Description for the general public

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, in particular *Porphyromonas gingivalis*, 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, our understanding of how oral pathogens modulate biological processes inside host cells to evade the immune response while promoting chronic inflammation is still limited. On the one hand, it is well established that inflammatory responses of gingival epithelial cells, which constitute the first line of defense against oral bacteria, are suppressed by *P. gingivalis*, which impairs the host immune response and facilitates survival and dissemination of bacteria. Surprisingly, gingival fibroblasts, which are the main cell type present deeper in the connective tissue, remain an understudied cell population in this context. This represents a significant gap in our knowledge of periodontitis pathogenesis as it is has recently been recognized that fibroblasts are not merely passive bystanders that maintain tissue structure, but are capable of actively responding to pathogens and damage and thus play an immune sentinel role. Interestingly, our preliminary observations indicate that, in contrast to epithelial cells, interaction of gingival fibroblasts with *P. gingivalis* amplifies their sensitivity to inflammatory activation. We hypothesize that whereas *P. gingivalis* suppresses the immune response in the close proximity of the dental plaque, promotes pathological activation of gingival fibroblasts deeper in the gingival tissue it. This in turn leads to exaggerated and unrestrained production of inflammatory mediators that cause host tissue breakdown, which generates nutrients that are used by oral pathogens.

The aim of this project is to characterize how *P. gingivalis* and other oral pathogens interact with the inflammatory environment to amplify pathogenic inflammatory response of gingival fibroblasts, identify their underlying mechanisms and determine if they can be a potential therapeutic target of innovative therapies. We will use novel technologies, such as global profiling of gene expression and three dimensional in vitro tissue model, in combination with functional and mechanistic studies of primary cells extracted from the gingival tissue of patients with periodontitis and healthy individuals. It will allow us to build a comprehensive model of fibroblast interactions with oral pathogens under inflammatory conditions, which will significantly increase our knowledge of the cellular mechanisms underlying periodontitis development and progression. The obtained results will also contribute to characterization of new strategies used by pathogenic bacteria to inflammatory tissue damage. Finally, these studies will provide important information on the therapeutic potential of targeting bacterial factors and host proteins/pathways involved in these interactions in the clinic.

Periodontitis affects up to 30% of the human population and 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. Importantly, apart from tooth loss-related morbidity, patients with periodontitis have increased risk for developing systemic diseases, such as rheumatoid arthritis, atherosclerosis, chronic obstructive pulmonary disease and Alzheimer's disease. The impact of periodontal disease on human health is therefore immense and better understanding of cellular mechanisms underlying development and perpetuation of inflammation is needed to develop new strategies for treatment and/or prevention of this chronic disorder. **Studies performed within this project, characterizing the roles of gingival fibroblasts and their interaction with oral pathogens in driving the chronic inflammation, 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.**