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Hot Topic

From autonomy to community; new perspectives on tumorigenicity and therapy resistance

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ABSTRACT

Subclones of cancer cells evading treatment represent the major challenge in oncology. Despite recent advances, tumors not responding to treatments are still a severe risk to cancer patients, and oncologists have, as of now, little effective therapy to offer patients with systemic cancer disease. The widely discussed cancer stem cell (CSC) paradigm was originally launched as an explanation to the existence of small cell populations resistant to therapy within the heterogeneous tumor, but has so far unfortunately, offered little concrete improvement in cancer treatment regimes. The launch of the CSC hypothesis did, however, highlight the significance of therapy targeting specific tumor-driving processes, and even more importantly, an increased awareness of a phenomenon well known to stem cell researchers; non-genetic phenotypic heterogeneity of cells with common origin. Here, the scientific background of the CSC theory is revisited and the evidence for CSCs is discussed, along with the importance of considering CSC's dependency of their habitat for survival and growth. Furthermore, recent advances in cancer cell heterogeneity and new possibilities for studying therapy responses in cell clones within the natural tumor environment using patient derived xenograft (PDX) models, are reviewed.

Introduction

The diverse cell populations constituting the human body are functioning together in a choreographed collaboration and are constantly under renovation. Lifelong maintenance is essential for the survival of the whole organism. This task is controlled and performed by a small minority of slow dividing, long-lived cells with remarkable differentiation and expansion potential. To be able to exert their duty, stem cells give rise to heterogeneous progeny under strict homeostatic control. Tissue integrity and health of the entire organism, are preserved by the stem cells' ability to balance self-renewal and differentiation according to environmental stimuli and genetic regulation [1,2] (Fig. 1 upper panel).

Launch of the cancer stem cell hypothesis

The theory on cancer stem cells (CSCs) was proposed as an explanation to why cancer therapy fails to eradicate all cancer cell subpopulations. In a review by Reya et al., it was suggested that oncogenic transformations in normal stem cells was the cause of cancer, thereby causing a hierarchical organization of cancer cells where a subpopulation of neoplastic cells with stem cell properties was responsible for tumor maintenance and progression [3]. The theory, furthermore proposed that metastasis was a consequence of CSCs spreading to a new location. Normal stem cells were, due to their longevity, proposed to be the natural candidates to congregate the transforming mutations required to become cancerous. Furthermore, their self-renewal capacity and differentiation abilities would be the foundation of intra-tumor heterogeneity. It had long been well accepted that disease relapse and metastatic spread was caused by resistant clones within heterogeneous tumors [4]. According to the hypothesis, the more differentiated clones of cancer cells, should not have unlimited self-renewal capacity and

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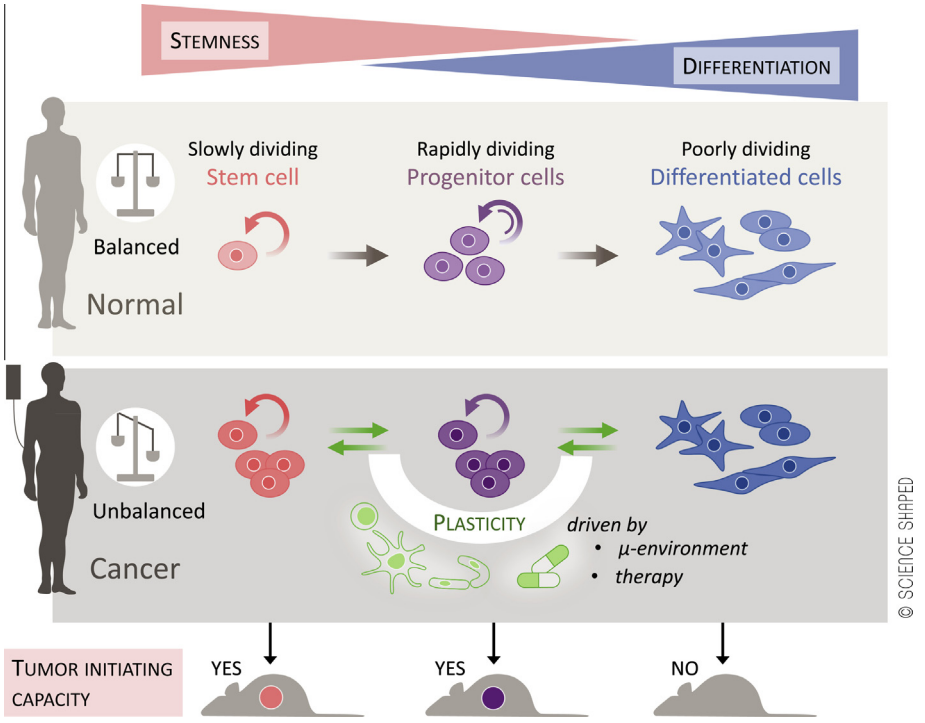

