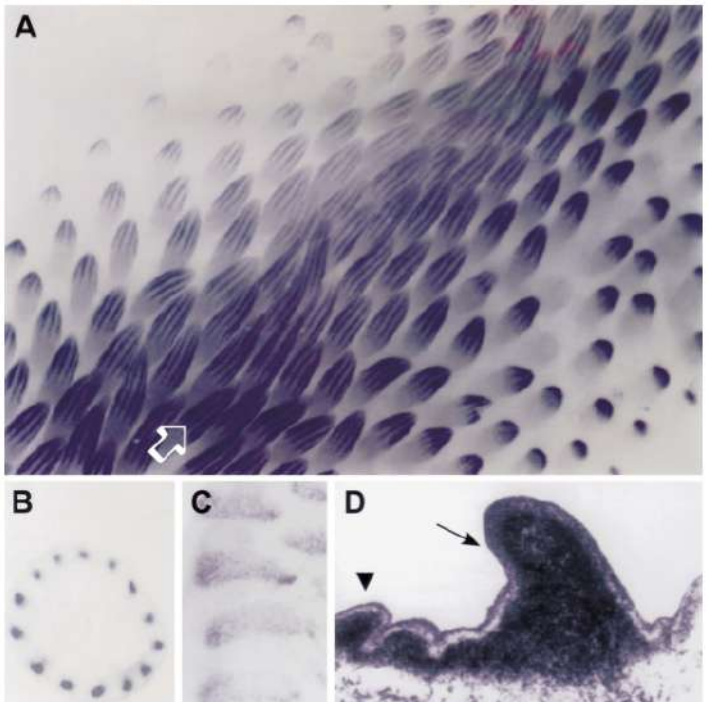


Figure 1
Mouse adult ruga pattern and its visualization in the fetus by *in situ* hybridization against *Shh* gene. (A) The roof of the oral cavity of an adult mouse showing the palatal ridges (*rugae palatinae*) on the hard palate. (B) Mouse rugae pattern with numbering used in this study. Note that ruga 7b was called 8b in other studies (Peterkova et al. 1987; Charles et al. 2007). (C) In ED16.0 fetus, *Shh* gene expression pattern (as seen by whole-mount *in situ* hybridization) prefigures the adult ruga pattern. (D) Sagittal section through the same embryo as in C, showing *Shh* expression in the epithelium at the tip of rugae (see magnification in the low left corner). The absence of *Shh* signal in the rugae 1–4 can be explained by its discontinuity in the anterior rugae at this stage (see C).

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



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.

Shh jako morfogen zakládá *patrnost* opakujících se struktur (zuby, peří, palatální výběžky, ...)

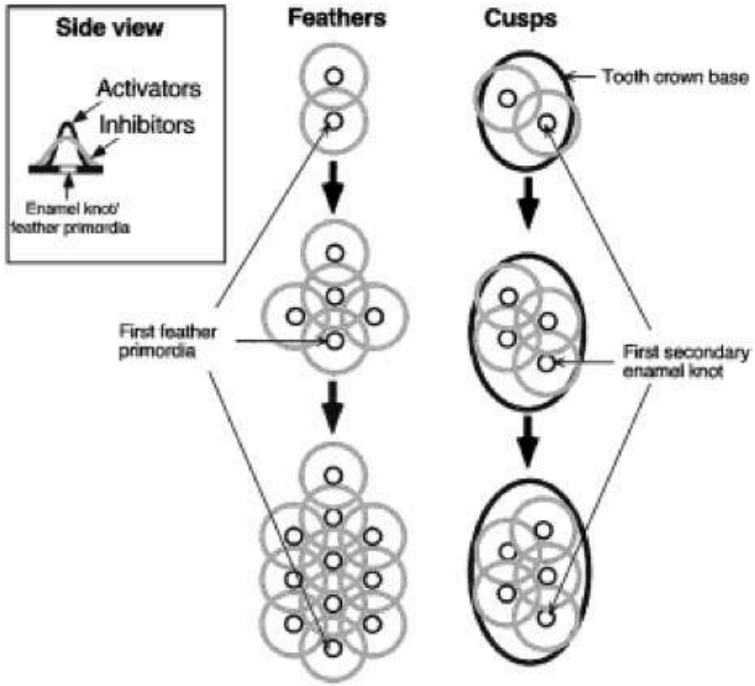


Fig. 5. Feather patterning and cusp patterning have many similarities. Feathers and cusps form as iterations of similar sets of signaling molecules. For example, as a model to regulate patterning, FGF4 functions as an activator promoting cusp/feather bud initiation and growth. Inhibitors such as BMP4, which have a more diffuse expression domain, control the minimal distance between adjacent secondary enamel knots/ feathers. The total number of cusps on a tooth would be limited by the size of the tooth crown base.

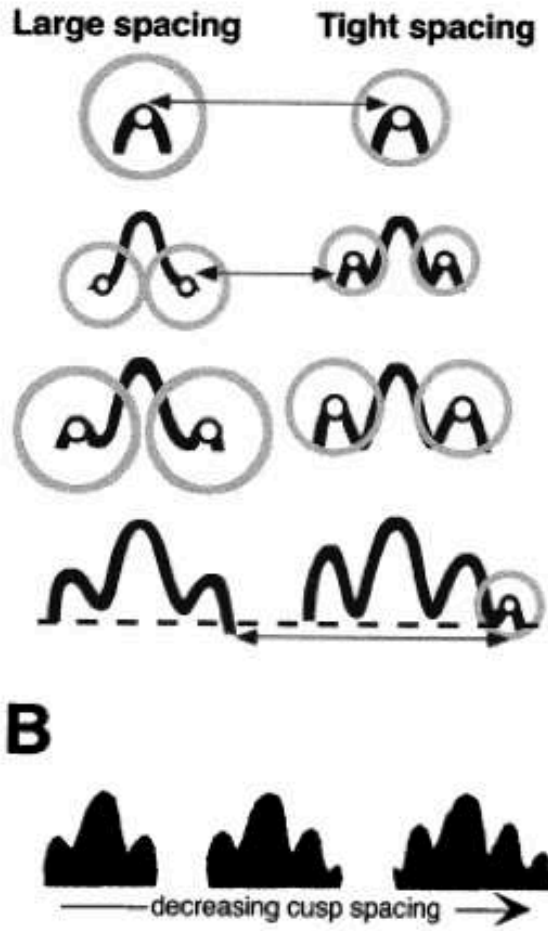
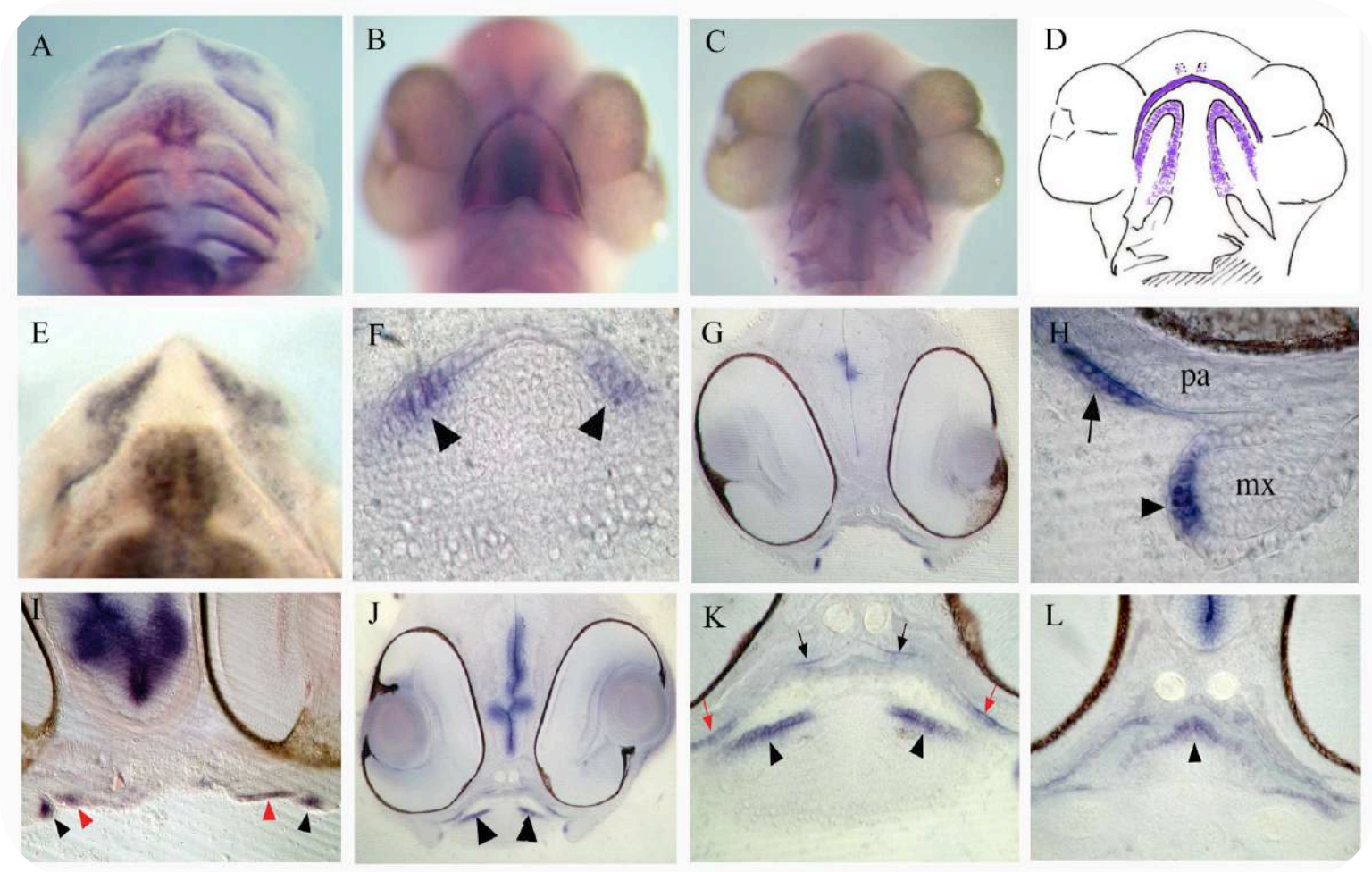


Fig. 6. Patterning cascade mode of cusp development. **A:** Small initial differences in cusp spacing have cumulative effects on later developing cusps. **B:** Only small changes in the spacing of cusps can increase or decrease cusp number and the size of small cusps. The crown height affects the realized cusp numbers globally, while the patterning cascade affects the potential cusp pattern. More complex teeth are likely to have partly independent patterning cascades at different parts of the crown (e.g., paracone-protocone-Carabelli cascade; paracone-metacone cascade).

