Discovering new targets and determinants of metastatic spread is a key unmet need in high-grade serous ovarian cancer (HG-SOC), which is plagued by high rates of recurrence. In the more aggressive tumors, the invasion of cells through the extracellular matrix (ECM) involves the formation of actin-based protrusions, invadopodia, as hubs of adhesive and cytoskeletal signaling pathways, operating ECM degradation. Their formation is a dynamic process requiring the combined and synergistic activity of ECM-modifying proteins with cellular receptors, and the interplay with surrounding stromal cells, which will feedback and further stimulate mechanosignaling, where invadopodia might act as mechanosensing structures (1). In this context, the endothelin-1 receptor (ET-1R) signaling drives HG-SOC progression and invadopodia function through the scaffolding function of β-arrestin1 (β-arr1) (2-4). Since the gradual ECM breakdown and release of ligands for integrin receptors, especially β1-integrin (Intβ1), might increase cancer cell invasion and metastasis via invadopodia formation, we are investigating in 3D model of HG-SOC whether ET-1R/β-arr1 regulates invadopodia operating through a cross-talk with Intβ1 signalling and downstream effectors, such as integrin-linked kinase (ILK), to converge specific signals at invasive protrusions. We are also dissecting how the ET-1R/Intβ1 signaling mediates the dialogue between cancer and stromal cells, in promoting ECM remodelling in the metastatic niche, by using a 3D organotypic model of HG-SOC. We assemble the organotypic model with defined compartments of cancer and stroma, containing HG-SOC cells along with primary mesothelial cells and cancer-associated fibroblasts (CAF) in the high dense collagen, to mimic omental niche encountered during metastasis. At translation level, we are testing the co-targeting of ET₄R and Intβ1 in HG-SOC xenografts and 3D organotypic models as a potential drug combination for controlling HG-SOC metastatic spread. We use ambrisentan, an FDA approved ET₄R antagonist, for the pharmacological blockade of ET₄R, in combination with the small peptide (ATN-161), to inhibit integrin α5β1 function, alone or in combination with platinum-based chemotherapy. The crosstalk between mesothelial cells, CAFs and HG-SOC cells will be investigated also in a biomimetic system and an organ-on-chip device, using a microfluidic-based technology. This device and the synthesis of polyethylene glycol (PEG)-based hydrogels, with easy adjustable matrix stiffness and mechanical properties to recapitulate the metastatic niche and its alignment, help us to ascertain how the different degree of matrix organization and related changes of stiffness support tumor cells/CAF invadopodia function and invasive behaviour upon ET-1R/β-arr1 and Intβ1 activation.

References:

Keywords: organoids; cancer cell invasion and metastasis; invadopodia.

Contacts: laura.rosano@uniroma1.it