Epidemiological research indicates periodontal disease (PD) commonly known as periodontitis is one of the most frequently identified chronic diseases with the prevalence reaching up to 50% of the human population. During PD chronic gum inflammation leads to massive damage of the periodontal tissue and bone destruction, which is associated with loss of the teeth. Recently, an emerging number of clinical and epidemiological studies indicated strong comorbidity of PD and other diseases like Alzheimer's disease, Parkinson's disease, cardiovascular diseases, rheumatoid arthritis, diabetes, non-alcoholic fatty liver disease, cancers, or premature birth. Despite these data, the molecular mechanism linking PD with development of the above diseases is barely defined. *Porphyromonas gingivalis* and its secreted proteolytic enzymes called gingipains are crucial etiological factors in the development of periodontitis and many studies revealed the commitment of proteolytically active gingipains in PD progression. Importantly, apart from local influence in gingival pockets, gingipains can be efficiently distributed to distinct tissues and organs affected by PD-related diseases like brain, liver, joints, or esophageal and colorectal cancers. Recent publications indicate that diffusion of enzymes beyond anaerobic bacterial biofilm to the microenvironment with an increased level of oxygen limits the proteolytic activity of gingipains. Moreover, **p**roteolytical **i**nactive **ging**ipains (piGING) have a significant impact on biology of human cells. Therefore, our hypothesis is that piGING play a significant role in progression of systemic diseases by modulation of biology of the distal tissues-forming cells. Thus, we will perform a comprehensive analysis of the role of piGING on the physiological functions of brain cells (neurons, astrocytes, microglial cells), cells of the synovium (fibroblasts, monocytes, T lymphocytes) and esophageal and colorectal cancer cells. During the research, we would like also to identify tissue/cell-specific receptors responsible for piGING recognition. In summary, determination of the research hypothesis presented in this project will help in better understanding of the mechanism of disease commonly observed in patients suffering from periodontitis.