Review

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Refining the role for adult stem cells as cancer cells of origin

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Significant progress has been made to identify the cells at the foundation of tumorigenesis, the cancer cell of origin (CCO). The majority of data points towards resident adult stem cells (ASCs) or primitive progenitors as the CCO for those cancers studied, highlighting the importance of stem cells not only as propagators but also as initiators of cancer. Recent data suggest tumor initiation at the CCOs can be regulated through both intrinsic and extrinsic signals and that the identity of the CCOs and their propensity to initiate tumorigenesis is context dependent. In this review, we summarize some of the recent findings regarding CCOs and solid tumor initiation and highlight its relation with *bona fide* human cancer.

Decoding the cell of origin in cancer

Cancer is a complex disease due to the wide variety of cellular and molecular mechanisms associated with its initiation and progression. It is accepted that cancer cells divide and proliferate uncontrollably because of the accumulation of somatic mutations in normal tissue, which confers a selective growth advantage in the mutated progeny [1]. However, the cells that make up a tumor are heterogeneous; often making it difficult to determine the CCO, which is the normal cell that acquires the mutational load necessary to first initiate cancerous proliferation. Furthermore, since cancer is a transformative process, the cells composing advanced cancers may no longer contain morphological or molecular characteristics of the CCO [2]. The identity of the CCO could be critical to the generation of more effective treatments and preventative strategies. If CCOs can be identified and targeted specifically, it would be possible to stop cancer before it has a chance to undergo expansion. Molecular or physiological attributes specific to CCOs could be exploited to slow or block progression, thus avoiding treatments that simply kill dividing cells. This has led to significant recent efforts to define CCOs for all types of cancers, and numerous lines of evidence point towards ASCs as possible CCOs [3].

It is worth noting that CCOs are likely different from cancer stem cells. CCOs are the first cells to initiate a tumor, but cancer stem cells exist within a growing tumor and are defined by their ability to propagate tumors when serially transplanted [4]. Although cancer stem cells have many properties and gene expression patterns similar to ASCs, it is not clear whether there is a direct relation between the CCOs and cancer stem cells. It is possible and probable that cancer stem cells evolve from cells other than CCOs after tumor initiation. Cancer stem cells are covered elsewhere in several important reviews [4–6]. Here, we focus on CCOs and discuss the intrinsic and extrinsic mechanisms that regulate their ability to initiate various cancers.

ASCs and CCOs: is there a link?

ASCs make for a compelling target of tumorigenesis because of several basic properties. First, they are long lived, and thus capable of persisting long enough to accumulate DNA damage. Second, ASCs in general are multipotent (sometimes unipotent), and this could explain the variability of cell types found within most tumors. Third, ASCs, while normally quiescent, do have significant self-renewal potential, which could be critical for tumor expansion. ASCs are also capable of giving rise to a limited number of cell types [7–11]. For example, intestinal stem cells are able to differentiate into all the various secretory cell types of the villus, but not brain or muscle cells. Finally, experimental evidence from lineage tracing suggests that ASCs may in fact be the CCOs in various solid tumors [3]. However, numerous exceptions to this theory have also been identified, where various environmental insults appear to influence the nature of CCOs, and these are also discussed below.

ASCs are found in many of the major adult organs and are essential for tissue homeostasis as well as regeneration in response to injury [12–17]. Most ASCs were discovered on the basis of their relative quiescence and their ability to reconstitute differentiated cell lineages of the tissue or organ in which they reside [8,18–22] (Figure 1). Either upon activation by natural turnover/cycling or in the case of regeneration due to injury, ASCs give rise to multilineage restricted progenitors or, as they are often called, transit amplifying cells (TACs) (Figure 1). These cells divide rapidly and then differentiate to generate the bulk of cells required for tissue turnover or regeneration. Due to their rapid division, TACs are also targeted by chemotherapeutics that act on cell division pathways to kill cancer cells, most

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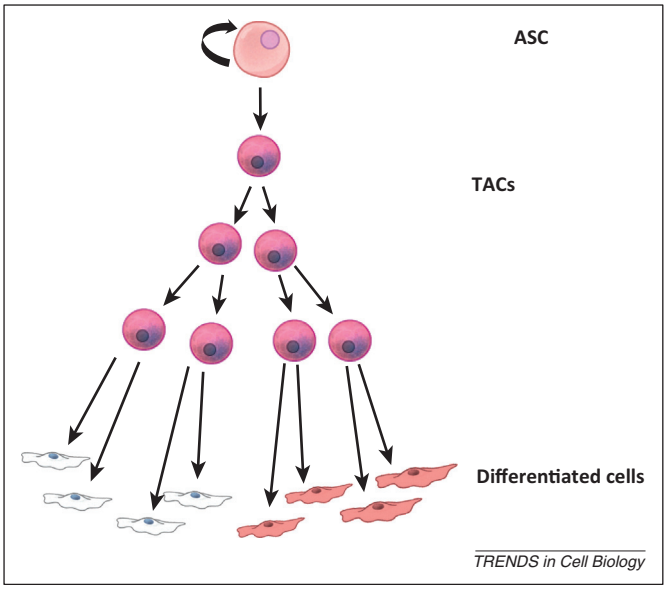

