Targeting intestinal stem cells in cancer.
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The Wnt signaling pathways plays critical roles during embryonic development and in adults through modulation of proliferation, cell migration and differentiation. Inappropriate activation of the Wnt pathway through mutation or misexpression can result in tumorigenesis, in particular in the gastrointestinal tract where Wnt pathway activation is observed in most colorectal tumors. The intestinal epithelium is turned over every 5 days on average and is very dependent on stem cell activity. Crypt based columnar cells (cbc) expressing the Lgr5 receptor have been identified as intestinal stem cells and play a key role in intestinal homeostasis and/or regeneration. Here we show that leucine-rich repeat-containing G protein-coupled receptor 5 (Lgr5) identifies a population of intestinal CSCs across mouse derived organoid tumours engineered to recapitulate the clinical progression of human colorectal cancer (CRC). We demonstrate that phenotypical attributes of stemness, including tumour-initiating capacity (TIC) are endowed within the $Lgr5^{+}$ cancer cell compartment. We further show that selective Lgr5 lineage ablation restricts primary tumour growth, but does not result in tumour regression. Instead, tumours undergo stasis and are maintained by proliferative $Lgr5^{-}$ cells. These cells continuously attempt to replenish the CSC pool, which then leads to rapid re-initiation of tumor growth upon treatment cessation. Interestingly, CSCs appear to be indispensible for the formation of distant metastasis.