Wojciech Grabiński – abstract

Yeast system for screening SARS-CoV-2 main protease inhibitors

The COVID-19 pandemic, caused by the *Betacoronavirus pandemicum* virus (SARS-CoV-2), has resulted in the death of millions of people worldwide. One of the proteins required for SARS-CoV-2 to function is its main protease (M^{pro}), making it one of the most important targets for potential drugs. The aim of this thesis was to develop a safe, inexpensive and rapid screening system based on the yeast *Saccharomyces cerevisiae* to study M^{pro} activity and search for its inhibitors. This system allows the controlled expression of the M^{pro} gene under the control of the *GAL1* promoter. The proposed system allows for the determination of M^{pro} activity both through its toxic effect on yeast cell growth and through measurement of changes in fluorescence level. The system showed sensitivity to known M^{pro} inhibitors, but also allowed the identification of new, previously undescribed inhibitors, such as meisoindigo. In addition, the results indicated a relationship between M^{pro} activity and mitochondrial function. M^{pro} was observed to be particularly toxic under conditions that require active mitochondria in cells. Based on measurements of cellular respiration levels and microscopic observations, M^{pro} was shown to reduce oxygen consumption, disrupt the inner mitochondrial membrane potential, and cause deformation of mitochondrial structure. In addition, this thesis presents a literature review of the extensive use of yeast in SARS-CoV-2 research, including the analysis of M^{pro} activity, the study between viral- host protein interactions, vaccine production, and the formation of SARS-CoV-2 replicons. This dissertation presents an effective yeast system for the detection of M^{pro} inhibitors and provides new insights into the effects of M^{pro} on key subcellular structures such as mitochondria, expanding our understanding of the mechanisms of SARS-CoV-2 action.