Dental priming: *Shh* & the odontogenic band



Fraser et al. 2006

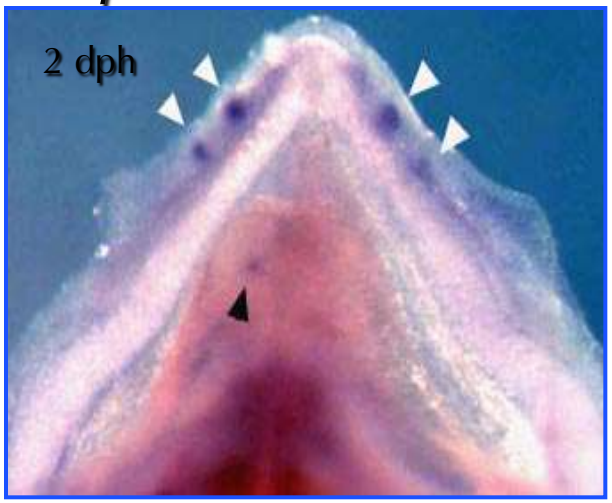
Shh: stage 22-Rainbow Trout (*O. mykiss*)

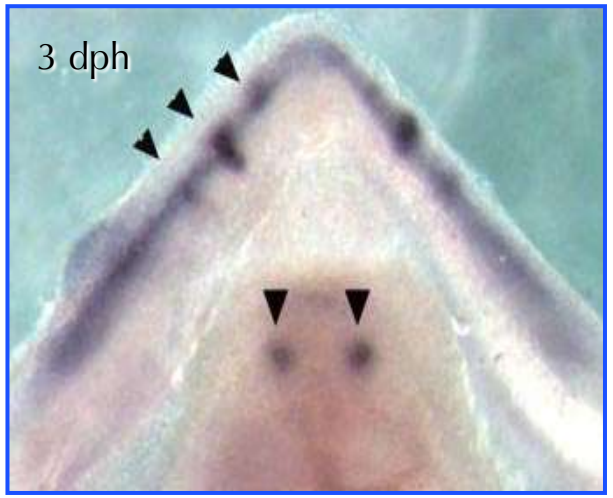
Initiation of teleost Odontogenesis

shh

- **shh** - early dental <u>epithelial</u> marker
- Identifies the odontogenic band
- Upregulation of shh in first tooth buds

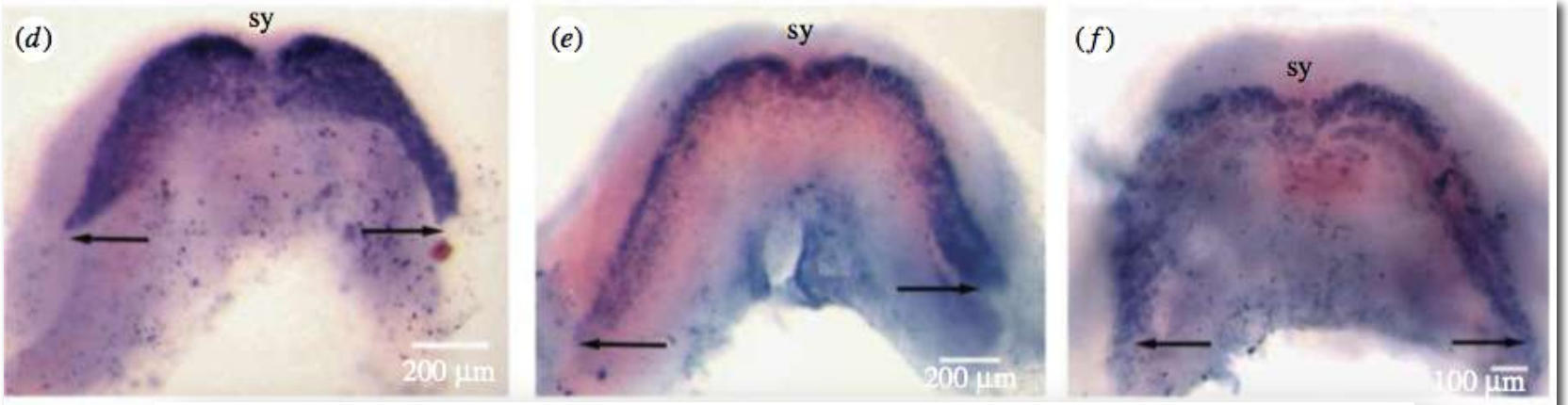
bmp-4





- **bmp-4** dental <u>mesenchyme</u> marker
- Identifies the odontogenic mesenchyme
- Upregulation of bmp-4 in first tooth dental papilla

Fraser et al. 2006



PROCEEDINGS OF THE ROYAL SOCIETY B

Proc. R. Soc. B (2009) **276**, 1225–1233
doi:10.1098/rspb.2008.1526
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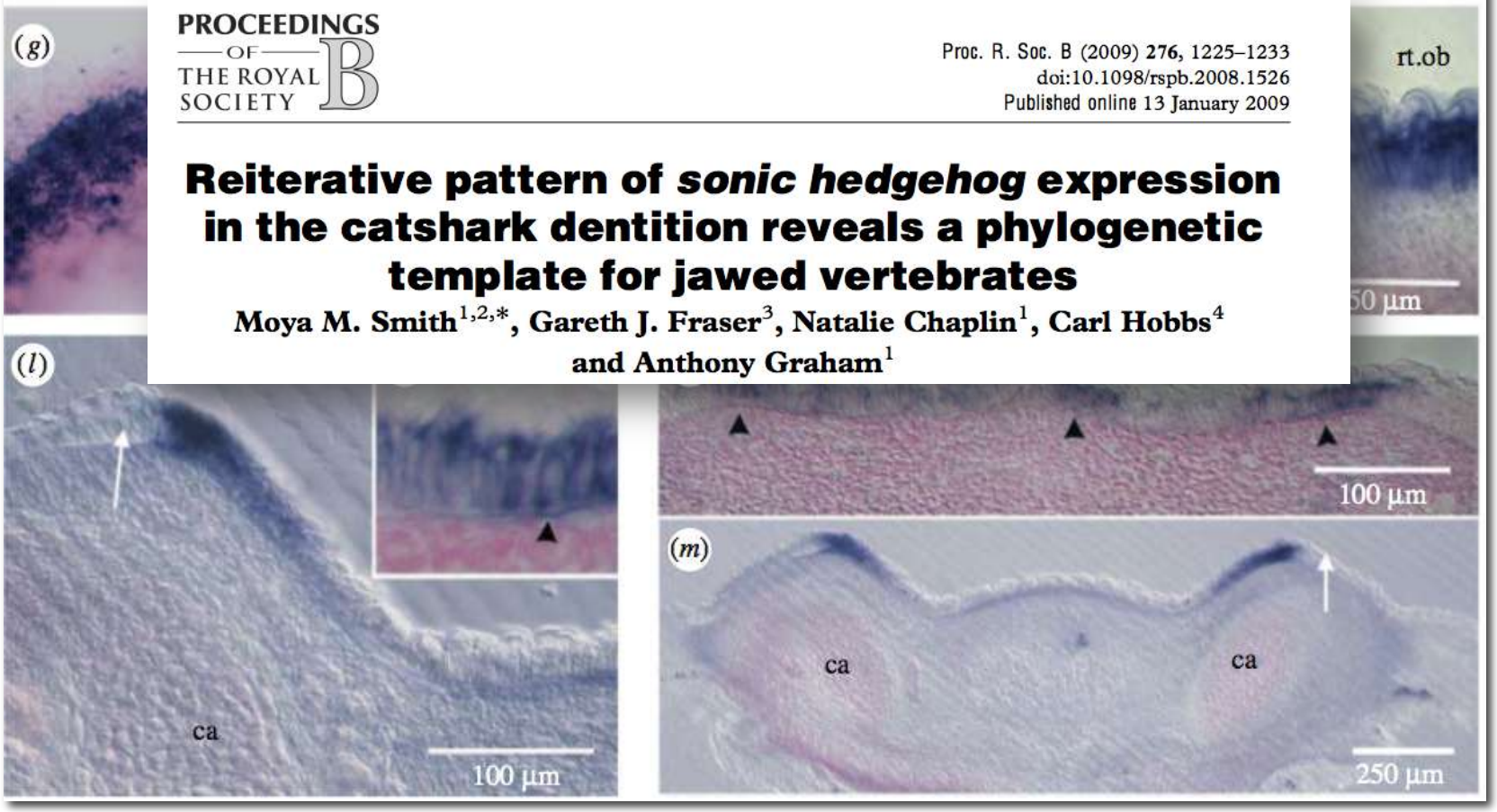
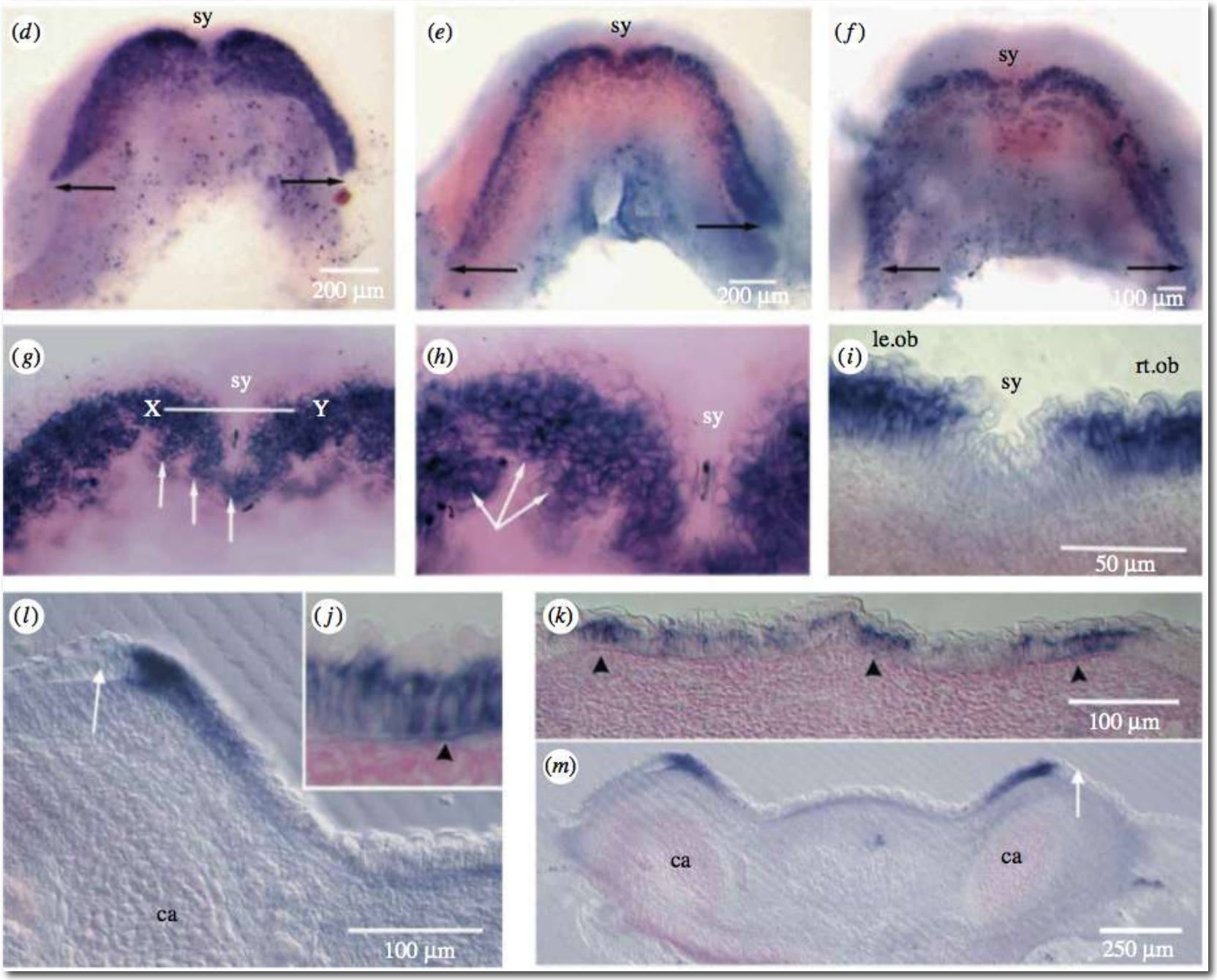
Reiterative pattern of *sonic hedgehog* expression in the catshark dentition reveals a phylogenetic template for jawed vertebrates

