Collagen-hyaluronic gels as an environment for a controlled change of mechanical properties of spheroids under shear forces

1. Project objectives

Recent findings on deformability of single cancerous cells and the importance of surrounding extracellular matrix (ECM) have demonstrated a close and strong link between physicochemical and biological/molecular properties of the cell-ECM system. These findings led to the hypothesis that the interplay between the mechanics of ECM and cells is one of the key hallmarks deciding which cells start to disseminate to form metastatic sites. The presented research project aims to develop and characterise three dimensional (3D) hydrogels modified with ECM proteins as a mean to study an environmental impact on spheroids built of cells from the bladder and pancreatic cancers.

2. Research description

The project aims to understand how shear and compressive forces drive genetic, morphological and mechanical properties of cancer spheroids. This project will employ tailoring 3D collagen-hyaluronic hydrogels with specific physicochemical properties, including hydrogel mechanics, composition, and ECM protein concentrations (Fig. 1).

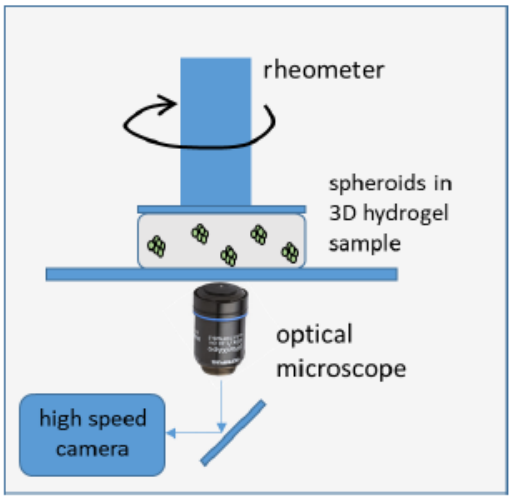

Figure 1. The idea of the project. A rheometer will be used to induce shear and compression forces within 3D hydrogels mimicking ECM with embedded cancer spheroids (bladder and pancreatic cancers). Applied forces will deform spheroids. Their deformation will be recorded by a high-speed camera (in a real-time dependent manner).

Cells in their natural conditions undergo continuous exposure to mechanical forces leading to shear or compressive deformations. Thus, we postulate that shear forces can contribute significantly to the process of cell escape from the spheroid surface.
Unlike standard cell culture conditions involving plastic surface (2D conditions), 3D environments allow a cell to interact with integrins simultaneously on a whole surface, not only at the bottom part, as in 2D conditions where the cells are attached to a flat surface. Thus, in the proposed project, a rheometer will be applied to investigate the viscoelastic properties of two classes of samples, i.e. hydrogels and hydrogels with embedded spheroids. Such samples will undergo shear deformation in the range mimicking physiologically relevant mechanical forces. By monitoring the mechanical properties of hydrogels with and without spheroids, it will be possible to resolve how cells interact with ECM. Simultaneous, independent recording of spheroids deformation using an optical microscope will allow studying changes of spheroid mechanical properties and integrity as a function of the applied shear stress in a real-time manner. This helps to understand which conditions are needed for a cancer cell to escape from the spheroid surface to a hydrogel environment mimicking ECM. The spheroids will be embedded in hydrogels with tunable mechanical properties of various composition (collagen, hyaluronic acid and incorporated ECM proteins such as laminin, tenascin C.

3. *Expected impact*

Designing and tailoring 3D collagen-hyaluronic hydrogels with embedded cancer spheroids provides an important tool to study the relation between mechanical and morphological properties of spheroids in the condition of applied shear and compression forces. Coupling rheometer with complementary observation techniques such as optical/fluorescence microscopy allows correlating the time-dependent microstructure of cells/tissues with rheological properties. The enlarged functionality of the measuring system will deliver a real-time response of cancer spheroids to prolonged action of mechanical forces. Such an approach delivers a rheometer as a technique characterising changes in rheological properties during cancer progression. We expect to provide a new understanding of mechanisms involved in cell spreading and, thereby, adaptation to mechanically various conditions. This will provide a means to recapitulate tumour invasiveness, potentially applied to drug-resistance studies.