IBEC-VHIR INTERNATIONAL PhD PROGRAMME

Position

1. Project Title/ Job Position title:
Role of Matrix Viscoelasticity and Pannexin-1 Channels in Pancreatic Cancer

2. Research project/ Research Group description

Our group 'Microenvironments for Medicine' at IBEC engineer biomaterials with controlled properties for applications in cell engineering, to support in vitro models and as tools for mechanobiology. Here, in collaboration with Trond Aasen (Senior Investigator at Vall d'Hebron Institut de Recerca) we will engineer viscoelastic hydrogels to understand the role of pannexin-1 in sensing matrix viscoelasticity in pancreatic cancer cells.

The group at IBEC led by Manuel Salmeron-Sanchez focuses on the design of advanced biomaterials to engineer the cellular microenvironment, which has the potential to impact health by translating fundamental research into innovative therapies. We know that the extracellular matrix is viscoelastic yet most biomaterials that support tissue engineering and regenerative medicine approaches only consider the elasticity of biomaterials. We strive to design materials where elasticity and viscosity can be tuned independently to provide 2D and 3D hydrogels that support dynamic cellular processes and their physical remodelling.

The research group led by Trond Aasen at the Translational Molecular Pathology Laboratory at VHIR specializes in the molecular cell biology of gap junctions, connexins, and pannexin channels in relation to tumor pathobiology. We focus on intercellular communication and cell signaling between cancer cells and stromal cells. We employ 2D and 3D in vitro models, alongside analyses of tumor samples obtained from the pathology department.

3. Job position description

It is now well accepted that cells (including mesenchymal stem cells, and cancer cells) are sensitive to the rigidity of the extracellular matrix. The mechanobiology community has used hydrogels of controlled elasticity to demonstrate that cell response to substrate rigidity is explained by the so-called molecular clutch. Here, integrins pull on the substrate and this force is transmitted to the actin cytoskeleton through focal adhesions, in a way that when talin is unfolded and stabilised by vinculin then the clutch is engaged, force is transduced and focal adhesions grow. However, we know that the ECM is not elastic but viscoelastic, which means that there are dynamic processes that lead to the reorganisation of the ECM upon application of force by cells and so time-dependent phenomena such as stress relaxation emerge. We have made progress in understanding the interplay between viscoelasticity, the molecular clutch model, and also the role of other mechanotransductive channels such as piezo 1.

Recent studies suggest that other membrane proteins might play important roles in cell mechanotransduction by modulating the strength of cell adhesion and the transmission of forces between cells and the ECM. Here we will focus on mechanosensitive pannexin-1 channels that release extracellular ATP regulating purinergic signalling in tumor and stromal cells. We will investigate the functionality of pannexin-1 in pancreatic cancer cells on substrates of controlled viscoelasticity, to elucidate the role of this important mechanical property, and also the relationship to integrins and other membrane mechanoreceptors such as piezo 1.

At IBEC, the student will focus on engineering viscoelastic hydrogels of controlled properties and their characterisation using nanoindentation and Brillouin Microscopy along with the effect of cells on the viscoelastic properties of hydrogels.

At VHIR, the student will focus on the molecular cell biology and function of Pannexin-1, including unveiling how mechanosensing opens the channel and how downstream signaling pathways, including purinergic ATP signaling in tumor and stromal pancreatic stellate cells, affect the desmoplastic reaction of the extracellular matrix.

Group Leader IBEC

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4. Research Group: Microenvironments for Medicine

Collaborator in the other institution

1. Title: Senior Investigator
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5. Research group: Translational Molecular Pathology