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

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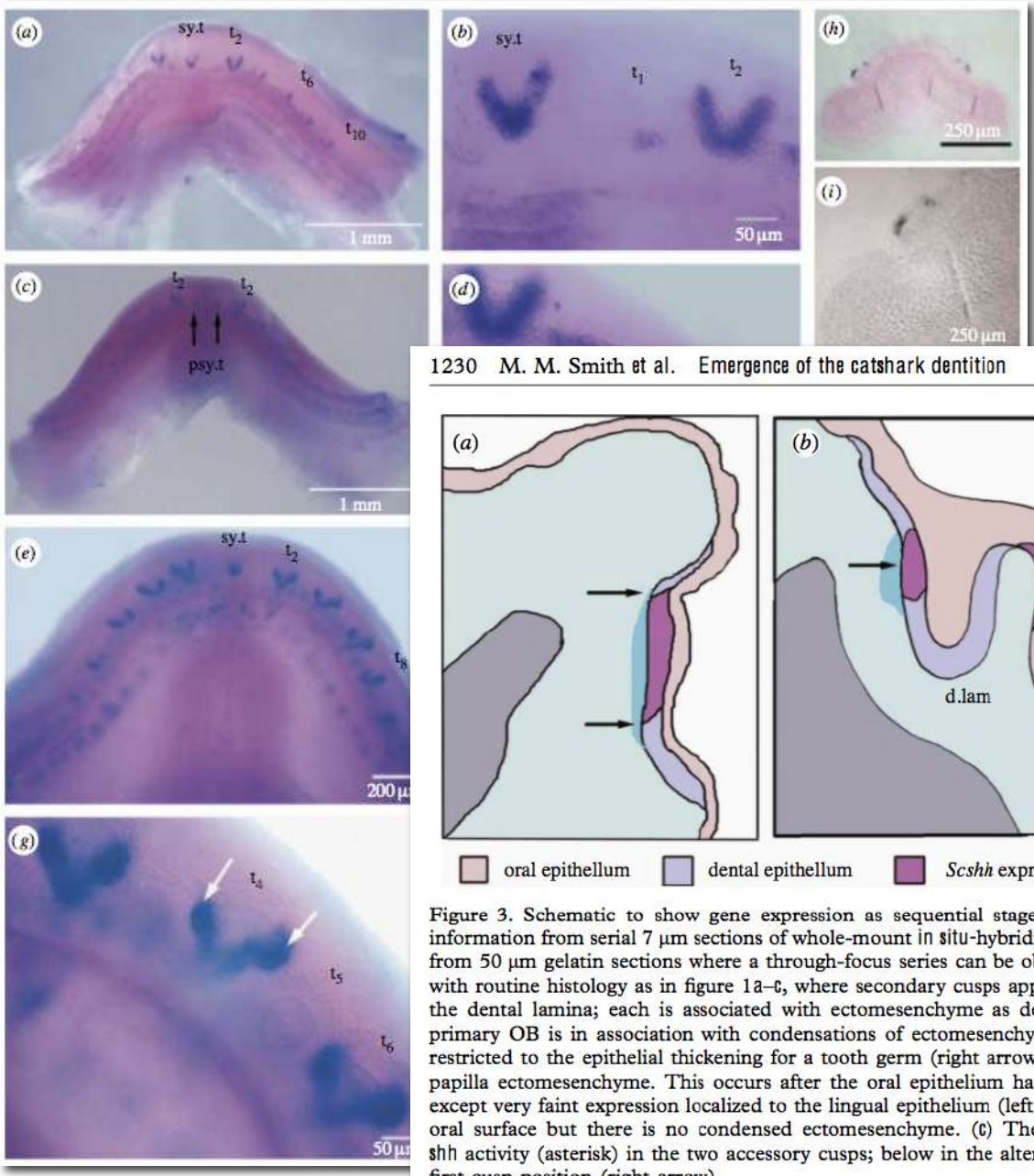
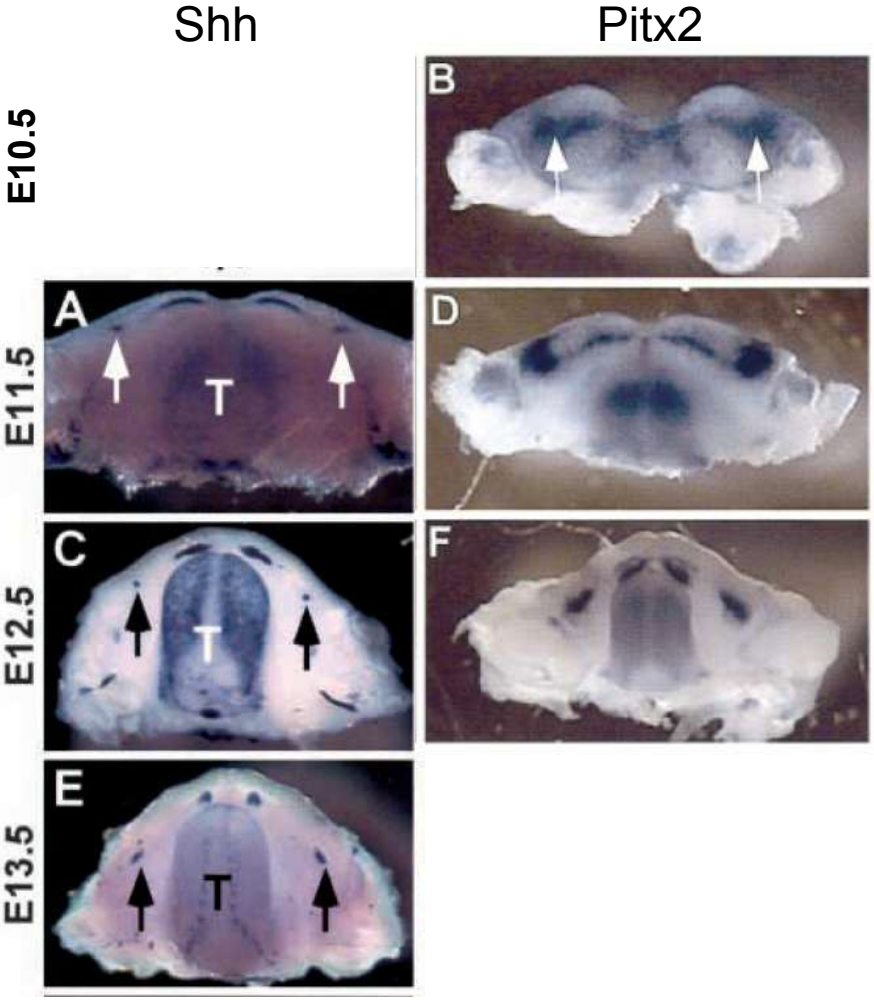
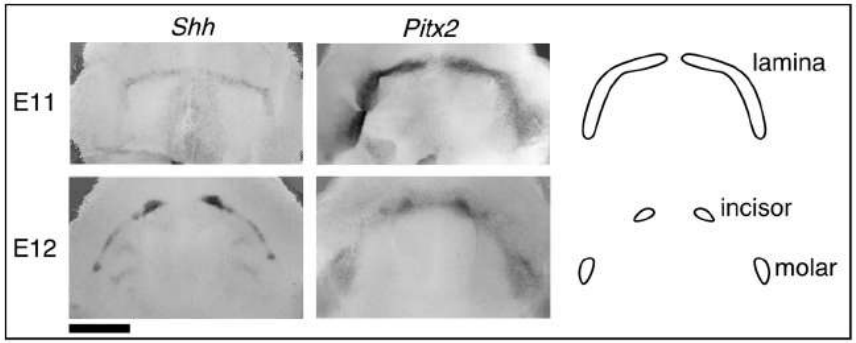


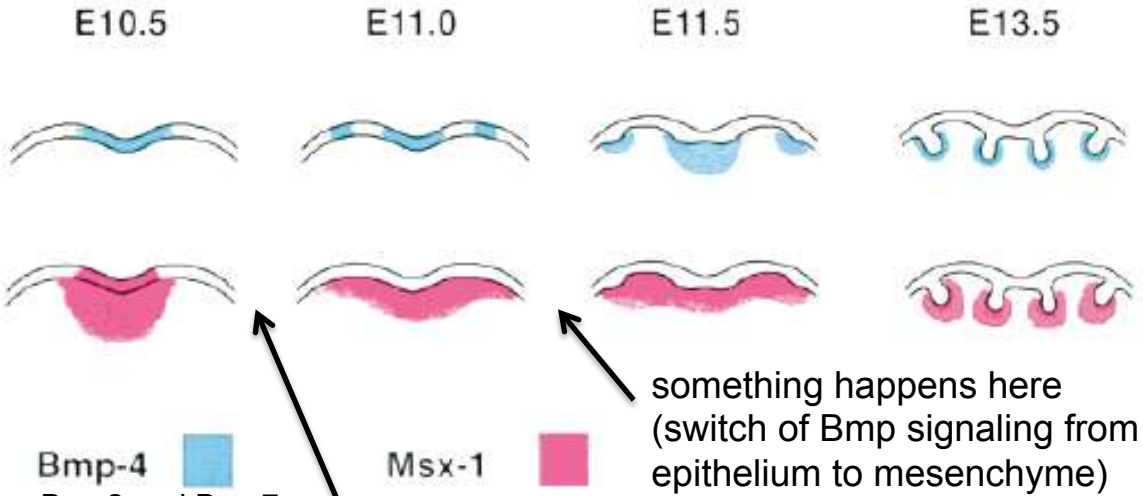
Figure 3. Schematic to show gene expression as sequential stages of odontogenesis. These are derived from composite information from serial 7 µm sections of whole-mount in situ-hybridized shh expression at several tooth sites along the jaw and from 50 µm gelatin sections where a through-focus series 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).

