

 CANCER STEM CELLS

Wnt — looking outside in

The Wnt signalling pathway drives stem cell self-renewal and is deregulated in most colon cancers; however, only a small proportion of colon cancer cells with Wnt-activating mutations have stem cell-like properties. Data from Medema and colleagues indicate that there is more to learn about the association between Wnt, stemness and the tumour microenvironment.

Using a reporter construct to assess Wnt activity, the authors found that only colon cancer cells with high Wnt activity exhibited stem cell properties, including the ability to form tumours when injected into nude mice. This increased activation of Wnt signalling was regulated by factors secreted from myofibroblasts in the stroma surrounding the colorectal tumours. When colon cancer stem cells were cultured with myofibroblasts, or treated with conditioned media derived from myofibroblasts, their differentiation was prevented. The most abundant factor secreted by these cells is hepatocyte growth factor (HGF), which activates MET expressed by the tumour cells leading to the phosphorylation of AKT and glycogen synthase kinase-3 β . The authors also observed phosphorylation of

β -catenin on serine 522, which is associated with its stabilization and translocation to the nucleus — where it activates transcription of Wnt target genes. This enhanced transcriptional activity triggered by HGF was blocked by a specific MET inhibitor. Interestingly, cells with low Wnt activity and which showed no expression of stem cell markers and limited tumorigenic potential gained the ability to form tumours after treatment with HGF or when co-injected with myofibroblasts.

HGF is also secreted by myofibroblasts from human primary colon cancer samples, and analysis of such samples showed tumour cells with nuclear β -catenin staining in close proximity to myofibroblasts.

These data provide evidence that myofibroblasts can establish and maintain stem cell properties in colon cancer cells through the regulation of Wnt signalling. They also suggest a strategy for targeting the self-renewal of cancer stem cells — blocking their interaction with the tumour microenvironment.

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ORIGINAL RESEARCH PAPER Vermeulen, L. et al. Wnt activity defines colon cancer stem cells and is regulated by the microenvironment. *Nature Cell Biol.* 25 Apr 2010 (doi:10.1038/ncb2048)



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