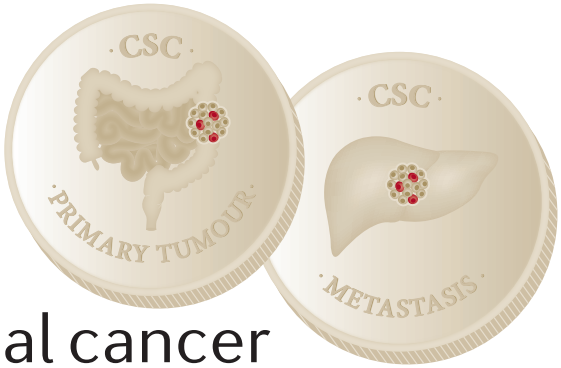
Nature Reviews Gastroenterology & Hepatology | Published online 21 Apr 2017; doi:10.1038/nrgastro.2017.52



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STEM CELLS

Two sides to cancer stem cells in colorectal cancer

New research demonstrates that the dependence of colon cancer on cancer stem cells (CSCs) differs between primary and metastatic tumours in experimental models.

CSCs have long been thought to be one of the main drivers underlying tumour progression and metastasis but experimental evidence providing functional insights has been lacking. Now, in a new study published in *Nature*, de Sousa e Melo *et al.* comprehensively examine the function of leucine-rich repeat-containing G-protein-coupled receptor 5 (LGR5)$^+$ CSCs in colon tumorigenesis. A variety of techniques were used, including the development of new *in vivo* models of colorectal cancer (CRC) and modelling using intestinal organoids.

The researchers first established a mouse model that recapitulated the clinical progression of human CRC. These mice were genetically engineered to express two of the most frequently mutated genes in human CRC (*Apc*, *Kras*), as well as a diptheria toxin receptor fused to enhanced green fluorescent protein under the endogenous regulatory region of *Lgr5* (so-called AKVL mice). This approach meant that LGR5$^+$ CSCs could be tracked and selectively destroyed by administration of diptheria toxin. Organoid cultures were then established from AKVL mice and then used to introduce sequential mutations in *Trp53* (AKVPL) and *Smad4* (AKVPSL) using CRISPR–Cas9 genome editing, mimicking the different stages of human CRC progression. Transplantation of these organoids into mice showed that they had different growth properties — indolent (AKVL), moderate (AKVPL), exponential (AKVPSL) — and tumour-initiating capacities (higher in AKVPSL versus AKVPL).

LGR5$^+$ CSCs were found to have high tumour-initiating capacity and to exhibit biological properties associated with cancer stemness. An increased CSC content seemed to be associated with increased tumorigenic potential. Strikingly, selective ablation of LGR5$^+$ CSCs restricted primary tumour growth, but did not lead to tumour regression. As long as diptheria toxin treatment was continued tumours remained in stasis, but as soon as the toxin was withdrawn rapid regrowth of the tumours occurred. The evidence collected suggested that the tumours were maintained by proliferative LGR5$^-$ cells in the absence of LGR5$^+$ CSCs.

Importantly, LGR5$^+$ CSCs were essential for metastasis, being critical for the formation and maintenance of liver metastases from the original CRC tumour. Treatment with diptheria toxin after implantation of AKVPSL organoids in the colonic mucosa of mice, and therefore selective removal of LRG5$^+$ CSCs, led to substantially decreased burden of liver metastases. Finally, injection of organoids directly into the portal vein resulted in liver metastasis in the absence of a primary tumour. Treatment with diptheria toxin in these animals led to a marked reduction of their liver metastatic burden, indicating that LGR5$^+$ CSCs are required for the maintenance of established liver metastases.

"The demonstration that LGR5$^+$ cells are dispensable for tumour maintenance is undoubtedly surprising. However, it adds to the compelling evidence for cell plasticity", writes Florian Greten in an accompanying commentary published alongside the original research paper. Greten goes on to highlight that the findings question the unidirectional hierarchy model that suggests there is a dedicated stem cell population in cancer.

These results suggest that the functional contribution of CSCs for tumour growth is intimately dependent on the influence of local environmental cues," explains author Frederic de Sauvage. "Further understanding of microenvironmental regulation of CSC plasticity may therefore provide new therapeutic opportunities."

Katrina Ray

ORIGINAL ARTICLE de Souse e Melo, F. *et al.* A distinct role for Lgr5$^+$ stem cells in primary and metastatic colon cancer. *Nature* **543**, 676–680 (2017)
FURTHER READING Greten, F. R. Tumour stem-cell surprises. *Nature* **543**, 626–627 (2017)