"Tooth site positioning"





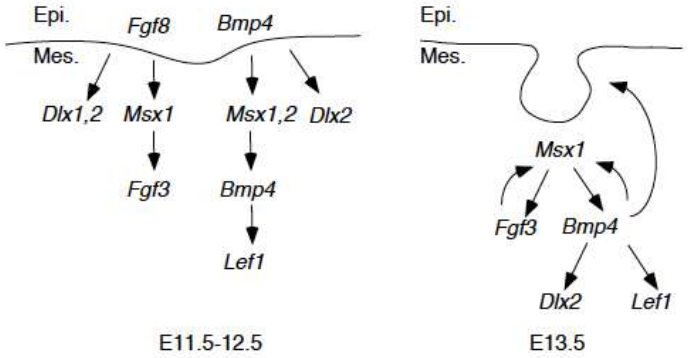
From patterning to odontogenesis



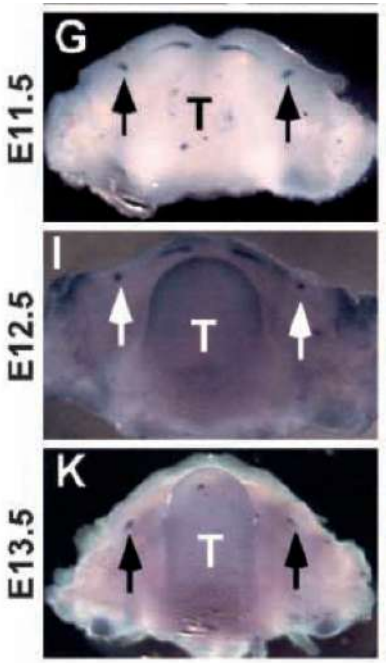
Bmp2 and Bmp7 are similar

something happens here (switch of Bmp signaling from epithelium to mesenchyme)

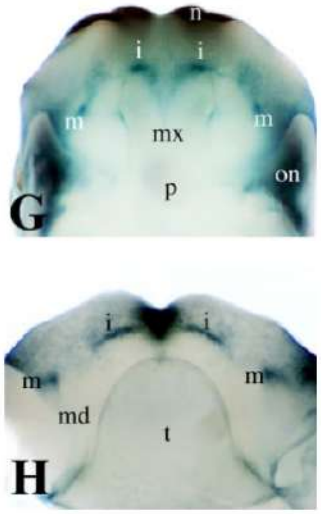
something happens here (switch from MA patterning to odontogenesis)



Bmp2



Bmp7



Morphoregulation of teeth: modulating the number, size, shape and differentiation by tuning Bmp activity

**Maksim V. Plikus,[a] Maggie Zeichner-David,[b] Julie-Ann Mayer,[a] Julia Reyn
Pablo Bringas,[b] J. G. M. Thewissen,[c] Malcolm L. Snead,[b] Yang Chai,[b] and
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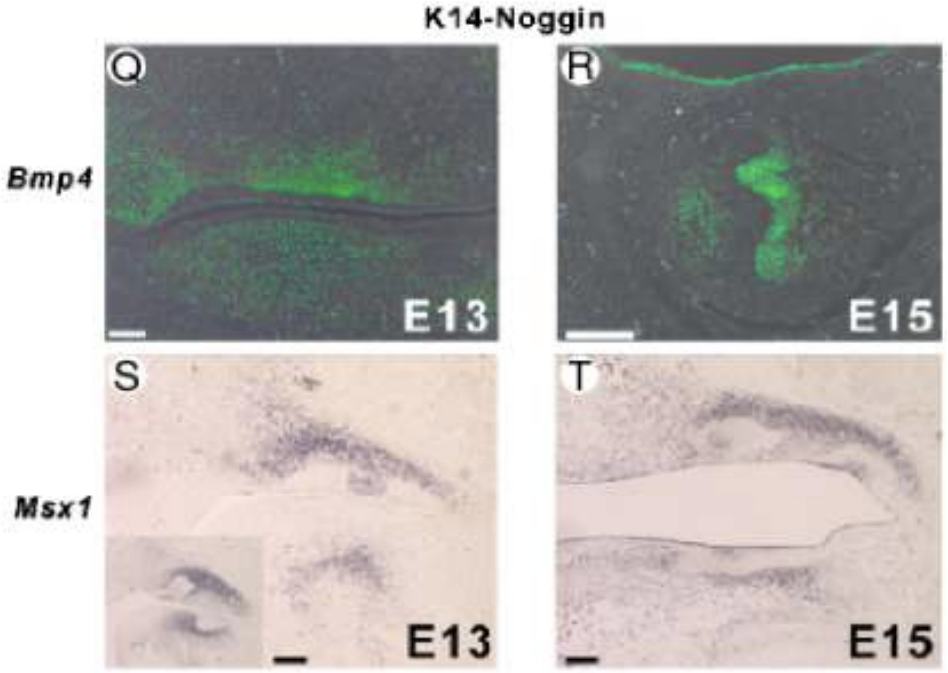
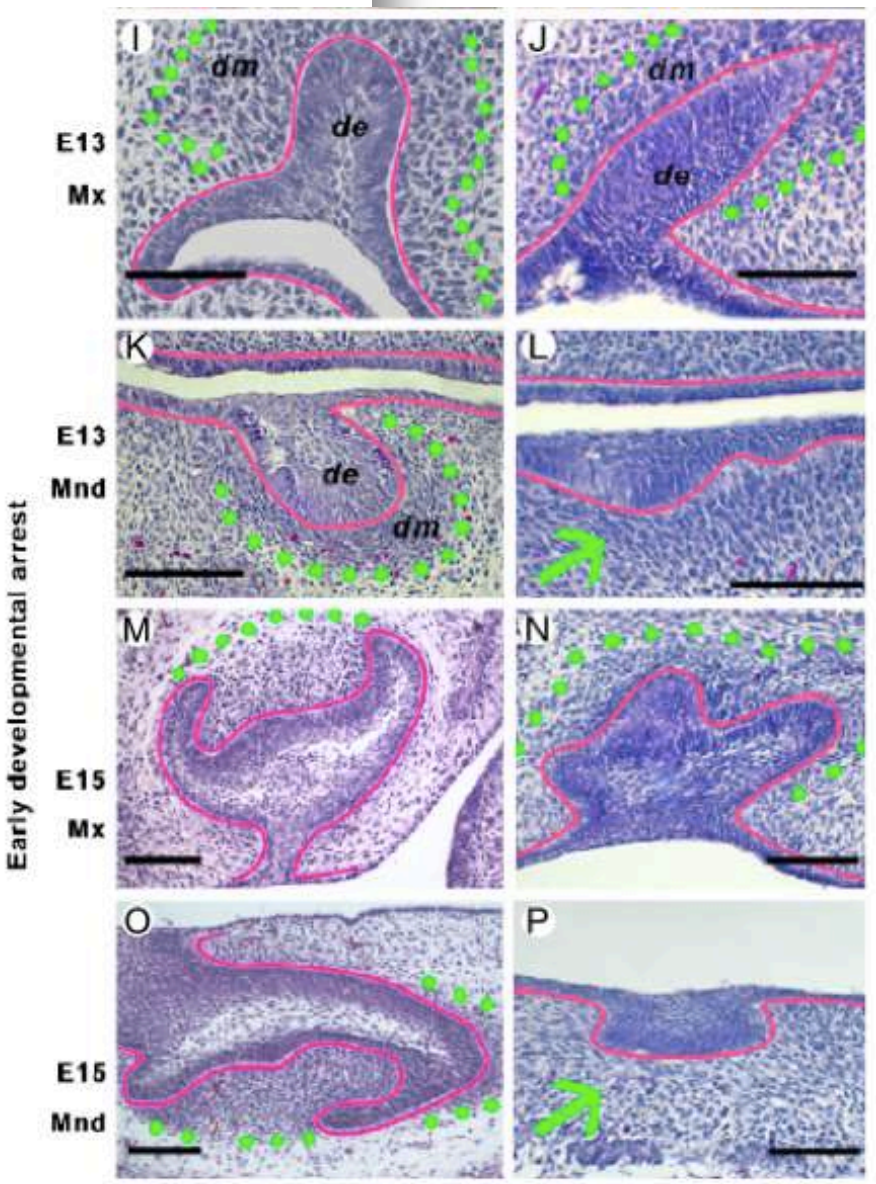
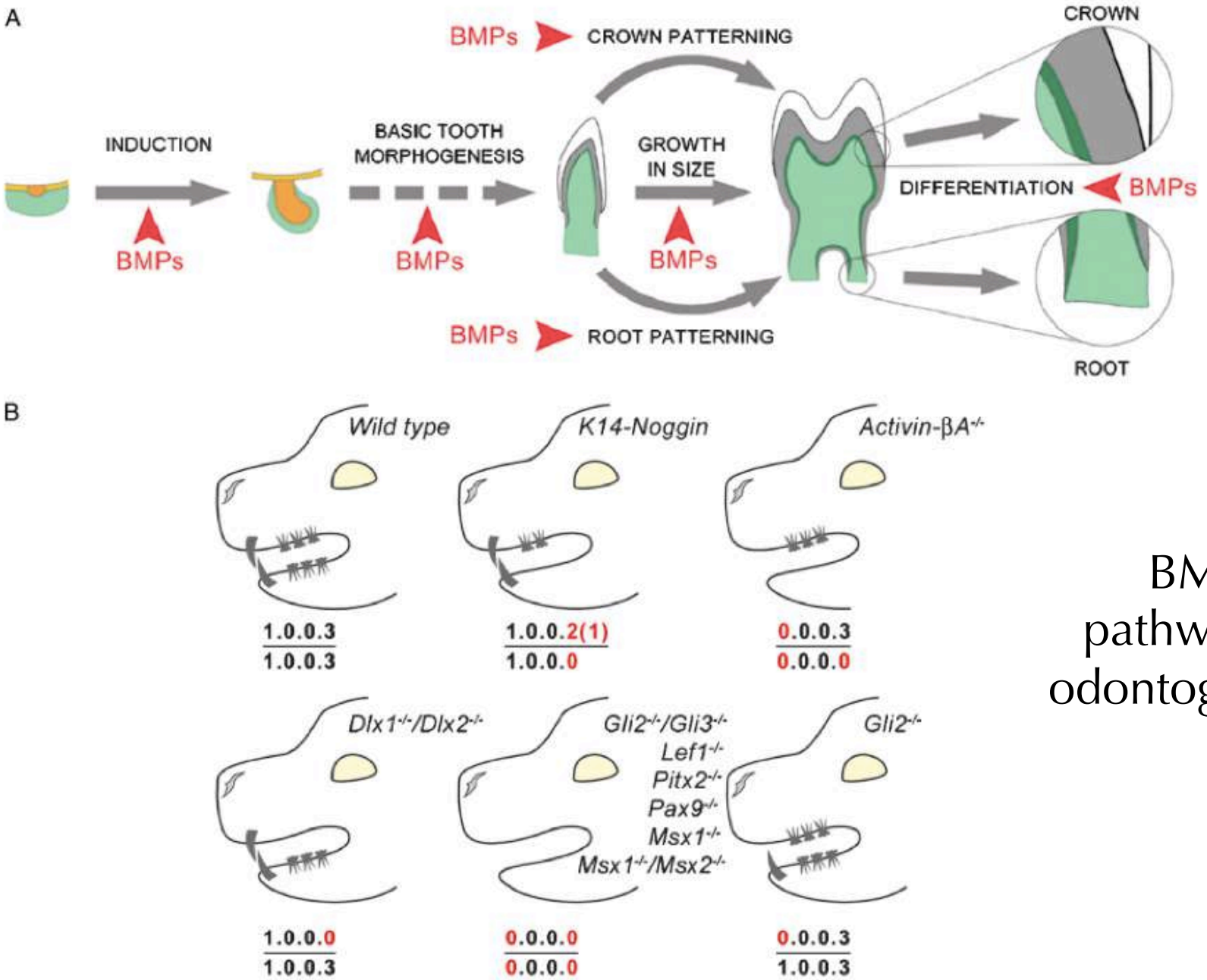
BMPs







