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Review

Cancer stem cell: Fundamental experimental pathological concepts and updates

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ABSTRACT

Cancer stem cells (CSCs) are a subset of cancer cells which play a key role in predicting the biological aggressiveness of cancer due to its ability of self-renewal and multi-lineage differentiation (stemness). The CSC model is a dynamic one with a functional subpopulation of cancer cells rather than a stable cell population responsible for tumour regeneration. Hypotheses regarding the origins of CSCs include (1) malignant transformation of normal stem cells; (2) mature cancer cell de-differentiation with epithelial–mesenchymal transition and (3) induced pluripotent cancer cells. Surprisingly, the cancer stem cell hypothesis originated in the late nineteenth century and the existence of haematopoietic stem cells was demonstrated a century later, demonstrating that the concept was possible. In the last decade, CSCs have been identified and isolated in different cancers. The hallmark traits of CSCs include their heterogeneity, interaction with microenvironments and plasticity. Understanding these basic concepts of CSCs is important for translational applications using CSCs in the management of patients with cancer.

Contents

1. Introduction

Tissue renewal is maintained by normal stem cells through a tightly regulated process of self-renewal and cell death (Pierce and Speers, 1988; Pardal et al., 2005). Dysregulation of this process is a key event in cancer pathogenesis (Al-Hajj et al., 2004). Cancer might be considered as an abnormal organ/tissue, in which minor subpopulations of tumorigenic cells having aberrant self-renewal capacities give rise to

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different lineages of cancer cells. Recent studies have indicated that these self-renewing tumorigenic cells called cancer stem cells (CSCs) are mainly responsible for resistance to chemo-radiation therapy and cancer relapses (Vermeulen et al., 2012; Aulmann et al., 2010; Fillmore and Kuperwasser, 2008; Francipane et al., 2013; Ghods et al., 2007; Resetkova et al., 2010; Williams et al., 2013). Research is needed to target the stem cell populations which attribute the tumour growth and progression. In this review, we presented the recent information of the basic concepts, development milestones and the characteristics of CSCs.

2. Cancer stem cell model

Cancer is constituted of a heterogeneous population of cells differing in morphology, gene expression, proliferative capacity and invasiveness. This heterogeneity may occur as a result of cancer being hierarchically organized with a subset of cancer cells, called cancer stem cells (CSCs) or cancer initiating cells, at their apex, which have the capacity of stemness (Clarke et al., 2006; Vermeulen et al., 2008). CSCs potentially explain several phenomena of cancer such as minimal residual disease, resistance to chemo-radiation therapy, cancer recurrence and metastases (Vermeulen et al., 2012). Also, CSCs are believed to play a key role in predicting the biological aggressiveness of cancer, due to their ability of self-renewal and multi-lineage differentiation (stemness) through either asymmetric or symmetric division (Lee et al., 2011). In contrast, offspring of offspring, the progenitor cells and differentiated cancer cells, lose the capacity for stemness, thus no longer contributing to biological aggressiveness, though they cause much of the overall damage (Lee et al., 2011). Although these scientific hypotheses are appealing, they lack conclusive experimental evidences and they have stimulated controversies among cancer scientists. The current gold standard method to identify CSCs is via serial transplantation of cancer cells in animal models. As this xeno-transplantation model is an operational definition, it probably underestimates the total CSC number and is biased to the detection of those CSCs with more aggressive biological behaviour (Quintana et al., 2008; Lapidot, 2001).

3. Evolution of the CSC model

Cancer is known to arise from a single cell in specific tissues through a series of genetic and/or epigenetic events that cause ectopic production of growth related genes. These alterations in turn interfere with the mechanisms that normally control a stable physiological cell output in that tissue or initiate genomic instability state (Nowell, 1976; Baylin and Jones, 2011; Greaves and Maley, 2012; Stratton, 2011). Thus cancer ideally comes from abnormal clones that, at least initially, preserve many properties of the hierarchical structure of the normal tissue in which the cancer has arisen (Valent et al., 2012). According to the CSC model, the ultimate result of this accumulation of genetic and epigenetic "hits" is the development of at least one cell with CSC traits that can produce more CSCs and more differentiated offspring. In the past, the CSC model was a static one. However, in recent times, it has been revised to a dynamic one, where CSCs were believed to be converted into more transient cell types. Accordingly, progeny of mutated cells may acquire the capacity for self-renewal through de-differentiation of progenitor cells as well as reversal of differentiation in fully differentiated cells (Scheel et al., 2011). Thus, CSCs are a functional subpopulation of cancer cells rather than a stable cell population.

