DESCRIPTION FOR THE GENERAL PUBLIC

Epidemiological studies showed that up to 40% of the population in developed countries suffers from various forms of periodontal disease. Among them the most popular is periodontitis. Scientist demonstrated that the induction and progression of the disease is mediated by bacteria infection, which strongly affects the proper regulation of the immune defense. Chronic inflammation observed in patients with periodontal disease leads to serious and irreversible damage of the periodontal tissue, which in turn is associated with loss of teeth. Over 500 species of bacteria were detected in the periodontal biofilm, however *Porphyromonas gingivalis* is consider as the predominant microorganism responsible for the development of the chronic form of the disease. Proteolytic enzymes named gingipains are main virulence factors of this pathogen. Many studies including clinical trials, were focused on the proteolytic properties of these enzymes, and demonstrated their commitment in the degradation of antimicrobial peptides, antibodies, complement components or inflammatory mediators such as cytokines. The biological action of gingipains is not limited to the gingival pockets, since their effectiveness and range of action is potentiated via efficient diffusion into surrounding tissues on small spherical structures called vesicles. Vesicles are secreted into gingival pockets filled with gingival crevicular fluid (GCF), composed of inflammatory exudate, phagocytes and cells debris. The dominant fraction in GCF is plasma, where proteinase inhibitors constituting 10% of all the protein content are capable of inhibiting gingipains. Due to the high concentration of proteinase inhibitors identified in GCF, the presence of catalytically inactive gingipains in the inflamed tissues should be considered.

Our recent studies have shown that gingipains deprived of their catalytic activity are able to induce an immune response by the production of inflammatory mediators. According to our knowledge, such observations have been documented but there is no data explaining the mechanism of this phenomenon.

Therefore, the aim of the proposal is a comprehensive evaluation of the pro-inflammatory mechanism of action of inactive gingipain. In the course of our research we want to identify the receptor, which recognizes a catalytically inactive gingipains on the surface of epithelial cells and professional phagocytes, and in further investigation, we will evaluate the intracellular signal transduction pathway leading to the observed induction of inflammatory mediators. We postulate that inactive proteases aggravate the development of inflammation in a different way than the active form of enzymes.

In summary, determination of research hypotheses presented in this project will give us clear and detailed information necessary for the better understanding of the mechanisms of *P. gingivalis* virulence. It will also verify current knowledge about the function of gingipains in the modulation of the inflammatory response and enable the improvement of the currently proposed therapies with inhibitors of the catalytic activity of gingipain. Importantly, these studies will open the discussion on qualification of gingipains to the group of multifunctional proteins called "moonlighting proteins".