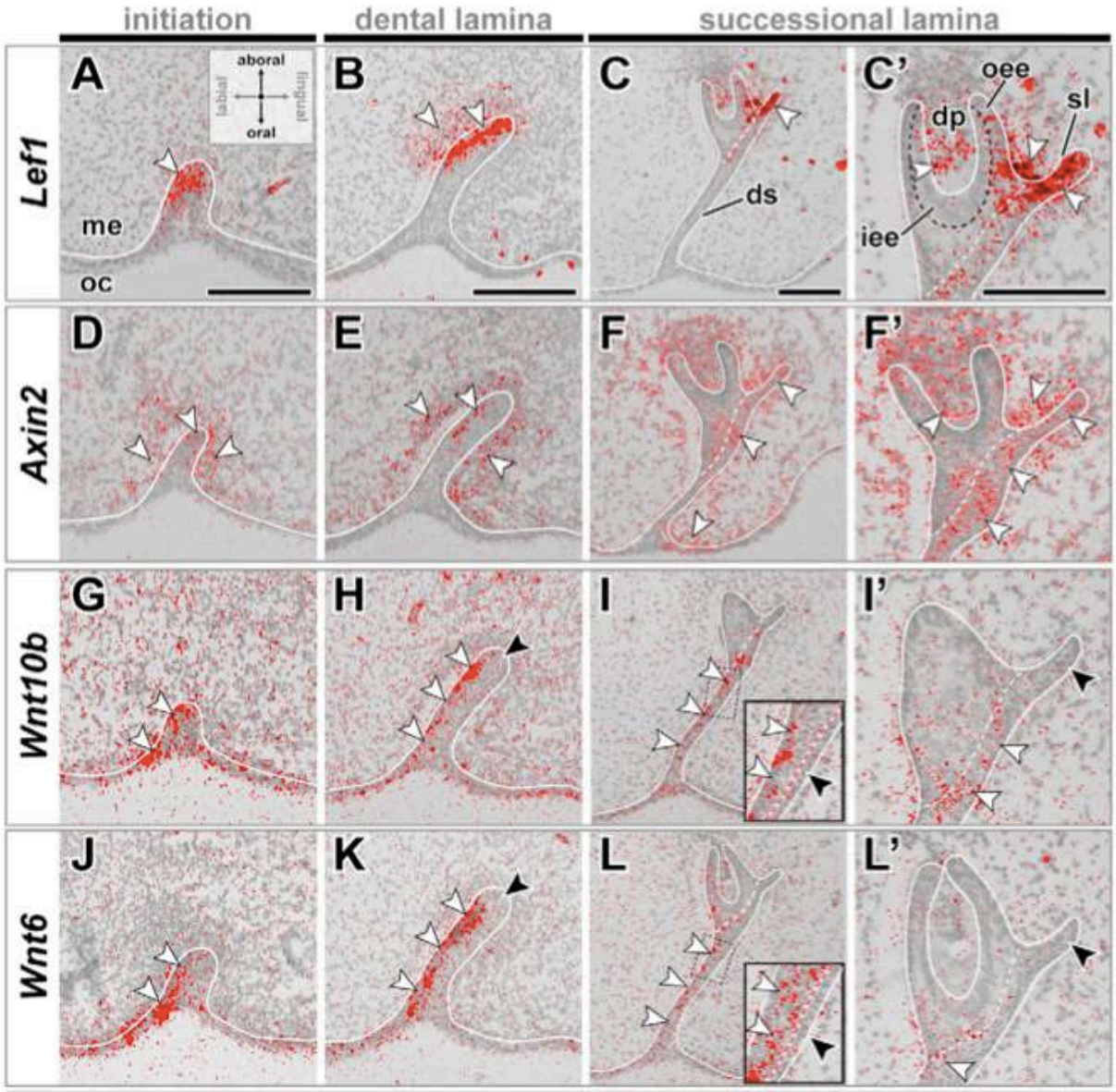
BMP pathway in odontogenesis

Fig. 8. Summary of the multiple dental defects caused by the disruption of the Bmp pathway in the oral epithelium. (A) Summary diagram of the tooth developmental events affected by the reduced strength of Bmp signaling in K14-Noggin mice. (B) Comparison of the dental formulas between WT, K14-Noggin, and other known mutant mice with reduction in teeth number.

A network of Wnt, hedgehog and BMP signaling pathways regulates tooth replacement in snakes

Gregory R. Handrigan, Joy M. Richman *

Department of Oral Health Sciences, Faculty of Dentistry, University of British Columbia, Vancouver, BC, Canada



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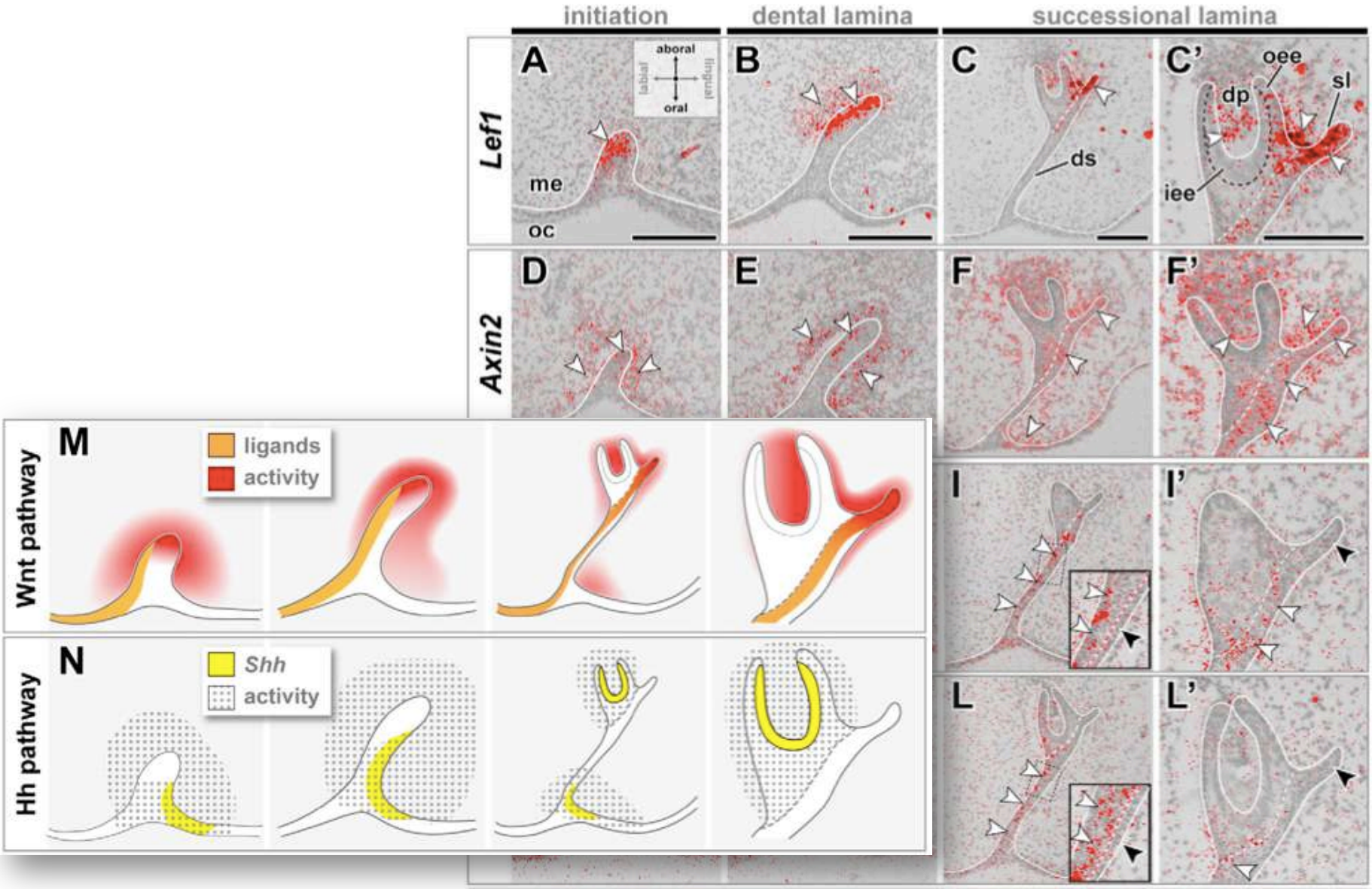

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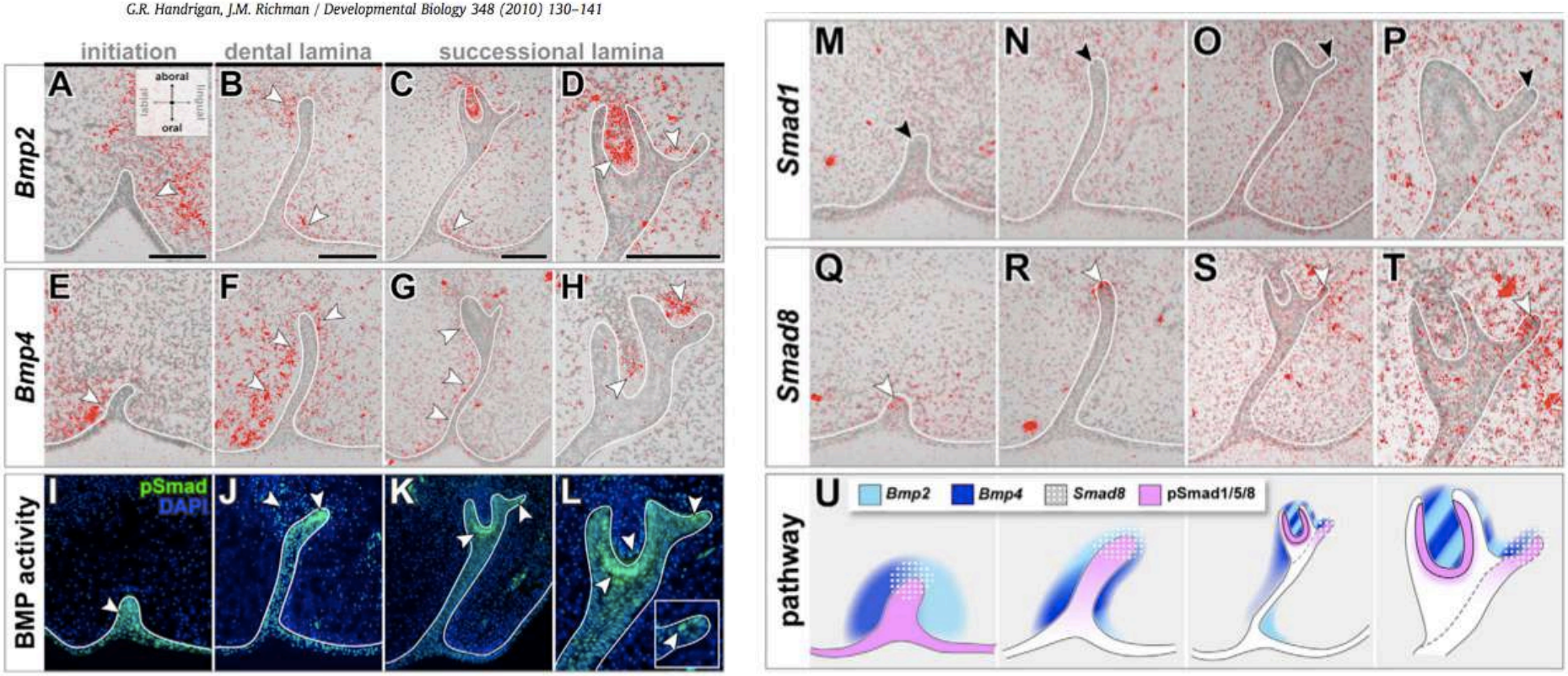

Fig. 4. Mesenchymal BMPs signal to the epithelium in python teeth. (A–T) Sections through ball python teeth showing transcripts (red signal) of *Bmp2*, *Bmp4*, *Smad1* and *Smad8* as well as nuclear phosphorylated Smad1/5/8 (I–L). White arrowheads mark areas of notable gene expression or cell proliferation, while black arrowheads indicate where they are absent. (A–D) *Bmp2* is expressed in mesenchymal cells on the lingual side of the epithelial thickening (A) and later on the labial side of the dental lamina tip (B). *Bmp2* is also expressed in mesenchymal cells next to the successional lamina and in the dental papilla of the tooth bud (C,D). (E–H) *Bmp4* is expressed in mesenchyme cells on the labial side of the dental lamina, dental stalk, and the successional lamina. (I–L) The tip of the dental epithelium is more intensely stained for pSmad1/5/8 than the mesenchyme at all stages. Phospho-Smad can also be detected in the inner enamel epithelium and in pre-odontoblasts (K,L). (M–P) *Smad1* expression, while faint in the dental tissues, is noticeably lower at the free end of the dental epithelium (black arrowhead). (Q–T) *Smad8* signal is strongest at the dental lamina tip and in the successional lamina (white arrowhead). (U) The relationship between mesenchymal BMPs and the Smad-responsive areas in the epithelium. Scale bars equal 100 μm.

