Together or not? The relevance of the interplay of staphylocoagulases and staphylokinase in the development of Staphylococcus aureus infections

Staphylococcus aureus is a pathogenic bacterium that causes local skin and soft tissue infections, including abscesses and chronic wound infections, as well as systemic bloodstream infections and related complications, such as infective endocarditis.
A unique feature of *S. aureus* is the ability to produce enzymes with opposite activity, staphylocoagulase and staphylokinase, which on the one hand promote the formation of fibrin in human blood and on the other can activate fibrinolysis and fibrin destruction (Fig.). The individual roles of these enzymes in the development of infections have been confirmed, e.g. in infective endocarditis, chronic wounds or in accelerating the spread of infection (Fig.). However, the consequences of their combined action are unknown.

We recently observed that *S. aureus* isolates responsible for causing blood infections in Poland represent varying levels of these enzymes reflected by the amount of induced fibrin or the ability to degrade it. We noticed that the majority of isolates (66%) produce fibrin and cannot degrade it, while about 20% both produce and break down fibrin. These characteristics of the bacterial isolates were found to be associated with patients' clinical outcomess. For example, isolates unable to lyse fibrin (lack of staphylokinase) were more likely to cause infective endocarditis, while isolates incapable of producing fibrin (lack of staphylocoagulase) or having a high capacity to produce both enzymes were more likely to be associated with the pneumonia. We therefore hypothesize that staphylococcus uses diverse strategies to control the amount of fibrin by either enzyme, which is important for bacterial adaptation to different sites of the human host during infection. We propose a project to characterize these different strategies employed by isolates producing different amounts of both types of enzymes using the most appropriate experimental models, including infective endocarditis and chronic wound infections in humanized mice. The infection experiments will be conducted using clinical isolates and their mutants, devoid of appropriate factors, which will allow to compare their relative importance in each of the models.

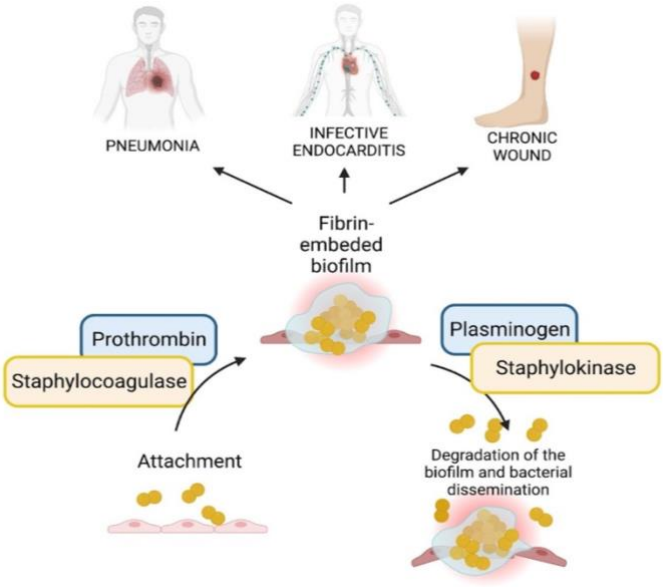

Fig. Schematic representation of the interplay between staphylocoagulase and staphylokinase of S. aureus and human prothrombin and plasminogen in the development of infection complications.

Over 80% of *S. aureus* causing bloodstream infections in Europe (incl. Poland) belongs to genetic lines, called clonal complexes of 5, 30, 45, 22, 8, 15 and 1. One of studied enzymes - staphylocoagulase, is highly diverse (polimorphic) between these genetic lines. We have observed that these differences are related to the enzymatic efficacy (speed of action) and further reflected by differences in the structure of the fibrin it produces. We propose to investigate the significance of this phenomenon using a number of innovative methods, including thromboelastometry, which allows the study of dynamic properties of blood clots. We will examine human blood coagulation parameters, i.e. coagulation time, clot size, its firmness and susceptibility to lysis as a result of the action of staphylocoagulases from various clonal complexes. This novel experimental tool will help identify new anticoagulants effective against the health-threatening interactions of *S. aureus* with the human hemostatic system.