Periodontitis is a group of multifactorial, inflammatory infectious diseases, which belong to the most prevalent infections in humans and are found worldwide as a major public health problem. They are initiated by an ecological shift in the composition of oral bacteria, resulting in inflammation and destruction of tooth-supporting tissues, eventually leading to teeth loss. In a wider context, periodontitis is a known risk factor complications from diabetes mellitus, cystic fibrosis, rheumatoid arthritis, atherosclerosis. In chronic periodontitis, analysis of bacterial species has revealed the presence of “red complex” bacteria (Porphyromonas gingivalis, Tannerella forsythia and Treponema denticola) and “orange complex” bacteria (e.g., Prevotella intermedia), the increased abundance of which is associated with the clinical features of the disease. Among them, P. gingivalis is considered the main etiological agent and key pathogen responsible for initiation and progression of chronic periodontitis. To initiate and establish an infection, P. gingivalis requires iron and heme, acquired from host environment by several mechanisms, including heme-binding protein (HmuY) and enzymes degrading proteins (gingipains). P. gingivalis displays a novel heme acquisition paradigm, whereby hemoglobin must be firstly oxidized to methemoglobin, facilitating heme release, either by proteolysis or capture via a heme-binding hemophore-like HmuY protein. However, interactions between periodontopathogenic bacteria in regard to heme acquisition and expression of virulence determinants are not well understood. We aim to continue investigations of P. gingivalis HmuY protein and to initiate advanced investigations of proteins similar to HmuY protein (HmuY homologs) from selected periodontopathogens involved in initiation and progression of chronic periodontitis, namely Prevotella intermedia and T. forsythia. Our main hypothesis is that other periodontopathogens utilize similar mechanisms to the P. gingivalis heme uptake systems and like P. gingivalis could also employ these mechanisms to acquire heme and increase infectivity. To obtain a desired breakthrough in the field of understanding and treatment of chronic periodontitis as well as engagement of periodontopathogens in other diseases, it is necessary to characterize the crucial proteins to the growth and virulence of periodontal bacteria. Although the role of P. gingivalis HmuY is relatively well understood several important homologs from other periodontopathogens have not been examined. Importantly, as we have shown recently, there is also evidence that other bacteria (e.g., P. intermedia or Pseudomonas aeruginosa) may help to support the growth of P. gingivalis by promoting methemoglobin formation for subsequent heme extraction by the HmuY hemophore. We suspect that HmuY homologs from other periodontopathogens may acquire heme, but importantly they may provide the P. gingivalis HmuY hemophore with heme, resulting in the increased virulence of the latter species and enabling P. gingivalis to play a role as a key pathogen in chronic periodontitis. Importantly, we suspect that P. gingivalis HmuY and its homologs produced by other periodontopathogens might play additional roles, such as engagement in host cell invasion, additionally increasing P. gingivalis virulence. To examine hypotheses of heme acquisition and to understand heme uptake at the molecular level, heme-binding studies and characterization of protein structure of HmuY proteins will be performed. Analysis of P. gingivalis invasion of macrophages and P. gingivalis intracellular survival in macrophages should result in defining of the function(s) of HmuY proteins in P. gingivalis virulence. Characterization of TLR7-dependent signal transduction in macrophages will unravel the function of this receptor in response to P. gingivalis and HmuY proteins. We expect that results obtained in this study will not only be of interest from a basic science point of view and significantly deepen our understanding of the heme uptake mechanisms in periodontopathogens and their importance for bacterial virulence, but will also unravel other potential function/s of HmuY proteins, including cooperation/competition between periodontopathogens in invasion of host cells. Finally, we expect that results gained in this study could have benefits far beyond the characterization of periodontal infections.