STEM CELLS

Competitive behaviour of cancer mutations

Tissue stem cells are putative cells of origin for various cancers, but the immediate effects of cancer driver mutations in these cells in physiological contexts are poorly characterized. Two new studies have now identified complex and heterogeneous effects of cancer mutations on stem cell populations *in vivo*.

Li *et al.* used a genetic mouse model in which inducible expression of Cre recombinase in the haematopoietic system activated a floxed allele of $Nras^{G12D}$; *NRAS* is an oncogene that is commonly mutationally activated in various human leukaemias.

The activation of $Nras^{G12D}$ in haematopoietic stem cells (HSCs) increased their proliferation. Additionally, $Nras^{G12D/+}$ HSCs outcompeted wild-type HSCs during their engraftment of a new recipient mouse in a transplantation assay and had increased long-term self-renewal following serial transplantation through multiple recipients. The increases in both proliferation and self-renewal were intriguing because HSC hyperproliferation that is caused by other mutations typically leads to the long-term exhaustion of HSC reserves.

As a potential explanation, the authors showed that $Nras^{G12D}$ has a bimodal effect in HSC populations: although proliferation was increased in most cells, it was decreased in a subset of HSCs to increase self-renewal. Indeed, the low-proliferative proportion of $Nras^{G12D/+}$ HSCs were the most effective at engrafting recipient mice.

Finally, the authors characterized the gene expression and signalling consequences of $Nras^{G12D}$ activation, and they identified a key role for signal transducer and activator of transcription 5 (STAT5) signalling for mediating both the increased proliferation and the engraftment potential of $Nras^{G12D/+}$ HSCs.

In a separate study, Vermeulen *et al.* used genetic mouse models in which the induction of Cre in intestinal crypt stem cells *in vivo* sporadically activates or inactivates a floxed allele of a chosen oncogene or tumour suppressor gene. In addition, Cre activity activated a fluorescent marker to allow tracking of the subsequent fate of these mutant cells in the colon.

Crypt stem cells continuously replace each other through cell–cell competition, and the authors focused on genetic changes that are known to commonly occur in human colorectal cancer to assess their effect on stem cell competition. They found that *Kras* activation increased the competitiveness of crypt stem cells but not to an entirely deterministic level: 80% of cell replacement events that involved *Kras*-mutant cells led to the replacement of adjacent normal stem cells, whereas the *Kras*-mutant cells were eliminated by normal cells for the rest of the occasions. For the inactivation of adenomatosis polyposis coli (*Apc*), only biallelic inactivation substantially increased the competitiveness of the stem cells. Interestingly, most $Apc^{+/-}$ cells were eliminated by surrounding stem cells, and only a subset progressed to hyperproliferative $Apc^{-/-}$ cells. Surprisingly, inactivation of the DNA-binding activity of p53 through a dominant-negative *Trp53* allele did not significantly increase crypt stem cell competitiveness until conditions of inflammation were induced in the colon. Thus, the effects of mutant oncogenes and tumour suppressor genes are context dependent and can be buffered by intrinsic tissue-level tumour suppressor mechanisms.

It will be interesting to characterize the physiological consequences of additional cancer-associated mutations in a wider range of tissues and to see whether such studies suggest therapeutic avenues to eliminate cancer stem cells.

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ORIGINAL RESEARCH PAPERS Li, Q. *et al.* Oncogenic *Nras* has bimodal effects on stem cells that sustainably increase competitiveness. *Nature* http://www.dx.doi.org/10.1038/nature12830 (2013) | Vermeulen, L. *et al.* Defining stem cell dynamics in models of intestinal tumor initiation. *Science* **342**, 995–998 (2013)