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EDITORIAL

Convergence of normal stem cell and cancer stem cell developmental stage: Implication for differential therapies

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Abstract

Increased evidence shows that normal stem cells may contribute to cancer development and progression by acting as cancer-initiating cells through their interactions with abnormal environmental elements. We postulate that normal stem cells and cancer stem cells (CSC) possess similar mechanisms of self-renewal and differentiation. CSC can be the key to the elaboration of anti-cancer-based therapy. In this article, we focus on a controversial new theme relating to CSC. Tumorigenesis may have a critical stage characterized as a "therapeutic window", which can be identified by association of molecular, biochemical and biological events. Identifying such a stage can allow the production of more effective therapies (e.g. manipulated stem cells) to treat several cancers. More importantly, confirming the existence of a similar therapeutic window during the conversion of normal stem cells to malignant CSC may lead to targeted therapy specifically against CSC. This conversion information may be derived from investigating the biological behaviour of both normal stem cells and cancerous stem cells. Currently, there is little knowledge about the cellular and molecular mechanisms that govern the initiation and maintenance of CSC. Studies on co-evolution and interdependence of cancer with normal tissues may lead to a useful treatment paradigm of cancer. The crosstalk between normal stem cells and cancer formation may converge developmental stages of different types of stem cells (e.g. normal stem cells, CSC and embryonic stem cells). The differential studies of the convergence may result in novel therapies for treating cancers.

Key words: Neural stem cell; Cancer stem cell; Convergence; Therapeutic

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INTRODUCTION

The survival rate for patients with solid cancers such as glioblastoma multiforme (GBM) has not improved even though multiple billions of dollars have been invested in cancer research since US president Richard Nixon declared war on cancer in 1971[1]. Cancer cells have been treated as invading aliens, which must be completely destroyed and removed[2]. Emerging evidence, however, argues for the need to view cancer differently. We and others have found that similarities and overlapping mechanisms between induced cell plasticity and cancer formation shed new light on the emerging picture of p53 sitting at the crossroads between two intricate cellular potentials: stem cell *vs* cancer cell generation[3]. A recent report shows that GBM neovasculature may be driven by cancer stem cells (CSC)[4-6] rather than recruiting mesenchymal endothelial progenitors[7-9]. Here, we propose that normal stem cells and CSC may share the same developmental stages. Understanding this paralleled multi-stage oncogenesis process may imply a differential therapy for treating tumors.

CANCER STEM CELLS

A growing body of evidence demonstrates that brain tumors may arise from a single, self-renewing cell, namely CSC[10]. CSC that have characteristics similar to brain stem cells, play a key role in cancer recurrence and resistance to current therapies[11]. These "bad seeds"- CSC - may have the ability to escape standard therapies, explaining tumor growth and new malignancies[12,13]. CSC have been identified in acute myeloid leukemia, breast cancer[14] and, most recently, brain tumors[15-17]. With a frequency as few as one out of thousands or even millions of tumor cells, CSC must be targeted and eliminated to prevent tumor relapse and to promote a cancer-free life. Cancer cells without stem cell properties may have little or no significance for cancer treatment or patient survival. However, the transplantation of native neural stem cells ("naïve") increased the survival of the recipient animals presumably by inhibiting tumor outgrowth[18]. Despite exciting initial reports of this anticancer potential, clinical potency of stem cell therapy in animal brain tumor models has proven disappointing. Amassed evidence shows that some normal naïve stem cells may contribute to cancer development and progression either by acting as cancer-initiating cells or through interactions with the environment[19-24]. However, it is believed that not all naïve stem cells have the potential to promote cancer progression, but only some naïve stem cells [e.g. mesenchymal stem cells, vascular progenitor cells (VPC)], possess these abilities to favor tumor formation principally due to their secreted pro-angiogenic and immunomodulatory factors. Only stem cells (e.g. native neural stem cells) reprogrammed or genetically altered to deliver anti-tumoral agents (protein, genes, viral, *etc.*) can exert a more robust anti-cancer effect[25-28] than naïve neural stem cells as demonstrated by Tyler *et al*[18]. Nevertheless, it is important and necessary to elucidate the cellular and molecular switch involved during the convergence of normal stem cells to CSCs.

