Mechanobiology of Cancer Summer School · 17-21st September 2019

Marija Plodinec – 19th September 9.00

Nanomechanical profiling of living epithelial tissues in health and disease and potential applications in routine clinical setting

Mechanical properties and physical interactions of cells and their microenvironment that occur at nanometre scale play a critical role in cancer progression and metastatic dissemination. The onset of metastasis occurs when cancer cells invade and breach the basement membrane (BM) that provides mechanical support to epithelial tissues. We have established an in vitro assay using native BM interface for culturing epithelial cells and demonstrated that native BMs isolated from human tissues act as a native substrate for culturing epithelial cells in terms of composition, architecture and stiffness. These are required to act jointly in order to achieve apico-basal polarity, tissue barrier formation and stiffness properties of the epithelial layer similarly to secretory epithelia in vivo.

During cancer progression in vivo, cancer cells can perforate BM using proteolysis and the cancer cell invasion is associated with decrease in cellular stiffness and correlated to changes in cell and BM morphology. The role of stromal cells in this process has not yet been resolved. Therefore, in collaboration with the Vignjevic lab we examined if carcinoma-associated fibroblasts (CAFs) isolated from cancer patients promote cancer cell invasion through a BM. In the presence of CAFs, moderately invasive cancer cells invade in a matrix metalloproteinase-independent manner. Using live imaging and atomic force microscopy, we could show that CAFs actively pull, stretch and soften the BM, forming gaps through which cancer cells can migrate. By exerting contractile forces, CAFs alter the organization and physical properties of native BM, making it permissive for cancer cell invasion.

Furthermore, physical properties of tissues measured at the nanometer (molecular) level provide fast and precise cancer diagnosis. Detecting extreme viscoelastic (soft) cancer cells in biopsies is a direct biomarker of cancer aggressiveness (Plodinec et. al., 2012). In an ongoing trial conducted in a routine clinical setting we distinguished benign from cancerous breast lesions ARTIDIS employs a micro-fabricated 20nm-sharp tip which indents 10,000 locations/sample to measure the stiffness of cellular and matrix structures. The data are gathered, verified and analyzed within a comprehensive platform; 2.54 million of AFM indentations in relation to over 100 clinical parameters /patient using artificial intelligence.In our interim analysis of core needle and vacuum biopsies (N=254), the ARTIDIS demonstrated the outstanding ability to rapidly differentiate benign from malignant breast lesions in a routine clinical setting. Moreover, results suggested that we are able to subclassify breast lesions into specific subtypes that could be associated with better or worse prognosis as confirmed by the post-AFM data extracted from the clinical follow up information. The final analysis will determine clinical utility and indications for future studies on nanomechanical characterization of breast cancer for prediction and treatment optimization.

Marija Plodinec, Ph.D is a cancer biophysicist who is disrupting the way cancer diagnosis and treatment prediction is performed in the clinics, using Physics. Dr. Plodinec studied physics in Zagreb and received her doctorate in 2010 from the Maurice Müller Institute at the Biozentrum of the University of Basel. For twelve years, she has driven the development of ARTIDIS, a medical device for fast and early diagnostics of breast cancer based on a physical probing of biomechanical forces, a work she begun during her PhD. During her many years as a research associate at the Biozentrum of the University of Basel and as a project leader at the University Hospital Basel, she has brought this technology from basic research to the first clinical studies. In 2014, together with a team of 3 people, Dr. Plodinec founded ARTIDIS AG, a swiss startup that aims at innovating cancer research, clinical diagnosis and treatment response prediction. Dr. Plodinec is a recognized expert in the field of physical sciences in oncology and has co-authored important scientific papers and patents in this field. She is also a member of several international organizations focusing on cancer research and its clinical applications. In November 2017, Dr. Plodinec became the CEO of ARTIDIS AG and a Member of Board of Directors.