Introduction

Most cancer deaths are not caused by the primary tumor, but by secondary tumors formed through metastasis, a complex and poorly understood process. The first steps of metastasis are invasion, when tumor cells escape from the primary tumor, and subsequent migration through the surrounding tissue (Figure 1). This process is determined not only by cell-intrinsic properties, but also by the properties of the cell-extrinsic factors of the tumor microenvironment, such as the extracellular matrix (ECM) surrounding the tumor. [1]

Recent research at Radboud University Medical Center, aimed at better understanding, has shown that the mode of invasion and migration of tumor cells is determined by a delicate interplay between cell-cell adhesion, density/stiffness of the ECM, and geometrical structure of the ECM that influences the level of confinement of the tumor cells. This interplay determines for example whether the cells migrate individually, or collectively. These studies have led to the hypothesis, that tissue pressure / compressive stresses play an important role too, however due to the lack of good experimental models allowing for independent pressure control, it has not been possible to test this hypothesis.

Project

Here we propose to design, realize, and apply a microfluidic device that enables to test this hypothesis. The starting point of the design is a chip used previously for the characterization of mechanical properties of cells, Figure 2. [2] It consists of two microfluidic chambers, separated by a thin, flexible membrane. By applying a controlled overpressure in one chamber, the membrane deflects into the second chamber which generates a known compressive stress / pressure in that chamber. As shown in Figure 3, in this project we will use this to apply pressure on a tumoroid of breast cancer cells, embedded in a collagen gel. This project entails (1) designing the chip (e.g. dimensions), (2) fabricating the chip (using soft lithography), (3) realizing the complete setup including the pressure system, (4) in close collaboration with RadboudUMC, carry out experiments using tumoroids. We will vary cell-cell adhesion, collagen density and stiffness, and pressure, and observe migration behavior and dynamic regulation of cell-cell adhesions.

References

[1] Sleeboom, Amirabadi, et al., Disease Models & Mechanisms, 2018

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