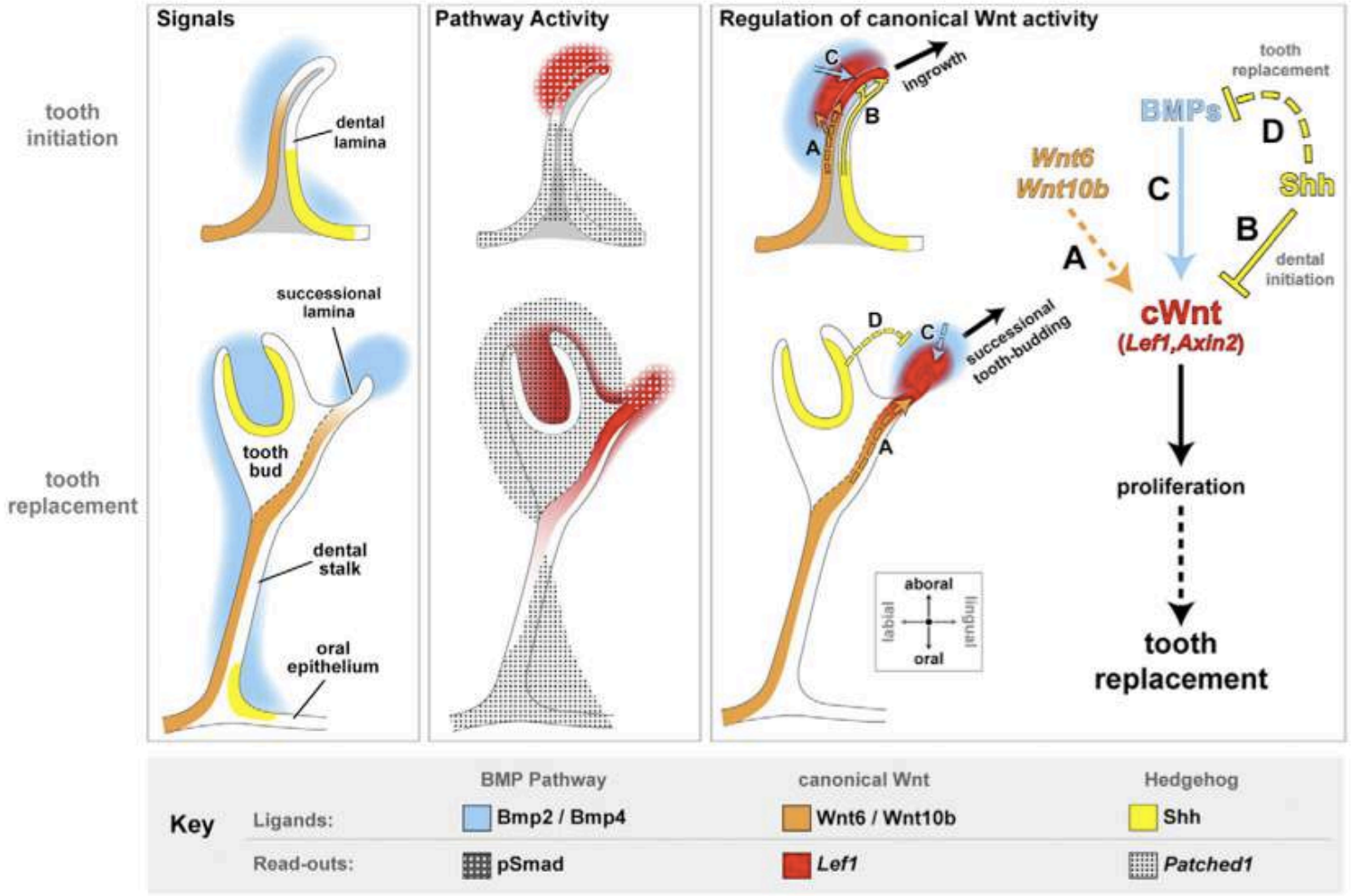

Fig. 6. Gene expression and molecular signaling during tooth initiation and tooth replacement in snakes. The hedgehog, BMP and canonical Wnt pathways are active during dental initiation (top row) and tooth replacement (bottom row). We examined the expression of pathway ligands (left box) and read-outs (middle box). On the basis of these data and gain- and loss-of-function experiments, we developed a model for how the three pathways interact (right box). Gene expression is generally conserved between dental initiation and tooth replacement. Wnt ligand genes and *Shh* are expressed on opposite sides of the dental lamina, while Bmp genes are expressed throughout the dental mesenchyme, with particularly strong expression near the dental lamina tip and later the successional lamina. The Wnt and Hh pathways are active in complementary domains in the dental lamina throughout tooth development in snakes. *Ptc1* expression is restricted to the base of the dental lamina, while *Lef1* expression is confined to the tip. In contrast, the two read-out genes are co-expressed in the tooth bud during tooth replacement. BMP activity, as revealed by phosphorylated-Smad staining, overlaps perfectly with *Lef1* expression at the tip of the dental lamina and in the successional lamina. Taken together, our ligand and read-out expression data imply these four signaling relationships during python tooth development: (A) Wnt ligands produced by cells on the labial side of the dental lamina and later the dental stalk induce Wnt activity at the tip of the lamina and in the successional lamina, respectively. (B) Shh signaling likely restricts Wnt activity to the tip of the dental lamina by direct planar repression during dental initiation. (C) Mesenchymal BMPs induce Wnt activity in the tip of the dental lamina and successional lamina and cell-autonomously in the mesenchyme. (D) Shh produced by the enamel epithelium of nearby tooth buds may restrict BMP expression to the mesenchymal cells immediately abutting the successional lamina during tooth replacement. Signaling relationships indicated with solid lines have been confirmed by functional experiments, while those shown with broken lines await confirmation.

Komplementární a antagonistické zóny aktivity fungují modulárně a umožňují nahrazování zubů či polyfyodoncii

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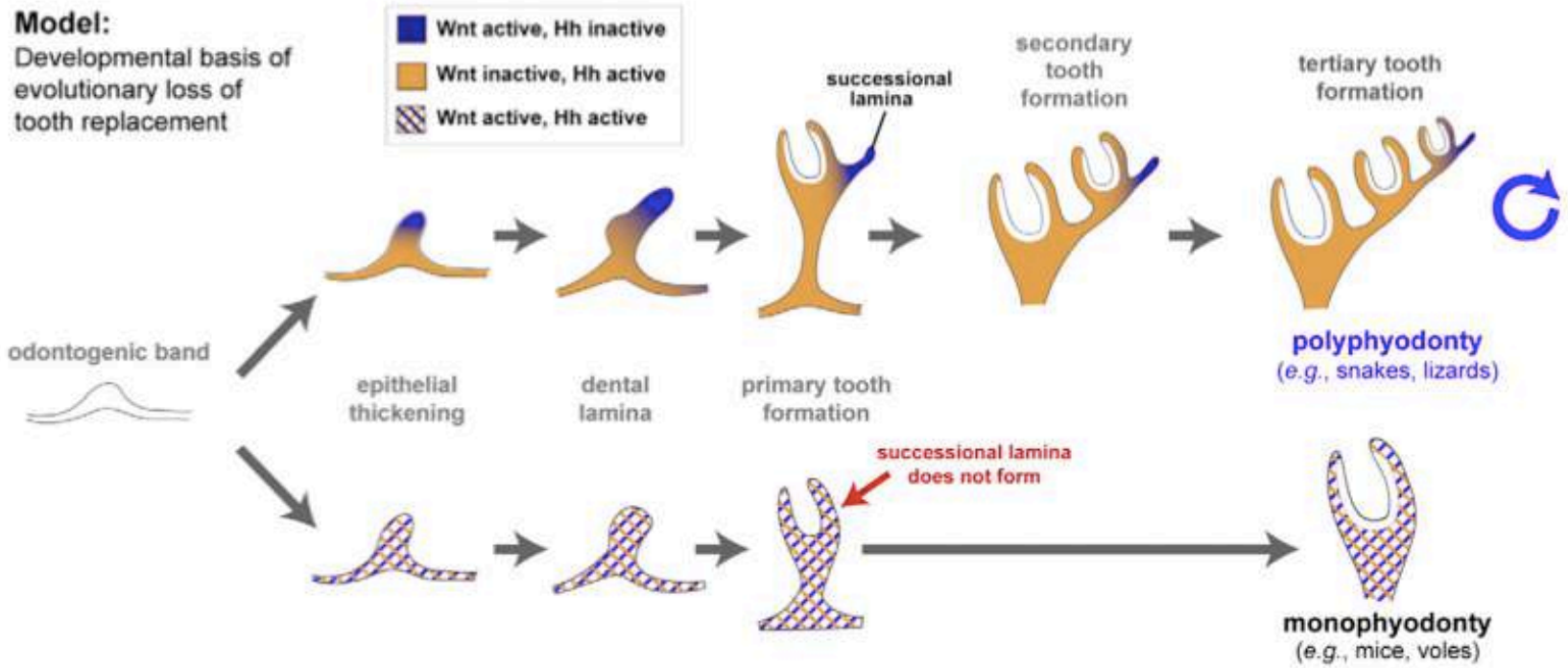


Fig. 7. An evo-devo model of variation in tooth replacement capacity in vertebrates. We propose that the evolutionary loss of tooth replacement in monophyodont species is based on differences in molecular signaling during dental initiation. In animals that replace their teeth, we suggest that the epithelial thickening must be specified into complementary Wnt-active/Hh-inactive and Wnt-inactive/Hh-active domains, which go on to form the successional lamina and outer enamel epithelium, respectively. In monophyodont species (e.g., mouse), there is no such regionalization of Hh and Wnt activity and, as a result, a successional lamina never forms. Without a successional lamina, tooth replacement cannot occur.

