

Testing the role of cell polarity in tumor-related inflammation.

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Background: Tumor-related inflammation is currently known as the 'seventh hallmark of cancer'; nevertheless it is still poorly understood. Most remarkably, inflammation can have both tumor suppressor or promoter effects ('good' and 'bad' inflammation, respectively). The contexts that define such effects are largely unknown. We recently identified an inflammatory-like response to tumorous growth in *Drosophila*, and defined a genetic interplay between the cytokine TNF- α , the Ras oncoprotein and the polarity tumour suppressor Scribble (Cordero et al, 2010). This demonstrates that the Ras oncoprotein constitutes a signaling switch defining a pro- or anti- tumor output after the activation of TNF- α and the innate immune system.

Aim: The objective of this project will be to test whether the mechanism is evolutionary conserved in mammals by using genetic mice tumours models, and clinical data. While the role of Ras and TNF- α in cancer is well documented, the role of mammalian scribble is just beginning to be analyzed. Very recent work indicates Scribble is a potent tumour suppressor in the breast and prostate epithelia.

- Initially, we will test whether the loss of Scribble modifies the skin tumour phenotypes of *Lgr5^{CRE}; Ras^{V12}* mice, a robust and fast new model for papilloma formation.
- Further experiments will utilize blocking antibodies for TNF- α and crosses with TNF- α KO mice, and analyses with inflammatory components such as macrophage infiltration.
- A second model will be to test for a dependency on TNF- α in the recent mouse model for prostate neoplasia *PBCre+;Scrib fl/fl;LSL-K-rasG12D/+* (Pearson et al, 2011); which combines scribble loss of scribble with K-Ras activation. We will test whether TNF- α is upregulated in this model and if so inhibit its function again with blocking antibodies and a genetic TNF- α KO background.
- Clinical data from both skin papilloma and prostate carcinoma will be analyzed for relative levels of Scribble, dp-ERK (a surrogate of Ras activation) and TNF- α expression and correlated with clinical outcome.

Together, these experiments could provide the first evidence for a role of the loss of epithelial polarity in triggering a tumour-promoting inflammatory response. The research fellow will also receive a thorough training in modern microscopy and mouse genetics.

Suitable candidates:

This project may be of interest to anyone who is training or intends to train in any solid-tumour related specialty including surgery, pathology, clinical oncology, medical oncology, and hematology.