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NEWS AND COMMENTARY

Evolutionary studies

Genetics, development, and palaeontology interlock

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A recent study provides insight into an important, previously missing regulatory step in tooth formation. The new knowledge helps to complete a model system that links three disparate disciplines in evolutionary biology: genetics, developmental biology, and palaeontology. Kassai *et al* (2005) describe the enamel knot inhibitor, *ectodin*, an inhibitor of bone morphogenetic proteins (BMPs), and show that expressing *ectodin*, is critical for proper morphogenesis of mammalian tooth crowns. More importantly they confirm the potential of teeth as a model system to synthesize evolutionary biology in a way that *Genetics, Paleontology, and Evolution* (Jepsen *et al*, 1949) could not.

Geneticists, developmental biologists and palaeontologists share evolution as a subject but few biological traits are amenable to study by all three; teeth are an exception. Teeth have legendary importance in palaeontology. These durable mineralized structures are so readily preserved in the fossil record that palaeontologist Alfred Romer is reputed to have said that one would gather from all the phylogenies of teeth that they lived, died, had sex, and reproduced as though they were organisms themselves. Mammalian teeth more than others feature in palaeontology because they are morphologically complicated – most vertebrate teeth are simple cones of one shape or another but mammals have multicusped teeth that interlock in myriad, species-specific ways. Consequently, mammalian species can be recognized in the fossil record from a single molar with nearly the fidelity that a field geneticist can recognize species from a tissue sample.

In genetics and developmental biology, the absence of teeth was, until recently, as infamous as their presence in palaeontology was ubiquitous. Genetic analysis was, until the 1990s, limited to a few measures of heritability in tooth size. Developmental biologists showed more interest, especially in the patterning of tooth types in the dentition (the field and clone theories) and how the interlocking morphology is controlled in occluding teeth, a morphology that arises before the teeth erupt and come into contact (Butler, 1956). But the tools to link molecular genetics, development, and tooth morphology were lacking.

The situation quickly changed when molecular developmental techniques expanded in the 1990s. For the first time one could identify the roles of genes and alleles in the generation of the complicated cusp patterns on mammalian teeth. In a landmark paper, Jernvall (1995) proposed a simple molecular developmental mechanism for the generation of diversity in mammalian teeth. The key to development in the tooth germ lies in small groups of cells, the enamel knots. Jernvall demonstrated how the enamel knots act as molecular signalling centres in the developing tooth germ. He argued that the enamel knots, which have a one-to-one correspondence with the tips of cusps in the finished tooth, control the rate of proliferation in the intervening epithelium to determine the spacing, height, and number of cusps. The tooth diversity described by Jernvall could be functionally linked to different dietary types, and hence amenable to ecological analysis, and it could be taxonomically linked to mammalian species living and extinct, hence amenable to palaeontological analysis (Figure 1).

Subsequent work by Jernvall and many others has confirmed and extended the original developmental model. New genes expressed in the enamel knots, the surrounding dental epithelium and the underlying mesenchymal dental papilla have been identified and their cascading interactions verified (Thesleff, 2003). Topographically broader molecular expression domains that control differentiation of incisors, canines, premolars, and molars have also been identified (Cobourne and Sharpe, 2003). In a truly stunning paper, Jernvall *et al* (2000) described the changes in molecular signalling that correspond to the evolutionary transformation of the typical mouse molar morphology into the derived, Christmas-tree morphology of voles and their relatives. And more recently Kangas *et al* (2004) demonstrated that *ectodysplasin* expression has pleiotropic effects on tooth morphology which modifies the numbers and shapes of the same cusps and features used by palaeontologists to identify species and study their phylogenetic relationships.

Even though literally hundreds of genes are expressed in a developing tooth germ (Kalski *et al*, 1996), their effects combine into a few simple parameters that describe the rate of cell proliferation; the activation and inhibition of enamel knots, and the rates of diffusion of signalling products through dental tissues. Salazar-Ciudad and Jernvall (2002) produced a computer model confirming that these parameters were necessary and sufficient to explain both the phenotypic changes in a developing tooth and the diversity of tooth shapes seen in mammals living and extinct. Their computer model provided for the first time a predictive tool that incorporated gene alleles, developmental interactions, and phenotypic variety that can be observed equally well in living and fossil mammals. The model provided an important bridge linking developmental genetics to studies of phenotypic variation and evolutionary transformation (Polly, 2004). Most of the parameters in their model corresponded to known signalling molecules in the developing tooth. The mechanism for enamel knot inhibition, however, was unknown and somewhat speculative. Still, their model would not work without it.

The recent paper by Kassai *et al* (2005) finds that this predicted enamel knot inhibitor indeed exists. These authors demonstrate that *ectodin* expression forms a negative image of the enamel knots in the developing tooth germ. This curious spatial distribution suggests that it is the missing inhibitor. By engineering an *ectodin* knockout mouse strain, the authors demonstrated that the gene regulated the number and spacing of enamel knots, thereby influencing the spatial arrangement of cusps and even the number of teeth. In some cases, the wild-type mouse molar phenotype was transformed into a rhinoceros-like tooth shape.

The confirmation of the existence of the inhibitor suggests that selection has favoured intrinsic regulatory mechanisms that canalize tooth development, preventing perturbations that would

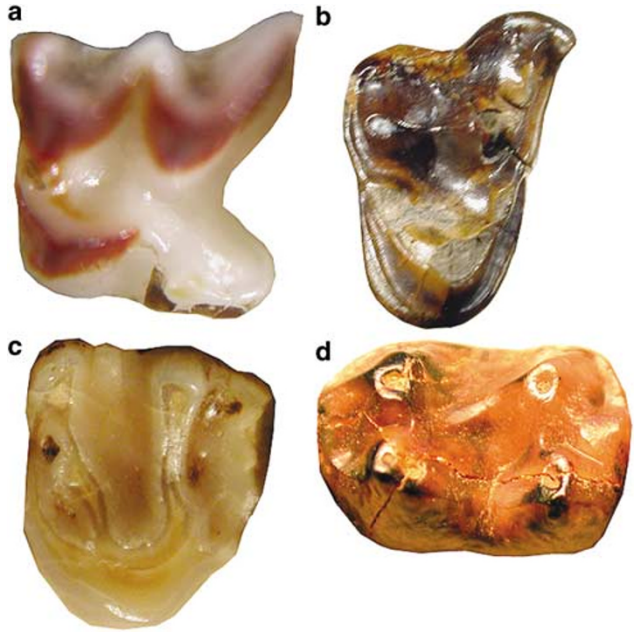

Figure 1 The genetics, development, and evolution of the molar teeth of the living shrew, *Sorex araneus* (**a**), the extinct carnivore, *Didymictis protenus* (**b**), the living woodchuck, *Marmota monax* (**c**), and the extinct horse, *Hyracotherium* sp. (**d**) can now all be studied together thanks to a new sophisticated understanding of tooth morphogenesis and explicit links through computer models to both the underlying genetics and the emergent range of phenotypes.

adversely affect the interlocking occlusal pattern. The discovery also adds another element of the control of tooth diversity that can be empirically verified in comparative studies of gene expression, providing yet another important link between genetics, developmental biology, and palaeontology.

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