Extracellular vimentin as a signaling molecule in the pathogenesis of inflammation and central nervous system damage in patients with COVID-19

SARS-CoV-2 is a β-coronaviridae virus first identified in December 2019. In March 2020, the World Health Organization (WHO) declared a pandemic that paralyzed health systems worldwide. While SARS-CoV-2 infection is most commonly associated with pathological inflammatory lesions in the lungs, COVID-19 can also cause lesions in other organs, including the brain. **Up to 40% of patients have been diagnosed with chronic neurologic symptoms, referred to as "covid brain fog" or "long-COVID". In most cases, these symptoms are relatively mild and go away without treatment (loss of consciousness, dizziness). However, a significant number of patients may develop acute, fatal complications (stroke, encephalopathy), making it critical to understand the mechanism and develop effective countermeasures.** How coronavirus damages brain vessels and subsequently brain tissues is not fully understood. Excessive secretion of inflammatory mediators (known as cytokine storm) and direct action of protein S (used by the virus to enter host cells) accompanying infection are indicated as some of the causes of blood-brain barrier damage in SARS-CoV-2 disease. The blood-brain barrier is a highly selectively permeable barrier between the peripheral circulation and brain structures, and its damage results in the increased crossing of harmful substances, including viruses and inflammatory proteins, that should not physiologically enter the brain, but it also protects the body from the systemic effects of active substances produced in the brain **The primary receptor utilized by the virus during infection is angiotensin II-converting enzyme (ACE2), but numerous reports indicate that ACE2 alone is insufficient, and the entry process is complemented by proteins that facilitate/modulate viral attachment at the cell surface. We have recently shown that the role of such a protein is played by extracellular vimentin located on the cell surface (*Suprewicz et al. Small 2022*).**

Vimentin is a protein that builds elements of the cytoskeleton of cells of mesenchymal origin (endothelial cells, fibroblasts, and immune response cells), which plays a role in fundamental processes, i.e., cell division, migration, or protection of the cell nucleus from mechanical damage. Extracellular vimentin can be secreted into the bloodstream by immune cells (neutrophils, macrophages) during inflammation. There are two forms of extracellular vimentin: on the cell surface and unbound to the cell surface. Surface vimentin functions as a coreceptor for bacterial and viral infections (including SARS-CoV-2), while vimentin in body fluids modulates the inflammatory response, which is probably highly dependent on its post-translational modifications following the secretion process. In addition, secretory vimentin is assimilated on the surface of other cells. **We hypothesize that exogenous vimentin is a modulator of blood-brain barrier permeability, and the molecular mechanism of this action in Covid-19 is indirect and results from the ability of vimentin to bind protein S, acting as a transporter, presenting protein S to receptors on the surface of cerebral microvascular cells.**

This project aims to define extracellular vimentin's role in the brain inflammatory process accompanying SARS-CoV-2 infection. We plan to evaluate the association between the assimilation of extracellular vimentin on the surface of different cell types (endothelium, astrocytes) and its post-translational modification. In addition, we will determine the mechanism by which cells can acquire vimentin. Using 2D and 3D models of the blood-brain barrier, the permeability and integrity of endothelial cells and the adhesion and migration of immune response cells in the presence of vimentin, protein S, and their combination will be determined. In the next step, the modulation of inflammation (secretion of inflammatory mediators) in the presence of the tested compounds will be assessed. The study will culminate in a molecular-level assessment of the signaling pathways whose stimulation of gene expression is characteristic of SARS-CoV-2 infection and inflammatory blood vessel damage.

The results obtained during this project may significantly increase our knowledge of the effects of extracellular vimentin and its post-translationally modified forms on endothelial and immune cell responses during SARS-CoV-2 infection. In addition, the data collected during this study may identify a new anti-inflammatory therapeutic target in patients with SARS-CoV-2.