CONVERGENCE OF NORMAL STEM CELL AND CANCER STEM CELL DEVELOPMENT

We hypothesize a convergence mechanism for development of different stem cells (normal stem cells, CSC and embryonic stem cells) as illustrated in Figure 1. Normal stem cells, defined as "S"; S0 defines stem cells in a self-renewal stage that actively replicate themselves. S0 are activated by environmental cues to go through different stages: S1 denotes activation, S2 denotes trophic mobilization and migration toward targeted locations, S3 denotes integration and engraftment, S4 denotes terminated differentiation. CSC, defined as "C" in Figure 1, share similar developmental stages: C1, C2, C3, and C4. S0 and C0 stage cells make additional copies of themselves before they go on to make cells of other stages S1, C1; S2, C2; S3, C3, and S4, C4, respectively. However, in the process of stem cell development, it is theoretically possible that genetic mistakes may be made; "S0" may convert to "C0" or CSC, and "S1" to "C1", *etc.* The cancer stem cell will then go on to follow the classic steps of differentiation, possibly the same as those of the normal stem cell. The "C1" will be activated to CSC, which are no longer in residency or quiescence. The "C2" cells become migratory and engraft themselves in a targeted tissue to become a "C3" engraftment. The integrated "C3" cells then differentiate to its final "C4" cancer cell stage. The "C4" cells may divide into a heterogeneous population, "C4a" "C4b" "C4c" … "C4x", derived from not only normal stem cells but also CSC. We know that normal stem cells "S0" replicate and, when activated, go on to "S1", "S2", "S3", and "S4" stages, respectively. The cells in the "S4" stage cells then differentiate into "S4a", "S4b", "S4c" … "S4x" which are also heterogeneous in nature.

Cancer itself can develop in either of two ways. One route is described in which the "S4" cells undergo malignant dedifferentiation. For example, mature glial cells in the brain dedifferentiate to glioma. Thus terminally differentiated cells can ultimately dedifferentiate into "C0" CSC, which remain regulated and produce more CSC. This is the classic origin of tumorigenesis, particularly in adults.

An alternative process that occurs in children involves the normal stem cell "S0" spinning off a "C0". The "C0" may progress to "C1" "C2" "C3" and "C4", creating terminally differentiated cancer cells. It is interesting to note that some terminally differentiated stem cells contribute to the establishment of terminally differentiated cancer cells[29]. Accumulated evidence also suggests that factors in the local extracellular milieu contribute to cancer development. For example, glioblastoma by definition

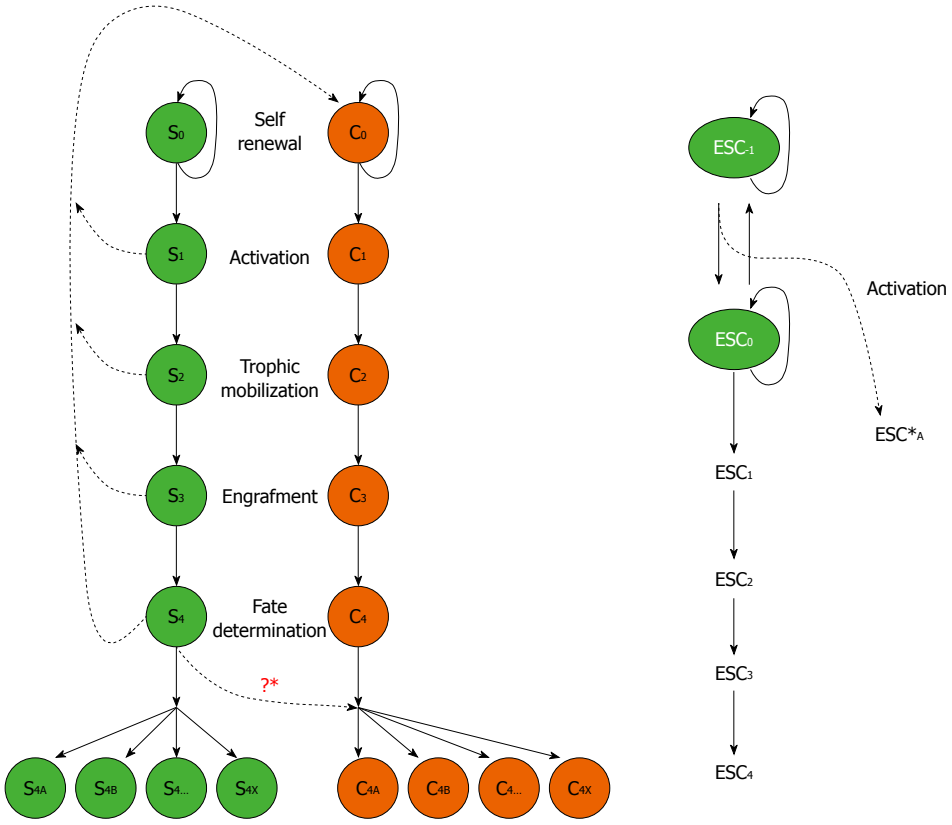

Figure 1 Developmental stages of normal stem cell (S) *vs* cancer stem cell (C). Right panel: Embryonic stem cells (ESC) may undergo similar stages in both normal stem cell and cancer stem cell development. However, at an earlier stage, ESC-1, there is a malignant convergence (See text for details).

