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The immune system provides protection against pathogenic microorganisms, but the immune response has to be controlled in spatial and timely manners to prevent damage of the host tissues and organs, and to facilitate healing. Uncontrolled immune response that does not resolve upon elimination of pathogens leads to the development of acute or chronic inflammatory diseases, many of which have high morbidity and mortality rates, and have a significant impact on public health.

Periodontitis is one of the most common chronic inflammatory diseases of mankind. It leads to the destruction of the tooth-supporting tissues and is initiated by pathogenic bacteria in dental plaque. Oral pathogens accumulating on the subgingival tooth surface, especially *Porphyromonas gingivalis,* cause chronic inflammation of the periodontium, which, if left untreated, can last for years causing erosion of tooth supporting structures and tooth loss. It is now understood that periodontal tissue damage is a consequence of a futile attempt by the host immune response to eradicate microbial invaders. However, we still know very little about how periodontal pathogens affect biological processes inside host cells to promote inflammation and evade killing by the immune system. One of such processes is epigenetic regulation of gene expression – changes in the structure of DNA and associated proteins which either promote or suppress gene transcription. This in turn results in changes in the levels of certain proteins produced by the cell, which has an impact on cell activation and response to bacterial infection. Among epigenetic processes, reversible acetylation of proteins plays an important role in the immune response and pathological changes in the acetylation system have been observed in several chronic inflammatory diseases. Because modulators of acetylation are already successfully used in the clinic to treat other diseases, it is important to understand how oral pathogens affect this process in periodontitis, and whether these changes can be targeted therapeutically to ameliorate inflammation or facilitate eradication of bacteria.

The aim of this project is to characterize alterations in the protein acetylation system in periodontitis, identify underlying mechanisms and evaluate the therapeutic potential of pharmacological modulation of acetylation in periodontal disease. ***First***, I will obtain gingival tissue samples from patients with periodontitis and analyze changes in expression and activity of the acetylation system components. ***Second***, I will determine how the periodontal pathogen *P. gingivalis* affects the acetylation system *in vitro* in cells of the gingival tissue that are in direct contact with the bacterium, including gingival fibroblasts, periodontal ligament fibroblasts and gingival keratinocytes, and characterize which bacterial components are responsible for these effects. ***Third***, I will perform a broad range of functional experiments to test if manipulation of acetylation regulators *in vitro* can revert/modulate the pathological consequences of altered protein acetylation in the host cells caused by *P. gingivalis*. Results of these experiments will allow me to comprehensively map epigenetic changes in protein acetylation in periodontitis, alongside their underlying molecular drivers, thus increasing our knowledge of the pathogenesis of periodontitis. They will also provide critical information on the therapeutic potential of targeting the protein acetylation system in this disease.

It is estimated that up to 30% of the adult population suffers from periodontitis and in approximately 10%, a severe form of the disease ultimately leads to tooth loss. Despite high prevalence and significant influence of periodontitis on the quality of life of patients, in many countries it is a neglected disease, both by population in general and by health-care personnel, and often tooth-loss due to periodontitis is considered an inevitable event associated with aging. However, apart from morbidity caused by tooth loss, periodontal disease is strongly associated with increased risk for other inflammatory diseases, including rheumatoid arthritis, atherosclerosis and chronic obstructive pulmonary disease. Because of that, the impact of periodontitis on human health is immense and better understanding of disease pathogenesis is necessary to develop novel strategies for prevention and/or treatment of this disease. Studies aimed at characterization of molecular mechanisms underlying periodontitis that could facilitate development of such strategies are therefore of great relevance to the public.