Stem cell competition: how speeding mutants beat the rest

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How mutations lead to tumor formation is a central question in cancer research. Although cellular changes that follow the occurrence of common mutations are well characterized, much less is known about their effects on the population level. Now, two recent studies reveal in what way oncogenic aberrations alter stem cell dynamics to provide cells with an evolutionary advantage over their neighbors (Amoyel *et al*, 2014; Baker *et al*, 2014).

See also: **M Amoyel *et al*** (October 2014)
and **AM Baker *et al*** (August 2014)

In most tissues, stem cells not only face the continuous demand of generating sufficient differentiated cells to maintain tissue integrity but also continuously battle each other for a position within the *niche*. Recent studies have employed quantitative analytical techniques to describe stem cell dynamics in remarkable detail. Strikingly the fundamental properties of these dynamics are universal, although the spatial features of the various tissues might be drastically different (Klein & Simons, 2011). Stem cells are routinely lost following terminal differentiation and replaced by neighboring symmetrically dividing stem cells in a stochastic manner (Fig 1A). In homeostasis, this process results in neutral competition between clones that is characterized by random expansion and retraction of clones (Klein & Simons, 2011).

Amoyel and colleagues now describe that also somatic cyst stem cells (CySCs) within the *Drosophila* testis follow neutral stochastic dynamics (Amoyel *et al*, 2014). Hence, also in this tissue, no long-lived stem cells can be detected that unceasingly produce

differentiated cells. Instead, maintenance of an effective cyst cell compartment relies on the functioning of a continuously changing equipotent stem cell population. Furthermore, the authors demonstrate that the expression of marker genes that are associated with the *Drosophila* CySC compartment importantly overestimate the number of functional stem cells.

To model the development of neoplastic outgrowths within the testis signals that are known to modulate CySCs were modified. In particular, inactivation of *patched* (*ptc*) resulting in constitutive Hedgehog signaling in CySCs led to rapid expansion of these cells. Intriguingly, although the *ptc*^{-/-} CySCs displayed a competitive advantage over wild-type CySCs, they were still regularly replaced by wild-type stem cells following stochastic events. Using well-designed experiments, the authors established that the increased proliferation rate of *ptc*^{-/-} CySCs is solely responsible for the increased competitive fitness of the clone. Increased stem cell proliferation augments the probability that their offspring populates a vacant adjacent niche (Fig 1B). This finding parallels a recent discovery in the intestine and highlights how oncogenic mutations can exploit a chief homeostatic process of random stem cell replacement (Snippert *et al*, 2014).

Until recently, much of our knowledge on stem cell dynamics was derived from genetic clonal tracing studies in model organisms such as *Drosophila* or mouse (Vermeulen & Snippert, 2014). Although it was generally assumed that dynamics in human tissue are fundamentally similar, the specifics remained largely undefined as evidently transgenic lineage-tracing in humans is unfeasible. Now, the Graham lab has employed an

elegant clonal tracing strategy in human intestinal tissue that relies on the stochastic inactivation of *cytochrome c oxidase* (CCO) by somatic mtDNA mutations that can be visualized using a histochemical assay (Baker *et al*, 2014). In rare cases, individual colon crypts display both CCO⁺ and CCO⁻ clones. By analyzing the changes in clone sizes within these polyclonal crypts along the crypt axis in 3D reconstructed images, the authors could temporally track the events occurring in the intestinal stem cell (ISC) compartment (loss of stem cells and expansion of neighboring clones). Using this data in conjunction with a previously developed stochastic population model of ISC dynamics, the authors established the occurrence of neutral competition between human ISCs (Lopez-Garcia *et al*, 2010). Furthermore, they could infer the presence of a rather limited number of functional stem cells, five to six, within each crypt of the human colon. Surprisingly, these numbers are very similar to the amount of functional stem cells in the murine crypts that are considerably smaller (Kozar *et al*, 2013).

The highlight of the study by Baker *et al* is the analysis of stem cell dynamics in adenomatous crypts harboring a homozygous inactivation of the intestinal tumor suppressor gene *APC*. The results showed that these glands contain an expanded number of stem cells that replace each other more rapidly than normal ISCs. Keeping in mind the findings of Amoyel *et al*, it is tempting to speculate that *APC*^{-/-} cells divide at a higher rate thereby initially outcompeting other cells and eventually overwhelming the homeostatic balancing mechanisms leading to an increased number of stem cells in mutant crypts (Fig 1C). This model also provides a compelling explanation for the

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Figure 1. Stem cell dynamics and oncogenic transformation.

(A) Both fly testis (cyst) stem cells and human ISCs behave in similar fashion. During homeostasis, stem cells continuously compete with their neighbors randomly replacing them or being replaced. (B) Amoyel *et al* have shown that mutations can confer a competitive advantage by speeding up the mutant stem cell proliferation rate which in turn makes the stem cells more likely to take up vacant niche positions. (C) A potential consequence of this elevated proliferation, once all stem cells are mutant, is the overwhelming of homeostatic control mechanisms leading to higher numbers of stem cells compared to wild type. This would explain the observation by Baker *et al* for human adenomatous crypts, where the crypts were found to have a larger number of stem cells with an accelerated stem cell replacement rate.

mechanism by which loss of *APC* provides a previously reported competitive advantage to cells (Vermeulen *et al*, 2013); *APC*^{-/-} clones contain an increased proportion of stem cells and as such are more resistant to stochastic loss of stem cells, and in addition, the rapid proliferation allows for efficient colonization of nearby vacant niches.

The conclusion, from both studies, that mutant stem cells are still often replaced by neighboring cells, and in fact that oncogenic stem cells replace each other even at an accelerated rate, is encouraging. It implies that a large part of the oncogenic stem cells are destined to be lost and that drugs that promote this feature might form the basis of

novel effective therapies and preventive interventions.

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