Importance of heme biosynthesis in the oral pathogen *Porphyromonas gingivalis*

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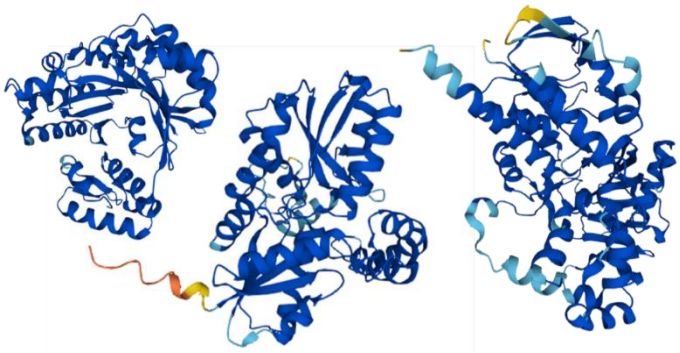
The Gram-negative oral biofilm bacterium *Porphyromonas gingivalis* (*Pg*) is a keystone pathogen in periodontitis, a globally occurring, polymicrobial inflammatory disease of the tooth supporting tissue. Iron and porphyrin acquisition are fundamental to the virulence of *Pg*, due to an incomplete set of genes encoding the heme biosynthesis enzymes (porphyrin auxotrophy), which is the prosthetic group of many biologically active proteins (hemoproteins). *Pg* is an inflammophilic bacterium that procures heme from hemoglobin present in the gingival crevicular fluid and also employs porphyrin uptake mechanisms for survival. In the *Pg* genome, only the final 3 (out of 8) heme biosynthesis enzymes are present: coproporphyrinogen decarboxylase, protoporphyrinogen oxidase and protoporphyrin ferrochelatase. The significance of the remaining heme biosynthesis machinery is unclear to date. Notably, the latter enzyme from *Pg* ATCC 33277 shows peculiarities in its sequence concerning binding of a [2Fe-2S] cluster, which might be relevant for the enzyme's activity.

In this project, the Pg heme biosynthesis enzymes will be studied for their structure-function relationship to obtain valuable information on their activity profiles and predict their contributions to the pathogen's iron/porphyrin equilibria. With the knowledge of structure-function relationships of these enzymes, it is possible to test the effect of their deletion or replacement with tailored mutant variants on the fitness of *Pg in vivo* as well as within the biofilm consortium.

This project will deliver important pieces of knowledge to better understand the processes related to iron/heme metabolism that contribute to bacterial pathogenicity. Such in-depth understanding is a necessary foundation for the future development of targeted interference strategies.



Secondary structure of heme biosynthesis enzymes