4. Origin of CSCs (Fig. 1)

The precise origin of CSCs is an ambiguous issue at present. There are three main hypotheses for the acquisition of the properties of a stem cell for cancer cells in the mainstream of the scientific world. These include the hypotheses of (1) malignant transformation of normal stem cells; (2) mature cancer cell dedifferentiation with epithelial–mesenchymal transition (EMT) and (3) induced pluripotent cancer cells.

The first hypothesis of the origin of CSCs proposed that CSCs are the product of malignant transformation of adult stem cells (Fillmore and Kuperwasser, 2008; Swords et al., 2005; Todaro et al., 2007). Smalley and Ashworth first suggested that CSCs may derive from normal stem cells that have acquired mutations and have lost their ability to self-regulate cell proliferation (Smalley and Ashworth, 2003). Cells with different malignant potentials would be present in any cancers with a defined set of genetic and epigenetic changes. Also, differentiated cells that have lost their tumour propagation capacity and cells that possess a clonogenic potential may exist in an established cancer (Vermeulen et al., 2008). These findings indicate that cells having the same genotypic makeup can exhibit a completely different potential to initiate a cancer.

There are normal stem cells in human bodies which are responsible for tissue repair, termed adult stem cells or somatic stem cells (Igarashi et al., 2008). Nowadays, more scholars support the hypothesis that CSCs originate from adult stem cells that have undergone accumulation of different degrees of epigenetic and genetic alterations and propose the following two reasons. First, for a normal somatic cell to transform into a malignant cell, it must accumulate many mutations. However as mutations are events of low frequency, the accumulation may take several years, even decades. In this process, no cell would survive so long, other than adult stem cells, with their properties of self-renewal and differentiation. Second, CSCs share several properties with normal stem cells, such as the capacity for self-renewal and the ability to differentiate, which would require still further mutation for a somatic cell to acquire.

On the other hand, studies have found that progenitor cells of CSCs can reacquire the self-renewal capacity through further genetic mutations and epigenetic modifications (Cozzio et al., 2003; Jamieson et al., 2004; Krivtsov et al., 2006). Thus, the second hypothesis for the origin of CSCs is that CSCs are acquired from tumour cells themselves via cellular dedifferentiation. Since normal breast stem cells and CSCs of breast cancer seem to have a mesenchymal phenotype and display gene expression characteristic of epithelial–mesenchymal transition, Weinberg's group demonstrated in 2008 that CSCs can be enriched within an existing malignancy, by "dedifferentiation" of mature tumour cells through an EMT pathway (Mani et al., 2008). EMT gives differentiated tumour cells the ability to self-renew, thus allowing the formation of distant sites of metastasis (Qiao et al., 2012, 2013).

A similar study was made by Brabletz's group in colorectal cancer. In that study, it was revealed that EMT-associated genes and stemness-associated genes were both expressed at the invasive front of cancer cells (Spaderna et al., 2007). More importantly, a study supported the above concept by detecting co-expression of EMT markers and stem cell markers in spindle tumour cells inside the blood vessels of patients with metastasis (Aktas et al., 2009). Due to the fact that invasion into the blood is the second step of cancer cell metastasis, the concept of migrating cancer stem cells should be an area for future study. Evidence of a potential link between cancer stem cells and EMT was reported in 2007. Before the milestone study of Weinberg's group in 2008, Zeng's group in 2007 isolated and identified a cancer stem cell–like side population in human nasopharyngeal carcinoma cell lines by flow cytometry (Mani et al., 2008; Wang et al., 2007). A total of 10,000 freshly sorted cells from this side population formed tumours in NOD/SCID mice. Cells formed outside this population, however, could not form tumours until the number increased to 200,000. More interestingly, growth of the side population cells in complete medium in vitro leads to morphology alteration into many long filaments, causing the cells to resemble fibroblasts, not polygonal squamous epithelial cells. It was implied that epithelial cancer stem cells were akin to fibroblasts, the prototype of migrating cancer stem cells.

The third hypothesis of the origin of CSCs is related to the recent development of induced pluripotent stem cells (iPS). Induced pluripotent stem cells (iPS) are artificially derived from a non-pluripotent cell