IN FOCUS

How Does Multistep Tumorigenesis Really Proceed?

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Summary: Identifying the cancer cells-of-origin is of great interest, as it holds the potential to elucidate biologic mechanisms inherent in the normal cell state that have been co-opted to drive the oncogenic cell state. An emerging concept, proposed here, states that cancer stem cells, key players in cancer initiation and metastasis, arise when transit-amplifying cells with mutant genomes dedifferentiate and enter the stem cell state. This model contrasts with the notion that cancer stem cells are the direct products of neoplastically transformed normal tissue stem cells. *Cancer Discov; 5(1); 22–4. ©2015 AACR.*

The reigning models of how human tumors form describe a succession of changes in tumor cell genomes and in epigenomes (i.e., heritable changes in gene expression programs). Thus, a tiny subset of randomly occurring changes happens to confer advantageous cell phenotypes, resulting in the clonal expansion of the cells that express these phenotypes. Eventually, the descendants of these cells will sustain yet another advantageous alteration, resulting once again in a clonal expansion. This process formally resembles the process of Darwinian evolution, with the proviso that it occurs in the microcosm of a tissue rather than in the wild. In the context of cancer, each of the clonal expansions generates a cell population with increased neoplastic phenotypes, culminating in the final, highly aggressive population that threatens the patient, both as a primary tumor and as the metastatic derivatives of this tumor (1).

Evidence is accumulating that both normal and fully neoplastic cell populations harbor subpopulations of stem cells (SC) that can both self-renew and spawn more differentiated progeny. In the context of cancer, neoplastic SCs are proposed to hold most, if not all, of the tumor-initiating potential. Moreover, a higher proportion of neoplastic SCs within a tumor often correlates with poorer prognosis. Experimentally, these functionally specialized cells can be defined through their ability to seed tumors following their initial implantation in appropriate host mice and subsequently during repeated cycles of serial passage in such hosts (2, 3).

Given the presence of SCs in normal tissues before the onset of tumorigenesis and yet others within tumors formed at the final stages of multistep tumor progression, it seems inevitable that all of the intermediate populations that arise successively, one after another, en route to full-fledged tumors also harbor such subpopulations. Of relevance here is the accumulating evidence that the SC programs in normal and neoplastic tissues rely on many common molecular regulators (4). Moreover, the organization of the normal SC hierarchy is also thought to apply to the cancer SC model, such that SC populations give rise to non-SC progeny, whereas the reverse process does not occur. That is, non-SC progeny cannot dedifferentiate and reenter the SC state.

Given the above, one reasonable model of how tumor progression proceeds depicts normal SCs as the initial targets of oncogenic transformation (5). Accordingly, a normal SC would sustain some type of heritable change, notably a genetic alteration, that generates a slightly altered SC; the latter would then spawn the larger cell population that is responsible for the altered behavior and histologic phenotype of the resulting early, preneoplastic cell population. This process would then repeat itself, with each population of SCs sustaining a heritable change and directly generating the next successor population, until the final SC population arises, i.e., the cancer SCs present in a highly malignant tumor (Fig. 1A).

This model is encumbered, however, by three inconsistencies that undermine its credibility. To begin, the rare stochastic changes that confer advantageous phenotypes are unlikely to occur if the population of potentially affected target cells is small; thus, small numbers of target cells yield proportionately small numbers of rare variants. Second, most types of heritable changes appear to occur far more frequently in actively dividing cell populations rather than in those that rarely divide. In general, it appears that epithelial SC populations divide far less frequently than their immediate progeny—the transit-amplifying/progenitor cells that are responsible for the exponential expansion of non-SC progeny and the lion's share of mitotic activity in a tissue. Third, the clonal expansion of variant cell populations depends, as cited above, on the display of certain advantageous cell phenotypes; undifferentiated SCs are far less likely to display such phenotypes than their progeny that have initiated programs of differentiation. Taken together, these dynamics suggest that a model in which normal SCs are the cells-of-origin for epithelial cancers is mathematically and biologically implausible.

An alternative process seems to suggest a far more likely mechanistic model of multistep tumor progression. This emerging model is based upon recent findings in a number of laboratories that hierarchically organized cell populations are