Odontogenní homeoboxový kód:

odlišné typy zubů jsou definovány molekulárním kodem konkrétní pozice vzniku

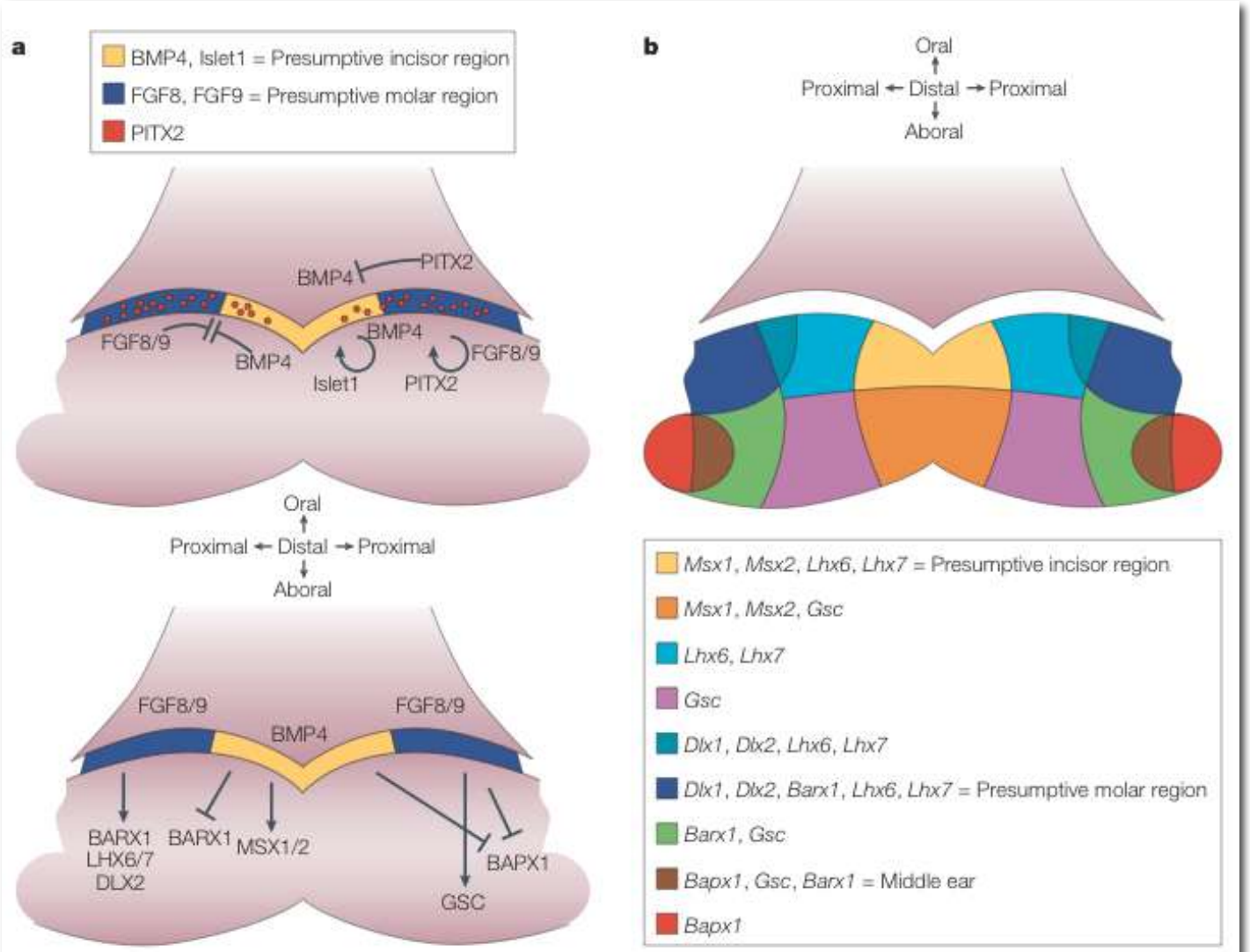
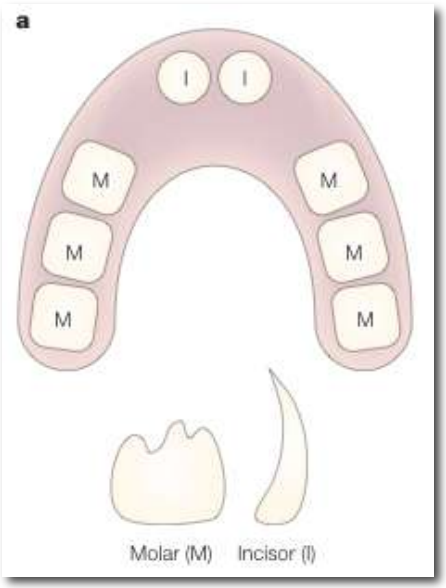


Figure 3 | **Pattern of gene expression in the developing tooth. a** | Signalling within the epithelium and between the epithelium and the mesenchyme at embryonic day (E)10.5. The diagram shows an isolated mandibular arch. Positive auto-regulatory loops and mutual repression within the epithelium leads 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 MANDIBLE 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.



Odontogenní homeoboxový kod

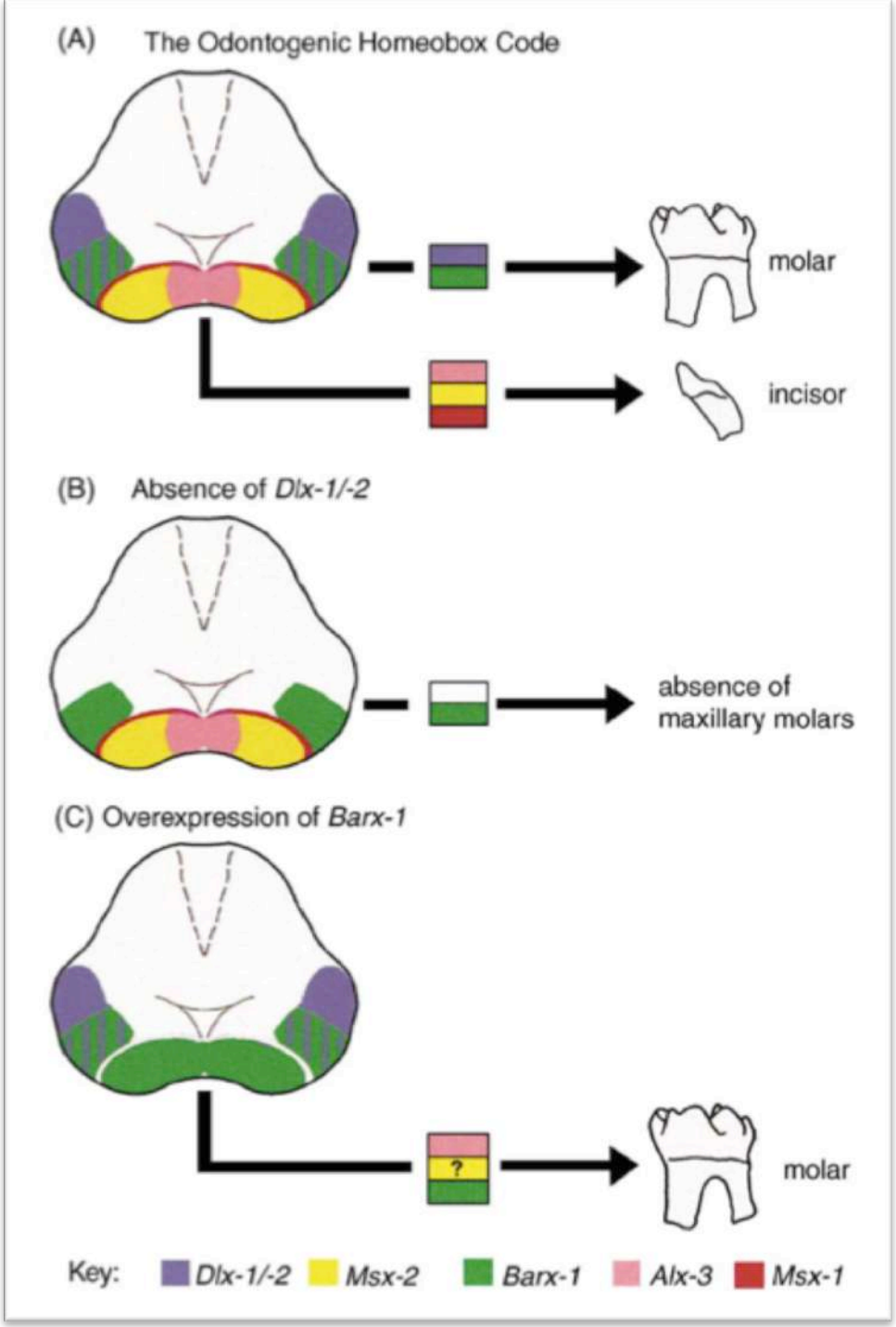


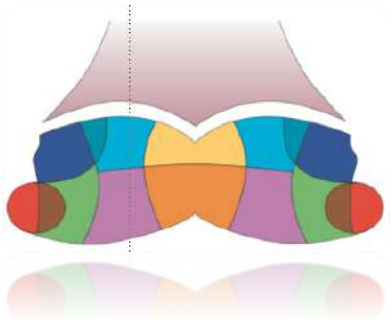
Figure 3 The odontogenic homeobox code. Schematic diagram illustrating homeobox gene expression in the ectomesenchyme of the maxillary and mandibular processes. (A) The restricted ectomesenchymal expression of several homeobox genes is thought to provide the necessary spatial information to determine tooth shape. In the proximal molar-forming regions *Dlx-1/-2* and *Barx-1* positive ectomesenchyme results in the formation of molar teeth. In the distal incisor-forming regions *Msx-1/-2* and *Alx-3* positive ectomesenchyme results in the formation of incisor teeth. (B) In mice lacking both *Dlx-1* and *Dlx-2* function, therefore having *Dlx-1/-2* negative and *Barx-1* positive ectomesenchyme in the molar-forming regions, maxillary molars fail to develop. Thus, whilst *Dlx-1/-2* are dispensable for mandibular molar development, they are essential for development of the maxillary molars. It should be noted that in the maxilla, incisors do not form instead of molars because *Alx-3* and *Msx-1* expression is also required for incisor specification. (C) Manipulation of homeobox gene expression, resulting in ectopic expression of *Barx-1* and loss of *Msx-1* (and possibly *Msx-2*) in the distal incisor-forming ectomesenchyme produces a transformation of tooth type; molar teeth form instead of incisors. Thus, a gain of a molar-patterning gene (*Barx-1*) and loss of an incisor-patterning gene (*Msx-1*) re-directs incisor morphogenesis into molar morphogenesis.

