Defining a role for mTORC1 in regulating focal adhesions and cell migration

Project ID: 271

Supervisory team

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Project description: Rapamycin is a drug that inhibits the mammalian target of rapamycin complex 1 (mTORC1), a master regulator of cell growth and metabolism. It has potent anti-tumour and immunosuppressive activity and has been shown to improve health in a variety of settings, but it also has side effects such as reduced wound healing efficiency that has limited its use in treatment of humans. Understanding how rapamycin and mTORC1 influence cell behaviour during wound healing will therefore lead to the development of therapeutics aimed towards mitigating the side effects of rapamycin, facilitating its further use as a therapeutic in a wide range of settings.The movement of keratinocyte and fibroblast cells into a wound represents a key process in efficient wound healing, and this cell migration is regulated by receptors found at the cell surface called integrins. Integrins engage with the surrounding environment and form adhesion complexes which act as both a physical link between the extracellular matrix that cells are attached to and the cellular cytoskeleton and as signalling hubs that control cell biology. The traction forces and downstream signalling generated by adhesion complexes are required for efficient cell migration, therefore regulation of these complexes represents a key mechanism by which cell movement can be controlled and modulated. We have recently shown that a spatially distinct pool of mTORC1 localises in the vicinity of adhesion complexes at the plasma membrane and is active at this location. Inhibition of mTORC1 using rapamycin leads to the formation of larger, more stable adhesion complexes, therefore we predict that mTORC1 regulates adhesion turnover and signalling during cell migration and that this represents a key mechanism by which rapamycin treatment leads to perturbed wound healing.This studentship will build on these findings and will have three key aims:1)Characterise the impact of mTOR inhibition on adhesion dynamics and migration in 2D and 3D environments.2) Identify adhesion-specific substrates of mTORC1 using a phosphoproteomic approach.3) Use site-directed mutagenesis and over expression of mutant proteins to determine the impact of mTORC1 substrates on adhesion composition, dynamics and cell migration.This project will mechanistically define how mTORC1 functions to regulate adhesion complexes and cell migration in fibroblasts and keratinocytes, therefore identifying pathways that could potentially be targeted to mitigate the inhibition of wound healing by rapamycin. It will utilise a range of techniques including 2D and 3D cell culture, advanced imaging approaches and proteomic analysis.

Our aim as the SWBio DTP is to support students from a range of backgrounds and circumstances. Where needed, we will work with you to take into consideration reasonable project adaptations (for example to support caring responsibilities, disabilities, other significant personal circumstances) as well as flexible working and part-time study requests, to enable greater access to a PhD. All our supervisors support us with this aim, so please feel comfortable in discussing further with the listed PhD project supervisor to see what is feasible.