Fig. 1. A schematic illustration of the differences and similarities between normal stem cells and so called "cancer stem cells". In normal tissues, asymmetric cell division and subsequent differentiation processes giving rise to heterogeneous progeny are strictly balanced. Malignant transformation may occur at all maturation stages and the transformed cell carries unscheduled proliferative capacity and the ability to create a tumor, i.e. it is a cancer stem cell. Cancer stem cells and their progeny may drift in maturation level, between phenotypes and in tumorigenic capacity. Less tumorigenic populations might act as growth support for the more aggressive ones, and can be triggered by microenvironmental cues to become tumorigenic. High plasticity, the ability to easily switch between differentiation stages and phenotypes enable cancer cells to adapt to changing conditions, e.g. therapeutic intervention. The clinical consequences are development of resistance and metastatic disease. © 2015 Science Shaped Ellen Margrethe Tenstad. All Rights Reserved.

hence be unable to give rise to new tumors, or cause disease relapse.

The CSCs hypothesis provoked an important debate on the origin of cancer disease leading to the current functional definition of CSCs as cancer cells that can self renew and instigate a new tumor [5]. It represented, at the time of launch, an attractive alternative to the prevailing theories of oncogenesis and even more importantly, to the conceptual thinking on how to eradicate the cancer disease [6]. In contrast to the classical "stochastic" clonal evolution model of oncogenesis which proposes that transformation results from random mutations and subsequent Darwinian selection, in the CSC model, only the resulting CSC could initiate a new tumor. Consequently, identification and eradication of the CSC population would be sufficient to eliminate the disease, and prevent subsequent relapse [3]. Characterizing and eliminating CSCs, thus, became a highly prioritized task in many research labs.

The prospective hunt for CSCs

Acute myeloid leukemia (AML) was the first cancer type where the existence of CSCs was indicated [7,8]. These studies were dependent on functional *in vivo* assays in immunodeficient mice [8,9]. Candidate CSC populations were characterized by xenotransplantation of the human leukemia cells in limiting dilution series. Establishment of severe combined immunodeficient (SCID) mouse (lacking B and T lymphocytes) [10] and the non-obese diabetic (NOD)/SCID mouse (lacking B, T and NK lymphocytes), greatly facilitated the discoveries of CSCs, and represented a seminal advancement within the field. Xenotransplantation stem-cell assay in NOD/SCID mice is still the most widely accepted assay for functional validation of CSC populations. Cancer cells that are able to initiate tumor growth in mice, and recapitulate the heterogeneity of the original primary patient tumor are considered to be tumor initiating cells (TICs) or CSCs [5]. The NOD/SCID models have opened a broad range of new possibilities for studies of engrafted human cells (discussed later) [11].

Several studies in human AML indicated that a rare subset of cells comprising as little as 0.01–1% of the total cell population were the only cells able to induce AML and reconstitute the human disease heterogeneity in NOD/SCID mice. These cells were defined as $CD34^{+}CD38^{neg}$ [8] and $CD90^{neg}$ [12]. Importantly, these AML-initiating cells had the same surface marker profile as normal immature multipotent progenitors, and could give rise to $CD38^{+}$ and Lin^{+} cells, consisting of more committed, mature populations. These studies in AML were the first to suggest that a stem cell hierarchy was the cause of functional heterogeneity in human cancer. Based on the phenotypic similarities and the hierarchical organization, the authors proposed that hematopoietic stem cells were the most likely target for transformation into a leukemic stem cell (LSC).

The discovery of cancer cells expressing stem cell properties in hematopoietic malignancies also raised the possibility that a CSC model could be applied to the description of solid tumors [13]. Several studies have indicated the existence of CSCs in multiple solid tumors and a number of cell-surface markers have been used for prospective isolation of subpopulations of cells enriched for CSCs. Some of the most widely used markers include CD44, CD24, CD133, EpCAM (epithelial cell adhesion molecule), ABCB5 (ATB-binding cassette B5) as well as Hoechst33342 exclusion by the so-called side population cells and ALDH1 (aldehyde dehydrogenase) activity.

The first solid malignancy from which CSCs were identified and isolated was breast cancer [13]. The isolated tumorigenic population was identified based on its cell surface phenotype, $lineage^{neg}$,