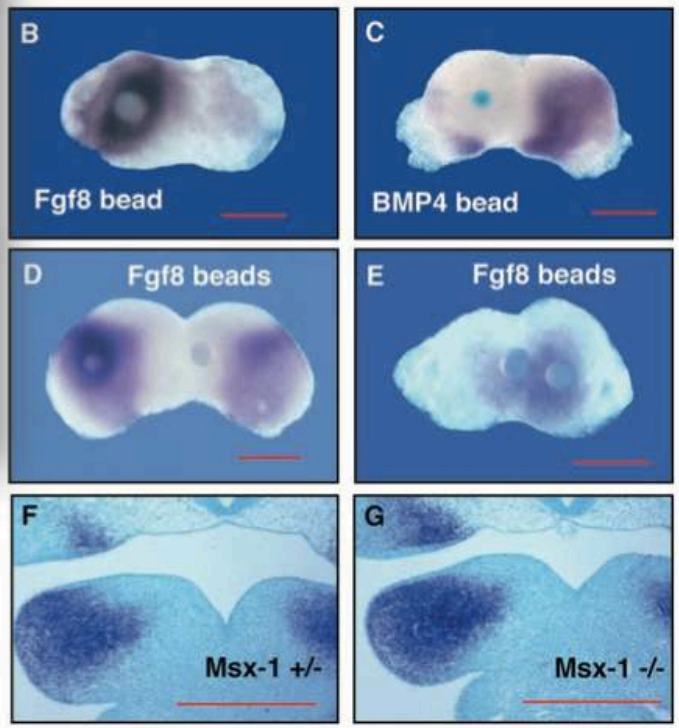
Transformace "zubní identity" z řezáku na špičák posunem exprese BMP a FGF

Transformation of Tooth Type Induced by Inhibition of BMP Signaling

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

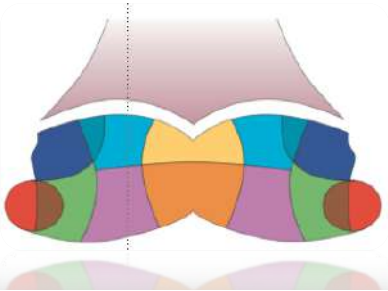
Mammalian dentitions are highly patterned, with different types of teeth positioned in different regions of the jaws. BMP4 is an early oral epithelial protein signal that directs odontogenic gene expression in mesenchyme cells of the developing mandibular arch. BMP4 was shown to inhibit expression of 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.





explants that were cultured for 24 hours are shown. (**B**) Induction of *Barx-1* (epithelium removed; Fgf8 bead present). (**C**) Repression of *Barx-1* (epithelium intact; BMP4 bead present). (**D**) Induction occurring only around the proximally placed bead (epithelium intact; Fgf8 beads present). (**E**) Induction in the distal region (epithelium removed; Fgf8 beads present). The mandibular arch in (**F**) Msx-1$^{+/-}$ and (**G**) Msx-1$^{-/-}$embryos is shown by the frontal section of an E10.5 head. The expression of *Barx-1* is unchanged. Scale bars, 500 μm.

Transformace "zubní identity" z řezáku na špičák posunem exprese BMP a FGF



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Abigail S. Tucker, K

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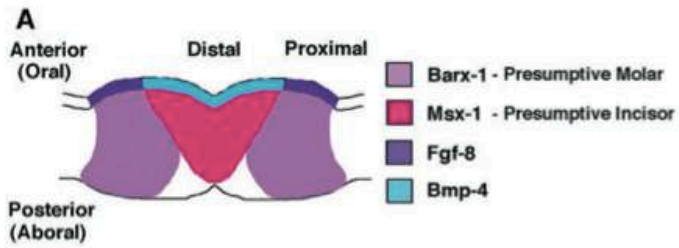


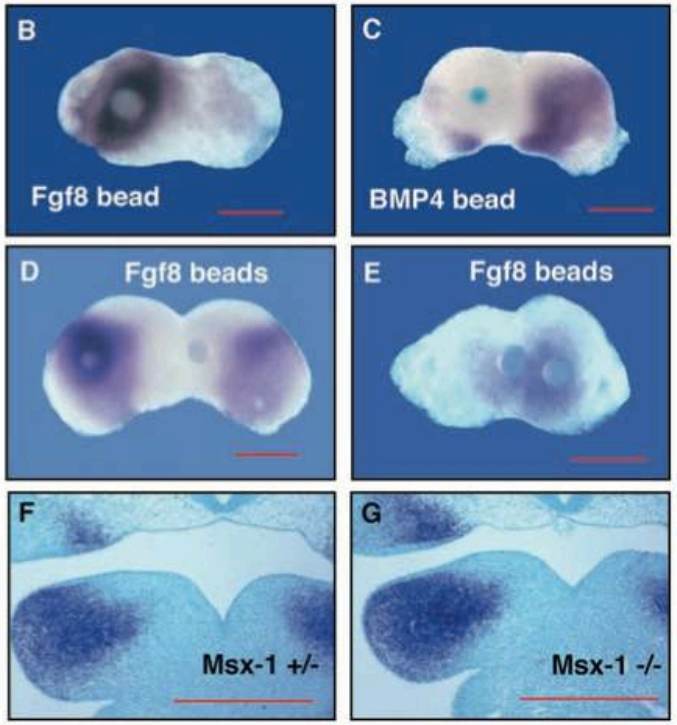
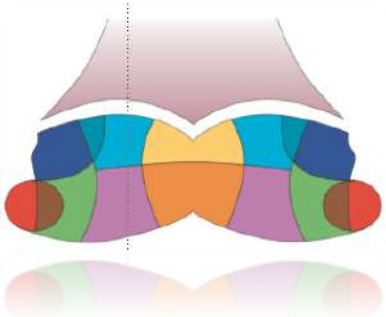


Fig. 1. Regulation of *Barx-1* expression. (**A**) Schematic representation of the expression domains of *Barx-1*, *Msx-1*, *Bmp-4*, and *Fgf-8*. (B through G) *Barx-1* in situ hybridization. E10 (B and C) and E9.5 (D and E) mandibular arch explants that were cultured for 24 hours are shown. (**B**) Induction of *Barx-1* (epithelium removed; Fgf8 bead present). (**C**) Repression of *Barx-1* (epithelium intact; BMP4 bead present). (**D**) Induction occurring only around the proximally placed bead (epithelium intact; Fgf8 beads present). (**E**) Induction in the distal region (epithelium removed; Fgf8 beads present). The mandibular arch in (**F**) Msx-1$^{+/-}$ and (**G**) Msx-1$^{-/-}$embryos is shown by the frontal section of an E10.5 head. The expression of *Barx-1* is unchanged. Scale bars, 500 μm.

Transformace "zubní identity" z řezáku na špičák posunem exprese BMP a FGF



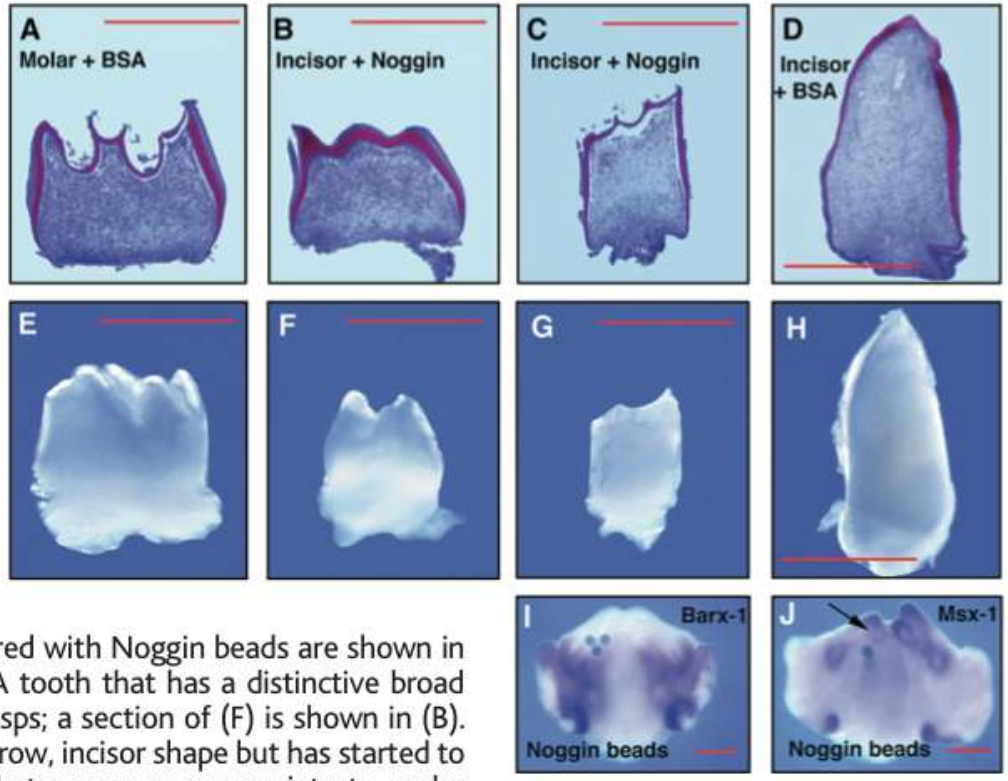
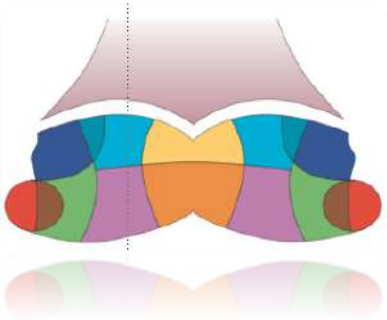


Fig. 3. Transformation of tooth identity from incisor to molar shape. (**A** through **H**) Teeth obtained from E10 tooth germs that were cultured for 2 days in vitro and implanted under host kidney capsules. A section of the multicuspid tooth shown in (E) that was formed from a molar tooth germ cultured 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 (*2*) (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.

Odontogenní homeoboxový kod?!?

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



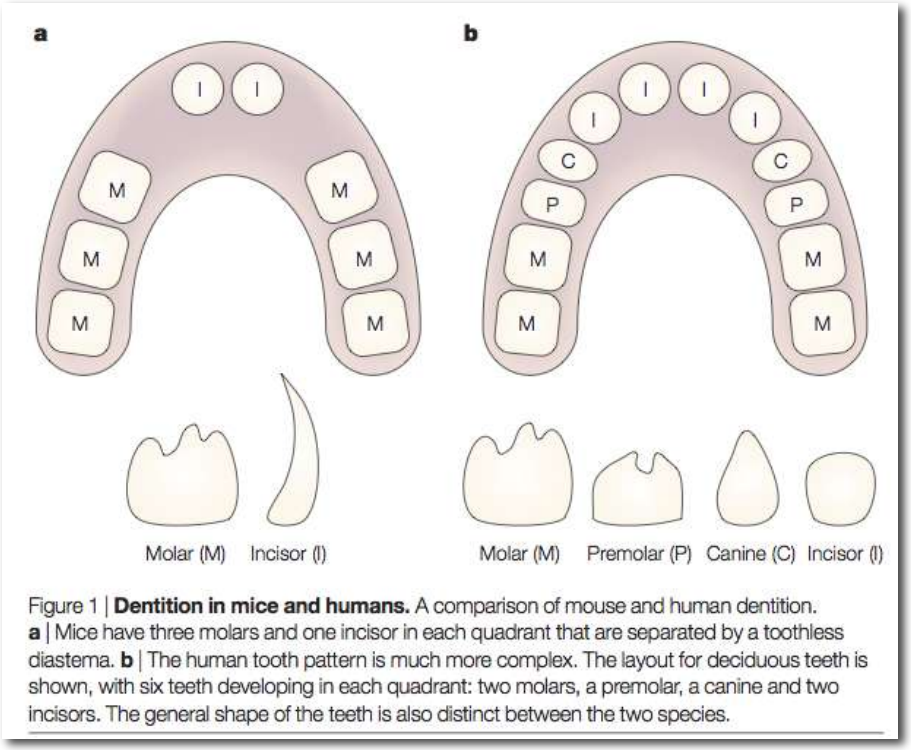


Figure 1 | **Dentition in mice and humans.** A comparison of mouse and human dentition. **a** | Mice have three molars and one incisor in each quadrant that are separated by a toothless diastema. **b** | The human tooth pattern is much more complex. The layout for deciduous teeth is shown, with six teeth 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.