Cell Signalling Laboratory

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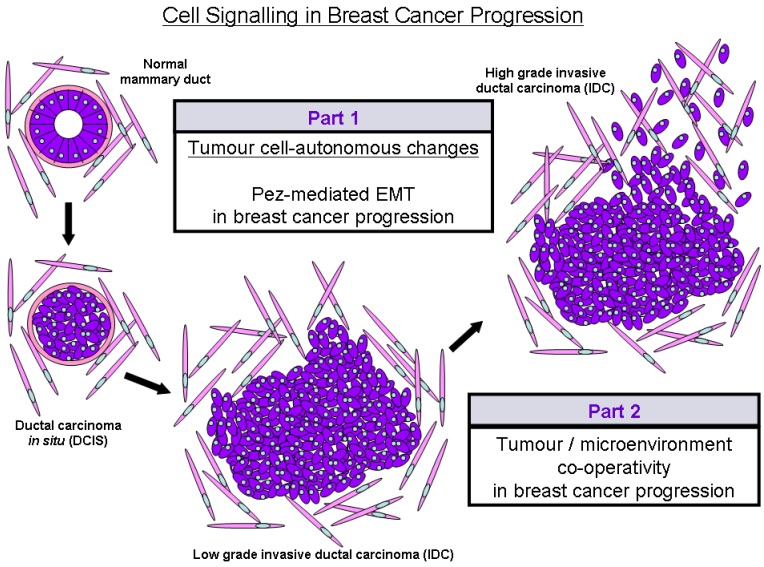
Research Overview

The interest of the **Cell Signalling Laboratory** is to understand how signals that are normally generated to maintain homeostasis, when dysregulated give rise to disease. Our disease model is breast cancer metastasis and our focus is to understand what turns a benign cancer cell which remains local and treatable to a metastatic cell capable of spreading to multiple organs. In solid tumours, which make up ~80% of human cancers, **metastasis** is the main cause of death.

We use cell biological, molecular biological, biochemical and microscopy approaches in our studies and where possible, verify our findings using animal models and human clinical samples.

Research Areas



1. Regulation of the cancer cell secretome

Cells secrete factors that can act upon themselves or on other cells for normal maintenance or homeostasis. Cancer cells, through mutations, can have an altered composition of secreted factors which can act to alter their immediate microenvironment. Importantly, the cancer 'secretome' can modify the behaviour of the surrounding resident fibroblasts or recruit bone marrow-derived cells to help modify the microenvironment to one that now promotes cancer progression to metastasis or drug resistance. More recent studies have shown that the cancer 'secretome' can prepare a metastatic niche in secondary organs to facilitate their ability to embed in those organs. Our studies in this area are centred around the **protein tyrosine phosphatase Pez (PTP-Pez / PTPN14),** which we have previously shown to regulate TGFβ secretion. In some cells, increased Pez expression and TGFβ secretion can result in them undergoing an epithelial-mesenchymal transition, an early step in the dissemination of breast cancer cells. Pez has also been shown to be mutated in colorectal and breast cancers. We are continuing to investigate its mechanism of action in cancer as well as newer efforts to identify **kinases and other phosphatases that regulate the cancer secretome**.

2. Regulation of the cancer microenvironment

MicroRNAs are relatively newly discovered small non-coding RNAs. Recognition of their roles in regulating cellular functions have increased enormously in the last few years. Using a cell culture model of epithelial-mesenchymal transition developed in our laboratory, in a collaboration with the Goodall Lab, we discovered a family of microRNAS (the miR-200 family) that are crucial regulators of the epithelial state. Dysregulation of expression of the miR-200 microRNAs in epithelial cancer cells render the cells more motile and invasive, thus making them more competent to metastasise. Bolstered by our success with this discovery, the Cell Signalling Lab has also endeavoured to identify **microRNAs** that may affect the cancer microenvironment to make it more conducive to promoting **metastasis** or **chemoresistance**.

Available Student Projects

PhD student projects are available in all the above areas of research. Several Honours projects are available from Part 1 to study mechanisms that regulate the cancer cell secretome and their effect on cancer cell phenotype. Please contact Dr Yeesim Khew-Goodall to discuss specific areas of interest.

Selected Recent Publications

1. Wyatt L, Wadham C, Crocker LA, Lardelli M and **Khew-Goodall Y**. The protein tyrosine phosphatase Pez regulates TGFβ, epithelial-mesenchymal transition, and organ development. *J Cell Biol* 2007 **178**(7):1223-1235.

2. Wyatt, L and **Khew-Goodall, Y**. PTP-Pez: A novel regulator of TGFβ signaling. *Cell Cycle* 2008 **7**(15):2290-2295.

3. Gregory, PA, Bert, AG., Paterson, EL, Barry SC, Tsykin A, Farshid, G, Vadas, MA, **Khew-Goodall, Y*** and Goodall, GJ*. The miR-200 family and miR-205 regulate epithelial to mesenchymal transition by targeting ZEB1 and SIP1. *Nat Cell Biol* 2008 **10**(5):593-601. ****equal contribution***

4. Gregory PA, Bracken CP, Smith E, Bert AG, Wright JA, Roslan S, Morris M, Wyatt L, Farshid G, Lim YY, Lindeman GJ, Shannon MF, Drew PA, **Khew-Goodall Y**, Goodall GJ. An autocrine TGFβ/ZEB/miR-200 signaling network regulates establishment and maintenance of epithelial-mesenchymal transition. *Mol Biol Cell*. 2011 Mar 16.