From Intestinal Stem Cells to Colorectal Cancer metastasis

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The accumulation of genetic and epigenetic alterations imposes distinct phenotypes and fates on tumour cells within the same cancer. Thus, cancers are amalgams of distinct tumour cell populations. An alternative mechanism to explain tumour cell heterogeneity was originally proposed by G. Barry Pierce in the 70s: "... carcinomas are composed of a mixture of malignant stem cells, which have a marked capacity for proliferation and a limited capacity for differentiation under normal homeostatic conditions, and of the differentiated, possibly benign, progeny of these malignant cells". This hypothesis implies that the diversity of phenotypes and behaviours of tumour cells could arise from a spontaneous differentiation process (Pierce and Speers, 1988). In the last decade, several laboratories including my own, have put forward key evidence supporting the view that Colorectal Cancer (CRC) complies with Pierce’s original model. In 2002 we proposed that alterations in the biology of colon stem cells (CoSCs) may be at the heart of the pathophysiology of CRC (Batlle et al., 2002; van de Wetering et al., 2002). Since then, the groups of Ruggero de Maria (Ricci-Vitiani et al., 2007), John Dick (O’Brien et al., 2007) and Mike Clarke (Dalerba et al., 2007), identified a population of tumour cells within human CRCs with the unique capacity to propagate the disease upon inoculation into mice. These works re-launched Pierce’s original idea that CRCs were organised through a hierarchy of cells with distinct tumourigenic potential. My laboratory at IRB Barcelona developed a technology that allowed the purification, gene expression profiling and in vitro expansion of human normal intestinal stem cells (ISCs) (Jung et al., 2011). This is the only methodology available to date to purify human ISCs, a work that paves the way for their use in regenerative medicine. Remarkably, it also discriminated the phenotypic diversity of CRCs and distinguished a cell population within human CRCs that resembled normal ISCs (Merlos-Suarez et al., 2011). The expression of normal ISC genes defines Colorectal Cancer Stem Cells (CRC-SCs). Functionally, purified CRC-SCs possess long-term self-renewal capacity and robust tumour initiation capacity when transplanted into immunodeficient hosts, whereas differentiated-like cells are poorly tumourigenic. Moreover, tumours generated by CRC-SCs recreate the cell heterogeneity of the original cancer, including the ratio of CRC-SCs versus differentiated-like tumour cells. In summary, differentiated-like tumour cells are essentially inert whereas CRC-SCs self-renew their own population and produce progeny that differentiates.

In an effort to understand the signals that maintain tumour stem cells we have unveiled the existence of a transcriptional circuit dedicated to prevent the expansion of adenoma stem cells during the onset of CRC (Whissell et al., 2014). Excess of beta-catenin/TCF4 signalling due to activating mutations in the WNT signalling pathway upregulates the levels of BMP factors, which enforces differentiation of Adenoma Stem Cells (AdSCs). In contrast, the transcription factor GATA6 directly represses BMP levels in adenomas. As a result, two cell compartments were established in adenomas: a BMP positive zone that comprises differentiated tumour cells and a BMP negative niche that hosts adenoma stem cells. These findings represent a key contribution to understand the mechanisms that regulate the tumour stem cell hierarchy and reveal for first time the existence of a niche that protects AdSCs from BMP signals. We also identified a distal enhancer in the BMP4 locus that is inversely regulated by beta-catenin/TCF4 and GATA6 in CRC cells. Remarkably, this enhancer contains several polymorphisms associated to susceptibility to develop CRC in the population. It remains to be studied whether these SNPs account for differential GATA6 or beta-catenin/TCF4 binding to the enhancer and therefore for differential expression of BMP4 in individuals displaying increased risk of CRC.

A large fraction of my team investigates CRC metastasis. About 40%–50% of all patients with CRC will present with metastasis either at the time of diagnosis or as recurrent disease upon intended curative therapy, representing the major cause of death by CRC. In the absence of genetic alterations that explicate metastasis, it remains a major challenge to design targeted therapies or to predict which patients will develop metastatic disease. We have discovered that CRC metastasis depends on a gene programme expressed by the tumour microenvironment...
upon TGF-beta stimulation (Calon et al., 2012). Functional studies indicate that cancer-associated fibroblasts (CAFs) increase the frequency of tumour initiating cells, an effect that is dramatically enhanced by transforming growth factor beta (TGF-beta) signalling. Using patient-derived tumouroids and xenografts, we show that the use of TGF-beta signalling inhibitors to block the crosstalk between cancer cells and the microenvironment halts disease progression (Calon et al., 2012). In summary, our recent contributions indicate that the progression of CRC towards metastatic disease is dependent on the cross-talk between tumour cells and the tumour microenvironment through TGF beta signalling. Our work paves the way to the use of TGF-beta inhibitors to treat metastatic disease in the clinical setting and also represents the basis for the development of a prognostic test to predict CRC relapse.

REFERENCES


