The mechanical and spectroscopic study of two- and three-dimensional cell culture systems to assess molecular mechanism of glioblastoma development

Human brain tissue is among the softest in our body. The extracellular matrix (ECM) of the brain tissue consists of relatively low content of fibrous proteins, like collagens but it is largely occupied by proteoglycans and glycosaminoglycans such as hyaluronic acid. The molecular composition of the brain undergoes modifications during the development of brain tumors, like one of the deadliest type – glioblastoma multiforme (Fig. 1). These modifications include significant increase of the collagen I and hyaluronic acid concentrations. As a result, matrix becomes more crosslinked and by that mechanically different. Moreover, increased pressure gradients inside the developing brain tumors are widely reported, what causes local increase in tissue stiffness. It is postulated that mechanochemical changes of the brain ECM's that accompany glioblastoma tumor development influence cellular behavior and allow tumor cells to efficiently migrate and increase their proliferation rate. The increase in cell migration and proliferation requires biochemical changes at the molecular level. Such changes can be detected by application of Raman spectroscopy, which allows for non-invasive measurements of living cells in their physiological conditions.

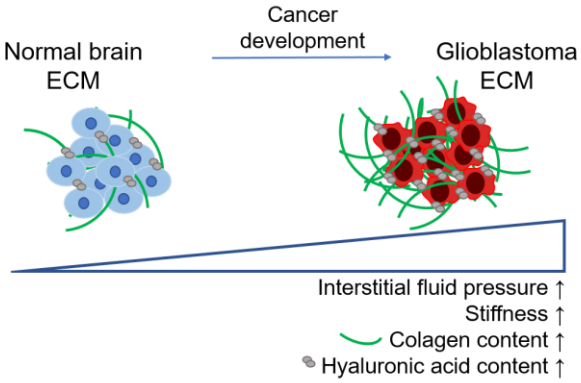

Figure 1. Extracellular matrix modifications during glioma multiforme development.

The proposed research project assumes the synthesis and mechanical characterization of two- and three-dimensional biopolymer matrices, which chemical composition and stiffness will recapitulate mechanochemical properties of normal and cancerous brain tissue. Such matrices will serve as the growing substrates for cell culture of normal human astrocytes and glioblastoma cells. Proliferative behavior of the cells will be estimated based on viability assays, what will allow to observe the influence of the stiffness and substrate composition on cell division. Subsequently, Raman spectroscopy will be employed, allowing for correlation of mechanochemical properties of ECM-mimicking matrices with biochemical composition of the cells.

The main goal of the proposed project is to identify molecular markers responsible for normal and cancerous cells adaptation to their mechanochemical microenvironment by controlled modification of its stiffness and chemical composition. This will broaden our understanding of the molecular mechanism of the glioma multiforme development and allow to improve the effectiveness of the anticancer therapies in the future.