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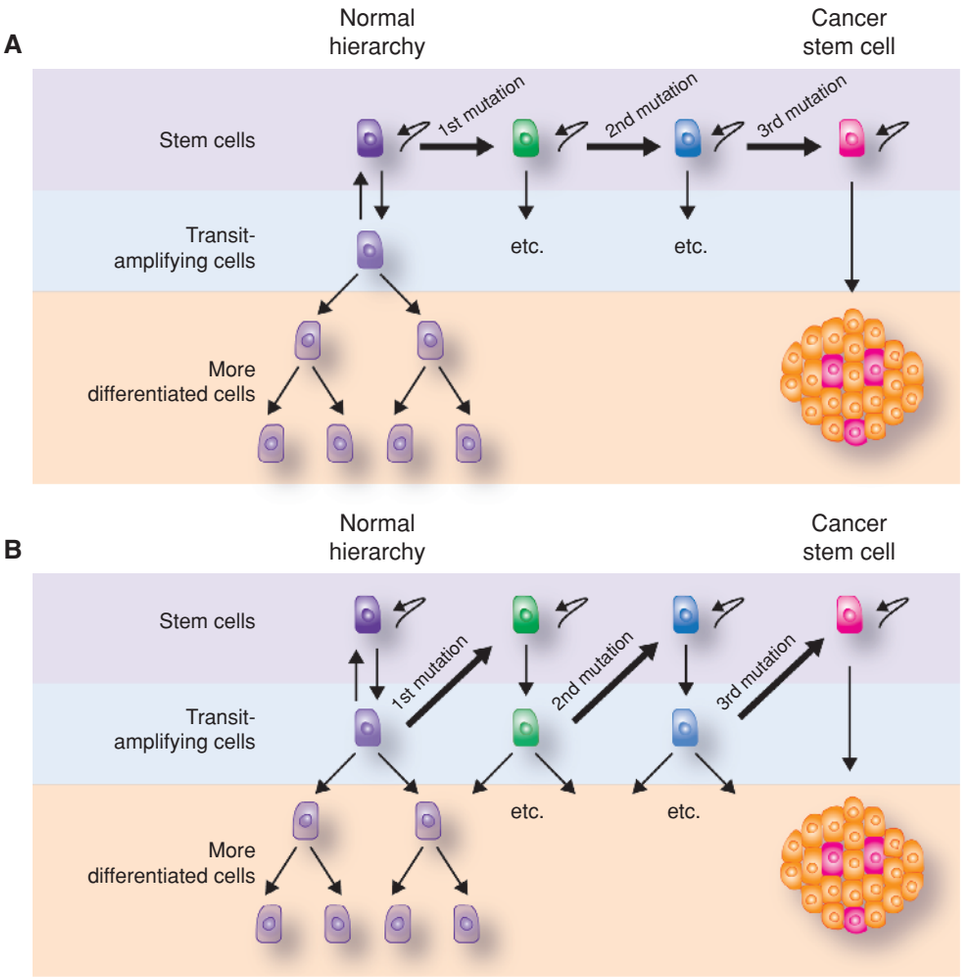

Figure 1. The involvement of SCs in multistep tumor progression can be depicted in two alternative mechanistic schemes. Both schemes embrace the notion that each participating cell population beginning with fully normal cells and culminating in fully neoplastic cells contains a subpopulation of SCs. **A,** in this scheme, one SC subpopulation, having acquired a heritable change such as a somatic mutation, evolves directly into the next SC subpopulation with no involvement of non-SCs in this multistep process. **B,** an alternative scheme proposes that the heritable changes in cell populations are initially acquired in non-SC populations, specifically transit-amplifying cells, often termed progenitor cells. Having acquired an advantageous change, progenitor cells introduce this change into an SC subpopulation via a process of dedifferentiation. Accordingly, SCs change progressively during multistep tumor progression but are not themselves the initial sources of these changes.

more plastic than previously imagined (6–10). Thus, depending on the genotype and the contextual signals experienced by transit-amplifying/progenitor cells, at least in epithelial tissues, such cells may dedifferentiate and thereby enter back into the SC pool. (The rates with which this occurs in various tissues in normal, neoplastic, and physiologically stressed tissues, e.g., those undergoing wound healing, remain to be measured.)

This reversal of the arrow of differentiation makes possible a quite different scenario of how multistep tumor progression actually occurs (Fig. 1B). Thus, pools of transit-amplifying cells may serve as the actual targets of somatic alterations and thus the sources of mutant genomes (or heritable epigenetic alterations), and thereafter feed these alterations back into corresponding SC pools. If so, this redirects our attention away from SCs as the key actors in the initiation and in the progression of human tumors, refocusing it on their mitotically far more active and more numerous transit-amplifying/progenitor progeny.

As an aside, we note that this alternative model holds important therapeutic implications: Therapies aimed at targeting the cancer SCs within a tumor will not be curative if the pool of cancer SCs can be continuously regenerated from plastic noncancer SCs that are capable of dedifferentiating and reentering the cancer SC state. Moreover, this plastic model of tumorigenicity suggests that the pool of cells capable of successfully seeding a metastatic outgrowth is not restricted to the existing pool of cancer SCs within a primary tumor. Instead, the more differentiated progeny of these cancer SCs may also initiate metastases if they are capable of reverting to the tumor-initiating cancer SC state at distant sites of dissemination.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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