Title: Modelling the dynamic complex of EMT in pancreatic cancer

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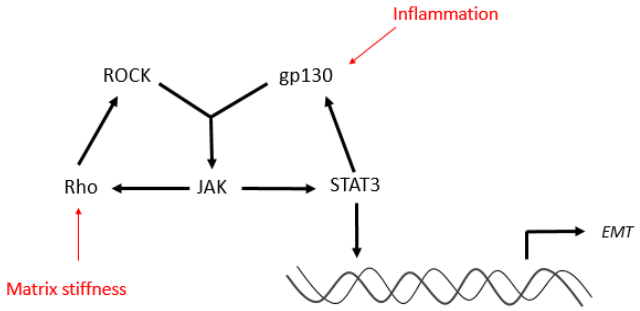
PDAC Modelling Project

Pancreatic ductal adenocarcinoma (PDAC) is the fourth most lethal cancer in the developed world, with > 200 000 deaths per year across the world. Currently, the 5-year survival rate is < 4%, and the cancer responds very poorly to chemotherapeutic agents. The PDAC stroma is highly fibrotic due to desmoplasia, the deposition of a dense and crosslinked extracellular matrix (ECM), and is particularly pronounced in PDAC. The stiffness associated with desmoplasia can promote tumour malignancy across multiple organs, as the rigid stroma forces a tensional homeostasis with high levels of cell contractility to counteract the stiff environment, inducing intracellular signalling and malignant transformation (Laklai et al. 2016). PDAC additionally shows high levels of inflammatory cytokines which promote malignancy (Roshani et al. 2014).

The epithelial–mesenchymal transition (EMT) is a process in which cells become more motile through loss of cell–cell adhesion and their apical–basal polarity. This process is suggested to be vital for progression of PDAC as well as chemoresistance (Karamitopoulou 2013). Substrate stiffness has been shown to induce EMT *in vitro* for pancreatic cancer cells (Rice et al. 2017). Inflammation has been linked with EMT in breast cancer(Sullivan et al. 2009) and pancreatic cancer (Khalafalla & Khan 2017). Possible links between substrate stiffness downstream signalling (ROCK and Rho) and inflammatory cytokine signalling through STAT3 have been suggested, with key experiments in melanoma cells (Sanz-Moreno et al. 2011).



Simplified working model of mechanical and inflammatory EMT network

The project will use computational modelling of signalling networks to determine the dynamics of the complex network surrounding induction of EMT in pancreatic cancer. Key questions include how the multiple signals can collaborate with each other to induce EMT, as well as perturbation studies to determine the key molecules and reactions, which will suggest possible therapeutic solutions.

Some good modelling papers to look at are (Sun et al. 2016) and (Steven et al. 2008). The Steven et al. 2008 paper is the sort of methodology we'll be using and has a lot of overlap in terms of the signalling pathways we'll be using.

Skills:

Design of measurement tools and experimental protocols are the basis of this project. The applicant is offered the opportunity to work within a highly interdisciplinary field in which engineering skills are applied to cancer research. As such, the project will involve communication of complex ideas to starkly different target audiences. In addition to developing the ability to quickly assimilate new concepts, the applicant is also expected to demonstrate strong problem solving and critical thinking skills in a laboratory environment.

References

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