# DEFECTS IN THE FORMATION OF THE DENTAL ORGAN

Sérgio Roberto Peres LINE

Piracicaba School of Dentistry / State University of Campinas (Unicamp)

Defects in tooth development are among the most common alterations in humans. Although enamel defects are not a threat to the patients' health, they may cause serious esthetical problems and interfere with masticatory and speech functions. Tooth agenesis and defects in enamel formation are among the most common alterations in human dentition. The importance of several genes in tooth development was evidenced by the lack of teeth in mutant knockout mice models and mutations in human families. Mutations in PAX9 coding sequences have been implicated in autosomal dominant oligodontia (the lack of more than 6 teeth) affecting predominantly permanent molars and second premolar. The origin of hydopontia (the lack of one to 6 teeth) is not well understood. In a previous study we have found that two polymorphisms in the promoter region of PAX9 gene are associated with hypodontia in humans (submitted for publication). These results led us to focus our analysis on the 5' region of PAX9 gene by studying: (1) the association of two other polymorphisms present in this region with hypodontia; (2) the influence of these (in spite of many studies being conducted, much remains to be unveiled) polymorphisms in the transcriptional activity of PAX9 gene by the use of reporter gene systems and gel shift analysis; (3) the comparison of the human promoter sequence with other primates from Africa (which have the same number of teeth as humans) and Brazil (which have three premolars in each hemi arc); (4) analyzis of the pattern of methylation in the CpG rich regions of the PAX9 promoter; (5) the influence of vitamin A, and dexamethasone on the activity of PAX9 promoter. Enamel defects are caused by genetic or environmental factors that interfere in the formation of this tissue. These factors can interfere with the metabolism of ameloblasts or interfere directly with the formation of enamel matrix. Mutations in the amelogenin, enamelin, amelobasltin and MM-20 genes were shown to cause severe enamel malformations known as amelogenesis imperfecta in humans and mice. However, the major causes of enamel defects in human population are environmental factors. Enamel defects can be caused by fluoride, lead, biphosphonates, virus infections and high fever. In spite of many studies being conducted, much remains about the role of the organic matrix in the mineralization of tooth enamel as well as how genetic and environmental factors will influence the formation of this structure. The aims of the present project are: (1) to study the birrefringency of the enamel matrix in the diverse phases of amelogenesis; (2) to study the effect of fluoride in the supramolecular organization of enamel matrix; (3) in collaboration with Dr. John D. Bartlett from Harvard Medical School and Dr. Ashok Kulkarni NIH-USA we intend to study the birrefringency of the enamel matrix in MMP 20 and amelogenin knockout mice (homozygous and heterozygous mice; (4) to study the effect of protease inhibitors *in vitro* on the birrefringency of enamel matrix.

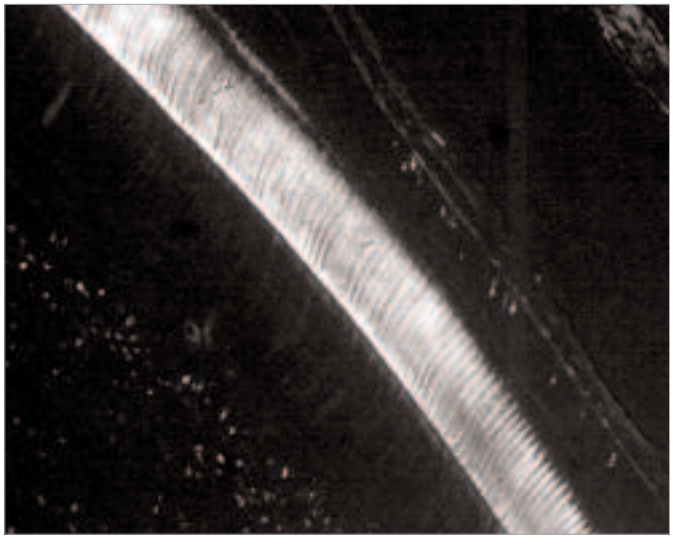

*Figure showing birefringence of the organic matrix of mouse dental enamel*

## SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

To date we have demonstrated that the organic matrix of dental enamel is highly organized and the level of organization can be studied by polarized light microscopy. Through this method, we showed that the supermolecular organization of the matrix can be altered by genetic mutations and environmental alterations.

We also found a region in the genes related with dental agenesis which appears to be related to the number of teeth present in mammal species (results not yet published).

## MAIN PUBLICATIONS

Espírito Santo AR, Bartlett JD, Gibson CW, Li Y, Kulkarni AB, Line SR. 2007. Amelogenin- and enamelysin (Mmp-20)-deficient mice display altered birefringence in the secretory-stage enamel organic extracellular matrix. *Connect Tissue Res*. **48(1)**:39-45.

Santos MC, Hart PS, Ramaswami M, Kanno CM, Hart TC, Line SR. 2007. Exclusion of known gene for enamel development in two Brazilian families with amelogenesis imperfecta. *Head Face Med*. **31;3**:8.

Mendoza G, Pemberton TJ, Lee K, Scarel-Caminaga R, Mehrian-Shai R, Gonzalez-Quevedo C, Ninis V, Hartiala J, Allayee H, Snead ML, Leal SM, Line SR, Patel PI. 2007. A new locus for autosomal dominant amelogenesis imperfecta on chromosome 8q24.3. *Hum Genet.* **120(5)**:653-62.

do Espírito Santo AR, Novaes PD, Line SR. 2006. Anisotropic properties of the enamel organic extracellular matrix. *Eur J Oral Sci*. **114 Suppl 1**: 333-7; discussion 349-50, 382.

Sérgio Roberto Peres LINE

Faculdade de Odontologia de Piracicaba
Universidade Estadual de Campinas (Unicamp)
Caixa Postal 52, Areião
13414-903 – Piracicaba, SP – Brasil

+55-19-2106-5333
serglin@fop.unicamp.br