Immunoprotective properties of human plasma gelsolin in fungal infections

Plasma gelsolin (pGSN) is a protein with pleiotropic biological effects and complex mechanisms of action, regulated by Ca^{2+} and phosphatidylinositols: in particular $PI(4,5)P_2$ and able to bind globular (G-) and filamentous (F-) actin. So far, we know that pGSN participates in buffering the bloodstream from F-actin released during the breakdown of cells and also preferentially binds positively charged bioactive lipids such as lysophosphatic acid (LTA), platelets activating factor (PAF), sphingosine-1-Phosphate (S1P), bacteria wall lipopolysaccharides (LPS), and lipoteichoic acid (LTA). Remarkably, pGSN concentration in the blood of patients with sepsis, acute respiratory distress syndrome (ARDS), and multiple dysfunction syndrome is substantially reduced and it might serve as a sensitive diagnostic and prognostic tool. In addition, pGSN has immunomodulatory properties: it might enhance the process of bacterial cell phagocytosis, or intracellular destruction of pathogens by immunocompetent cells - this is the first line of the so-called 'non-specific defense' against microbial infections.

In immunocompromised patients, the immune system is impaired, rendering them more prone to infections, even by less pathogenic microorganisms such as fungi. For instance, the amount of white blood cells in immunocompromised individuals is usually reduced, affecting several protective mechanisms, in particular phagocytosis. Furthermore, fungal infections that are associate with cancer treatment, chronic disease (diabetes), and organ transplantations, are increasingly important. Unfortunately, since the number of drugs with antifungal activity is significantly lower in comparison to antibacterial agents, fungal infections are a huge challenge for a modern healthcare. Even the existing antifungal drugs have many drawbacks, like ineffectiveness and strong toxicity; significantly limiting their therapeutic applications. Therefore, an improvement in host immune defense offers a therapeutic solution for patients in the risk groups, including those in subjected to chemotherapy as well as elderly patients.

The aim of the proposed project is to assess the ability of plasma gelsolin to reinforce the antifungal activity of human immune system, even when the number of neutrophils decreases, by stimulating the phagocytosis of lasting cells. The immunomodulatory properties of pGSN will also be evaluated in terms of expression of adhesive factors, mechanical properties, and vascular endothelial permeability since reinforcement of phagocytosis might be achieved by increase of neutrophil migration trough endothelial walls of the capillary system. The obtain data might serve as a base for development of a new therapeutic option for patients with immunodeficiency, which are predisposed to frequent, recurrent and life-threatening fungal infections. We also expect that due to the structural similarity of some fungal lipids.and already described molecules that interact with gelsolin, we will be able to identify the new molecular target point for pGSN and more likely for gelsolin delivered peptides. In summary, the project will expand knowledge about plasma gelsolin - a protein with significant clinical potential for patients with life threatening conditions.