Figure 1. Typical ASC hierarchy. Within most mature tissues, a hierarchy exists where cell turnover is controlled first by a self-renewing ASC. These relatively quiescent cells give rise to TACs. TACs go through several rounds of division and then immediately differentiate to form the various specialized cells of the tissue. The delicate balance of cell fate decisions summarized in this figure are typically controlled by well-known signaling pathways (such as Wnt, Tgf, Bmp, Shh, and Fgf) acting through both autocrine and paracrine mechanisms. Abbreviations: ASC, adult stem cell; TAC, transient amplifying cell.

obviously manifested as loss of hair and intestinal cells. In most cases, TACs quickly give rise to terminally differentiated cells that then perform the basic functions of the tissue or organ [23]. This type of hierarchy is present in most tissues, although tissues such as the epidermis and intestine experience tissue turnover and stem cell cycling with higher frequency [24]. While the identity of ASCs has not been confirmed in all tissues, most tissues are thought to possess them, with a few notable and controversial exceptions (liver and pancreas). These tissues are thought to regenerate by dedifferentiation of a differentiated cell type back to a proliferative state. However, this is thought to only happen in cases of regeneration in response to tissue injury; an example being the liver, where mature hepatocytes revert to a proliferative state in response to hepatectomy [25–30]. Cellular hierarchies based on developmental potential (ability to make more differentiated progeny) exist in all tissues, with stem cells and terminally differentiated cells at opposite ends of the spectrum.

ASCs appear to be regulated by intrinsic and extrinsic mechanisms. ASCs are intrinsically distinguished from their progeny on the basis of epigenetic, transcriptional, and potentially metabolic modes of regulation [14,31–34]. Dysregulation of these intrinsic factors such as the introduction of oncogenic mutations can result in cancer initiation [35]. Moreover, the extrinsic environment in which ASCs reside also regulates their identity and activity. ASCs live in specialized niches, which are often made up of several different cell types, frequently from different embryonic germ layers [19,36]. ASCs send and receive signals from their niche, such as growth factor signaling, extracellular matrix association, and mechanical regulation. Disruption of this signaling crosstalk or changes in the makeup of the niche can affect various aspects of ASC homeostasis such as the induction of ASC proliferation. Many of the pathways important for ASC to niche crosstalk are pathways also often aberrantly regulated in human cancer [9,37–39]. Below, we provide evidence for the role of ASCs as the CCOs of epithelial cancers including skin, intestinal, and prostate cancer.

Developmental hierarchy and cancer initiation

Tumors are heterogeneous and can display distinct phenotypic profiles such as morphology, gene expression, and proliferation. It has been assumed that the final morphology of the cells within a tumor can determine the CCO; however, cancer cells undergo a myriad of changes during tumor initiation to progression, suggesting that the final tumor cell may bear little resemblance to the CCO. Therefore, *a priori*, several scenarios are possible for tumor initiation (Figure 2A). With this realization, new lineage tracing methods have sought to uncover the origin of cancer from many tissues. Cell-type-specific promoters driving inducible Cre recombinase alleles has allowed for the prospective introduction of oncogenes or removal of tumor suppressors in postnatal murine models in intact tissue. These models are preferable to *in vitro* models or reconstitution/xenograft models as they contain the appropriate organization of the tissue and the presence of the native stromal, immune, lymphatic, nervous, and vascular systems. Taking advantage of lineage tracing mechanisms (CreER/CrePR) [40] and knock-in alleles [41] of oncogenes or floxed tumor suppressors [42], one can now initiate oncogenesis from particular cell types within an adult tissue by injection of an estrogen/progesterone antagonist. These experiments have suggested that pathological, retrospective studies on existing tumor tissue from human or mouse could be misleading when trying to identify the CCO.

The simplest interpretation of the data produced by these new prospective approaches is that ASCs are more likely to serve as CCOs in many cancers [3], such as those of the skin, prostate, intestine, and brain. Since ASCs are continuously available to maintain tissue homeostasis and to repopulate cellular compartments lost during injury in tissue, it has been speculated that only ASCs are present in the tissue for a sufficient length of time to accumulate the necessary genetic mutations for tumorigenic transformation and cancer initiation (Figure 2). Below, we discuss the current understanding of the CCOs of these cancers, which represent a variety of solid tumors from well-described tissues with defined hierarchies of differentiation potential. We propose that the CCO is context dependent and can change depending on intrinsic (genetic mutation and cell of origin) and extrinsic (homeostasis or injury/inflammation) stimuli.

Intrinsic factors influence CCOs

The developmental origins for each hierarchy could yield insight into the mechanisms by which tumors arise from ASCs, because the same dominant signaling pathways that specify cell fate also play important roles in ASC homeostasis [7,35]. Indeed, developmental pathways including Wnt, Tgfβ, Bmp, Shh, Fgf, and Notch signaling, have all been implicated in the development of epithelial