GROWTH FACTOR SIGNALLING AND SQUAMOUS CANCERS

The transforming growth factor beta (TGFβ) superfamily comprises approximately forty related cytokines, including the bone morphogenetic proteins, the growth and differentiation factors, activin, nodal and the TGFβs (TGFβ1, TGFβ2, TGFβ3). As well as playing important physiological roles during development and adult tissue homeostasis TGFβ family members can act as potent tumour promoters and tumour suppressors and their signalling pathways are frequently dysregulated in cancer.

Work in our laboratory seeks to understand the molecular basis of how, when and where TGFβ superfamily signaling can act to both promote and inhibit tumour progression. Dysregulation of TGFβ signaling is particularly prevalent in squamous cell cancers (SCC) and we are investigating the molecular landscape and drivers of disease progression in cutaneous SCC. Head and Neck SCC and other squamous tumour subtypes using systems biology and biological functional approaches.

TGFβ signaling in squamous cell carcinomas
TGFβ exerts its effects by activation of signal transduction pathways emanating from a heterotetrameric complex of TGFβ2 and TGFβ1 receptors whose formation is facilitated by ligand binding. TGFβ2 activates the kinase activity of TGFβR1 and this in turn phosphorylates SMAD2 and SMAD3, which then form hetero-oligomeric complexes with SMAD4, and regulate expression of hundreds of target genes. In collaboration with Owen Sansom’s and Irene Leigh’s group (Queen Mary University of London) we have shown that TGFβ receptors are inactivated in 30% of sporadic cSCC and that TGFβ signaling can have potent tumour suppressive effects in the face of other mutational events in vivo. We are currently investigating how driver gene combinations act in concert with loss of TGFβ signaling to influence cSSC progression. Despite TGFβ’s powerful tumour suppressive effects in cSCC, 70% of tumours display no obvious inactivation of the canonical signalling pathway. Analysis of the TCGA head and neck squamous carcinoma (HNSCC) data set revealed a similar potential loss/deregulation of canonical signalling components in ~30% of tumour samples with downregulation of TGFβ2 and SMAD4 being particularly prevalent (Figure 1). Strikingly, ~30% of tumours show overexpression of TGFβ1 and many tumours upregulate TGFβ signalling relative to normal tissue. Taken together, these observations indicate that TGFβ signaling may also act to promote tumour progression in both cSCC and HNSCC and we are focusing our initial efforts into understanding the potential tumour promoting effects of TGFβ signalling in cSCC and HNSCC in a panel of patient derived cell lines (PDCls).

cSCC is a life-threatening complication for patients who suffer from recessive dystrophic epidermolysis bullosa (RDEB), an skin blistering disease caused by germline mutations in collagen VII, an anchoring fibril component in the skin. Unlike in sporadic cSCC, RDEB SCC tumours do not contain inactivating mutations in TGFβ.

Figure 1
Carcinogen analysis of TGFβ canonical signaling components in HNSCC. Cobisearch (Canmry et al., Cancer Discov. 2012, and Gao et al., Sci Signal, 2013) analysis of HNSCC (TCCGA, PanCancer Atlas) reveals frequent mutational alteration and downregulation of mRNA expression of TGFβ2 and SMAD4 but overexpression of TGFβ1 and TGFβ2 compared to normal samples pointing to potential tumour suppressor and tumour promoter roles of TGFβ signaling.

Figure 2
Inhibition of endogenous TGFβ signalling blocks clonogenicity and invasion of RDEB cSCC tumour cells. Treatment of RDEB cSSC PDCls with the TGFBR1 kinase inhibitor SB-431542 blocks clonogenic potential (left panel) and invasion in 3D organotypic assays using RDEB cancer associated fibroblasts embedded in type 1 collagen. Matriptase gets tight parallel compared to DMSO treated controls.

Figure 3
Disease progression of human cSSC. Images illustrating disease progression (courtesy of Prof Charlotte Proby, University of Dundee). We are performing molecular profiling of human disease progression using NGS approaches, immunohistochemistry and spatial transcriptomics.

Figure 4
Multiplexed immunohistochemistry of human cSSC. Image of human cSSC primary tumour (courtesy of Dr Lisa Offier-Jones and John Le Querel) stained with the indicated antibodies.

Figure 5
Inhibition of endogenous TGFβ signalling blocks clonogenicity and invasion of RDEB cSSC tumour cells. Treatment of RDEB cSSC PDCls with the TGFBR1 kinase inhibitor SB-431542 blocks clonogenic potential (left panel) and invasion in 3D organotypic assays using RDEB cancer associated fibroblasts embedded in type 1 collagen. Matriptase gets tight parallel compared to DMSO treated controls.