

Cell Signalling Laboratory

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The main focus of the **Cell Signalling Laboratory** is to elucidate the signalling pathways that transform a non-migratory, non-invasive epithelial cell into a migratory invasive mesenchymal cell. The need for cells to move away from their tissue of derivation and take up residence in a new environment where they can proliferate and undergo further differentiation underpins the formation of new tissues and organs during embryonal development. In the adult, it also underlies the process of wound healing and when aberrantly reactivated, is the forebear to pathologies such as cancer progression and organ fibrosis leading to end-stage organ failure.

Epithelial cells that make up many tissues and organs are characterised by strong adhesion to adjacent cells rendering them quiescent and non-migratory. In contrast, fibroblasts or mesenchymal cells are isolated cells that have the capacity to migrate and invade their surrounding matrix. Thus, for epithelial cells in a tissue mass to migrate they must undergo a drastic morphological and functional transformation, the **epithelial-mesenchymal transition (EMT)**, into a mesenchymal-like cell. About 80% of human cancers are epithelial in origin and EMT is thus a prerequisite to metastatic disease, the main cause of death in cancer patients. EMT in development is induced in response to a number of growth factors and extracellular signals. The signalling mechanisms that regulate such a complex phenomenon is likely to be complex themselves but a growth factor that regulates EMT in development, the transforming growth factor β (TGF β), is also a potent promoter of metastasis in some cancers, including breast cancer and a major contributor to tissue fibrosis.

Current Projects

Recent work from the Cell Signalling Laboratory has identified a novel regulator of TGF β and EMT, the protein tyrosine phosphatase Pez. Together with our collaborators, we have also identified a family of microRNAs that act downstream of TGF β to regulate EMT.

1. The role of Pez and miR200 family microRNAs in development, cancer and organ fibrosis.

In preliminary studies, we have found that Pez may regulate TGF β signalling in human breast cancers and thus play a role in tumour progression to metastatic disease. We are currently looking to verify that Pez indeed plays a causal role in cancer progression using mouse models of breast cancer. We are also investigating the role of Pez and microRNAs in mammary gland development. Because of the strong association of TGF β and its ability to promote EMT in organ fibrosis, we will also investigate if Pez and/or the miR200 family of microRNAs play a role in kidney fibrosis (in collaboration).

2. Regulation of TGF β production and activation.

Although TGF β has been shown to promote metastasis in animal models of breast cancer and elevated levels of TGF β is an indicator of poor prognosis in cancer patients, our current understanding of how its levels are regulated are poor. We are therefore investigating the molecular mechanism by which Pez regulates the production or activation of TGF β and how this might impact on cancer and fibrosis.

Key publications:

1. Wadham C, Gamble JR, Vadas MA and **Khew-Goodall Y**. Translocation of protein tyrosine phosphatase Pez/PTPD2/PTP36 to the nucleus is associated with induction of cell proliferation. *J Cell Sci.* 113:3117-3123, 2000.
2. Wadham C, Gamble JR, Vadas MA and **Khew-Goodall Y**. The protein tyrosine phosphatase Pez is a major phosphatase of intercellular junctions and dephosphorylates β -catenin. *Mol. Biol. Cell.* 14:2520-2529, 2003.
3. Wyatt L, Wadham C, Crocker LA, Lardelli M and **Khew-Goodall Y**. The protein tyrosine phosphatase Pez regulates TGF β , epithelial-mesenchymal transition and organ development. *J Cell Biol.* 178:1223-1235, 2007.
4. Gregory PA, Bert AG, Paterson EL, Barry SC, Tsykin A, Farshid G, Vadas MA, **Khew-Goodall Y*** and Goodall GJ*. The microRNA-200 family regulates epithelial-mesenchymal transition by repressing the E-cadherin repressors, ZEB1 and SIP1. *Nat. Cell Biol.* 10:593-601. ***authors contributed equally.**