TOOTH MORPHOGENESIS

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Adv Dent Res 9(3)(Suppl):12, November, 1995

The histology of tooth development has been known for decades. We have been interested in factors that regulate this process. Our work has shown that tooth-specific morphogens have not been identified. Rather, it appears that molecules that regulate the differentiation and development of other organs also regulate tooth morphogenesis. It is possible that it is the combination of these different factors that is important. Key tools which we have used in our studies are immunohistochemistry and *in situ* hybridization employing antibodies and cDNA probes for known molecules, hypothesized to be important in tooth development.

There is now evidence from many studies that different molecular markers start to be expressed in the dental cell lineages very early. Of the cell-surface components, several growth factor receptors have been localized in developing teeth, and show distribution patterns which suggest that certain cells become committed early during tooth morphogenesis. Of the transcription factors, many have been localized during tooth development, particularly in the very early stages. Perhaps the most interesting transcription factors are the homeobox genes *MSX-1* (previously *HOX-7*) and *MSX-2* (previously *HOX-8*). They have been localized very early in the condensing dental mesenchyme and dental epithelium.

The differentiation of the dental cell lineages is a sequential process. It has been known since the 1950s that epithelial-mesenchymal interactions are perhaps the single most important "mechanism" that regulates tooth (and other organ) development. The main evidence for this comes from classical tissue recombination studies. Thus, the epithelium needs the mesenchyme, and *vice versa*, in order for tooth morphogenesis to take place. These interactions are really sequential and reciprocal. At very early stages, "dental" epithelium can direct "non-dental" mesenchyme to form a tooth. The reverse, however, appears not to be true. At later stages of development (*e.g.*, the bud stage), the "dental" mesenchyme assumes the key instructive role. Such interactions are necessary for cell proliferation, and for appropriate induction of regulatory genes like *MSX-1* and *MSX-2*.

What is the nature of the signals that mediate the epithelial-mesenchymal tissue interactions and which turn on these different genes? Our laboratory has generated evidence that during early tooth development, growth factors in the TGF-β family (including the bone morphogenetic proteins, BMPs) and the FGF family mediate inductive signaling. These factors appear to be expressed at the right places and right times. The BMPs are the most interesting growth factors at present, in particular, BMP-2 (expressed by dental epithelium) and BMP-4 (expressed first by dental epithelium and then by dental mesenchyme). Their expression is modulated at key points during dental development. Further, we have tested the effects of recombinant BMPs in our *in vitro* tissue recombination models and have shown that both BMP-2 and BMP-4 mimic the effects of epithelium on the dental mesenchyme. They also induce *MSX-1* and *MSX-2* expression. Thus, these BMPs appear to act as essential inductive factors for tooth morphogenesis.