DESCRIPTION FOR THE GENERAL PUBLIC

Periodontitis, colloquially referred to as “gum disease” is one of the most frequent diseases of the humankind. If untreated, severe periodontitis leads to premature tooth loss. In addition, periodontitis apparently contributes to other illnesses as aspiration pneumonia, rheumatoid arthritis, atherosclerosis or Alzheimer’s disease. Despite the fact that there are hundreds of bacterial strains in oral cavity, the most important species involved in periodontitis development is claimed to be *Porphyromonas gingivalis*. This pathogen has a wide list of adaptations that cause deregulation of host’s immune system, degradation of complement cascade proteins or antimicrobial peptides. The main reason for that are cysteine proteases called gingipains. The mechanism of gingipains maturation and secretion is only seemingly well-known as it is clear from the preliminary results underpinning the hypothesis of our project.

Our preliminary results show that posttranslational modification – phosphorylation – plays the crucial role in correct processing, secretion and activation of gingipains. This process involves transfer of phosphate group by a special kind of enzymes called kinases onto proteins’ tyrosine, serine and threonine residues. We hypothesize that in *P. gingivalis* this process is regulated by a two-component system (TCS) that includes two proteins: PorX and PorY. We have shown that deletion of the *porX* gene results in decrease of gingipain activity, as well as changes in their processing patterns and strongly weakens ability of *P. gingivalis* to cause disease in infected mice. Strains of *P. gingivalis* that have mutations of amino acid residues essential for function of the TCS proteins are already prepared in our laboratory. They will be used to confirm that these residues are involved in phosphate transfer from PorY to PorX and finally onto specific tyrosine residues in gingipains.

Using molecular biology tools we will engineer strains of *P. gingivalis* producing gingipains with Tyr residues substituted with Phe so they cannot be phosphorylated. Analyzing gingipains processing, subcellular localization and activity in these strains we will firmly confirm that the direct phosphorylation is essential for gingipains maturation and secretion.

Collectively obtained in this project results will elucidate a novel mechanism of bacterial control over virulence factors exemplified by phosphorylation of gingipain. This detailed knowledge of the essential pathogenicity trait of *P. gingivalis* could help to propose new therapies based on kinase/phosphatase inhibition and may be a step towards curing periodontitis and related diseases.