The role of histone-modifying enzymes in the epigenetics and pathogenesis of periodontitis.

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The human immune system is required for protection against pathogenic bacteria, but the immune response must be tightly controlled to prevent collateral damage of host organs, and to facilitate tissue regeneration. The immune response which does not resolve rapidly upon elimination of infecting microorganisms may lead to the development of chronic inflammatory disorders. Several of these diseases are characterized by high morbidity and mortality rates, and have a significant impact on public health.

Periodontal disease belongs to the most prevalent chronic inflammatory disorders. It leads to the destruction of the tooth-supporting tissues and is initiated by pathogenic bacteria in dental plaque. The disease is initiated and driven by a small group of anaerobic bacteria, such as *Porphyromonas gingivalis*, *Fusobacterium nucleatum,* and *Filifactor alocis*, which colonize the subgingival tooth surface below the gum lines, causing chronic inflammation of the periodontium. If inflammation is left untreated, it can last several years leading to erosion of tooth supporting structures and tooth loss. It is now commonly accepted that destruction of the periodontal tissue is a consequence of an unsuccessful attempt of the host immune system to eradicate pathogenic microbes.

In recent years, our knowledge of the pathogenic bacteria that cause periodontitis and their roles in periodontal disease pathogenesis has greatly expanded. However, we still know very little about how oral pathogens modulate biological processes inside host cells to evade the immune response while promoting chronic inflammation. Epigenetic regulation of gene expression is one of these processes. Epigenetic mechanisms are defined as changes in the structure of DNA and associated proteins (in particular, histones) which either promote or suppress gene transcription without alterations in DNA sequence. Changes in the levels of certain proteins produced by the cell as a result of epigenetic mechanisms may significantly impact upon cell activation and response to bacterial infection. Among epigenetic processes, modifications of histone proteins play an important role in the immune response and pathological changes in these modifications have been observed in several chronic inflammatory diseases. Because modulators of one such modification, histone acetylation, are already successfully used in the clinic to treat other diseases, it is important to understand how oral pathogens affect histone modifications in cells relevant to the pathogenesis of periodontitis, and whether these changes or their consequences can be targeted therapeutically to ameliorate inflammation or facilitate eradication of bacteria by the host immune system.

The aim of this project is to characterize pathological dysregulation of histone-modifying enzymes in periodontitis, identify their underlying mechanisms and determine if posttranslational histone modifications can be potential novel therapeutic targets. Our experimental strategy is based on a combination of analyses of gingival tissue specimens from patients with periodontitis with *in vitro* studies of gingival fibroblasts and macrophages infected with oral pathogens, which represent a model of interactions between bacteria and host cells. Results of these studies will be an important step towards better understanding of the roles of epigenetic processes in cells involved in periodontitis pathogenesis, which will significantly increase our knowledge of the molecular mechanisms underlying periodontitis development and progression. Finally, these studies will provide important information on the therapeutic potential of targeting histone-modifying enzymes in the clinic in periodontitis.

Periodontal disease affects up to 30% of the human population and it is estimated that approximately 10% of patients develop severe form of the disease which leads to inevitable tooth loss. However, despite very high prevalence, the social importance of this disease remains underestimated by health-care personnel and the general public, and often periodontitis-related tooth-loss is considered an inevitable consequence of aging. Importantly, apart from tooth loss-related morbidity, patients with periodontitis have increased risk for developing other systemic disorders, such as atherosclerosis, rheumatoid arthritis and Alzheimer's disease. The impact of periodontal disease on human health is therefore immense and better understanding of mechanisms underlying development and perpetuation of inflammation is required to develop new strategies for prevention and treatment of this chronic disorder. **Studies performed within this project, characterizing the importance of epigenetic mechanisms in periodontitis pathogenesis, will not only improve our understanding of the disease, but can also facilitate identification of new therapeutic targets, constituting a foundation for testing new drug classes in the treatment of periodontal disease in the future.**