must show necrosis, but why is this the case? A glioblastoma has the highest level of neovascularization of any tumor type. It is impossible to make a diagnosis of glioma in the absence of necrosis and neovascularization. Glioblastomas also have to recruit local cells to make blood vessels to support tumor growth. Thus if there is an inhibition of neovascularization, the glioma can only grow to the point of the maximum diffusion of nutrients from pre-existing blood vessels. Beyond that point, the tumor stops growing due to necrosis. Our previous work shows that p53 stops the growth of tumors[30,31]. A surprising recent observation suggests that an integrated differentiated tumor releases trophic factors, recruiting even mesenchymal stem cells (see above) into the area of the tumor. These integrated mesenchymal stem cells support the growth of tumor blood vessels. There is a very important link between "S4" and "C4" cells. In the parallel processes of activation in normal stem cells and CSC, trophic mobilization, engraftment, and commitment, therapeutic intervention may be possible when "S4" cells become"C4". This dedifferentiation stage makes CSC or malignant conversion, "S0" to "C0", an alternative treatment target, perhaps most appropriate for children.

Evidence supporting this scheme has emerged recently. One of the first developmental stages-specific factors is repressor element 1-silencing transcription/neuron-restrictive silencer factor (REST/NRSF). REST/NRSF is required to maintain the adult neural stem cell (NSC) pool and orchestrate stage-specific differentiation[32]. REST/NRSF recruits CoREST and mSin3A corepressors to stem cell chromatin for the regulation of pro-neuronal target genes to prevent precocious neuronal differentiation in cultured adult NSCs. Selective transplantation of ESC-derived VPCs in appropriate differentiation stages, contributes to adult neovascularization[33]. Another example, PW1 is involved in staging the self-renewing stem cells in a wide array of adult tissues[34]. Conditional Pten deletion in quiescent, and nestin-expressing radial glia-like precursors (RGL) initially promotes their activation and symmetric self-renewal but ultimately leads to terminal astrocytic differentiation and RGL depletion in the adult hippocampus[35]. However, little is known about the convergence of stem cells with tumorigenesis stages.

CLINICAL RELEVANCE OF STEM CELL CONVERGENCE

What can we do to stop normal cells from becoming a tumor? How do we take tumor potential away from embryonic stem cells? It is crucial to first address the malignant convergence from "ESC0" to "ESC-1," the first step of tumorigenesis (i.e. focus on the first step of the Genesis) (Figure 1, right panel). In our organotypic slice culture model, we can identify "stage-specific" cell populations as "ESC0" to "ESC-1" cells *vs* "S4" to "C4"[36]. Furthermore, we can perform a gene array subtrac-

tion for genetic profiling of these subpopulations to determine the molecular switching mechanism for the "malignant conversion". For example, in considering the cross-over of "S4" to "C4", most patients at this stage are given the high doses of chemotherapy, which may promote the convergence.

During the CSC differentiation process, there is a time when they are sensitive to chemotherapy which can be defined as a "therapeutic window"[37-39]. Intracranial placement of tumor xenografts under transparent glass cranial windows in nude rats models allows direct serial inspection of human brain tumor growth that can be used to study stage-specific tumor responses to therapeutics[40]. Chemotherapy results in unwanted killing of normal stem cells, which are necessary to help support the growth of the tumor. Following osmotic disruption of the blood-brain barrier (BBB) in humans, the time course to closure of the BBB, or the so-called therapeutic window, has important clinical implications for the design of therapeutic protocols[41]. Three-dimensional magnetic resonance spectroscopic imaging provides a unique biochemical "window" to study cellular metabolism non-invasively[42]. This has already demonstrated the potential for improved diagnosis, staging, and treatment planning in brain and prostate cancer. Certain agents like the VEGFR2 blockade create a "normalization window" - a period during which combined radiation therapy gives the best outcome[43]. This window is characterized by an increase in tumour oxygenation, which is known to enhance radiation response. The determination of this therapeutic window can allow maximization of the efficacy of the immunotherapy[44]. A non-invasive imaging system can be used to pin-point this therapeutic window[45].

Normal stem cells, which travel to tumors to support their growth, are subject to as much killing as the "trojan horse" of chemotherapy or radiation. However, therapeutic success relies on finding an effective strategy to select a stem cell subpopulation at a suitable stage when the cells are competitive and capable of targeting brain tumors. We have proposed the concept of a "therapeutic window" for stem cells, which may be defined more specifically a "biochemical therapeutic window", or even a "molecular therapeutic window" determined from genetic description. This selective process may produce more effective stem cells to treat cancers[46].

PERSPECTIVES AND FUTURE DIRECTIONS

To begin to unravel the biological behaviour of both normal tem cells and CSC, we have proposed conceptual models in order to help facilitate the design of new studies. Based upon our current studies, we postulate that a critical stage, defined as a "therapeutic window", can be thoroughly characterized by defining associated molecular[47,48], biochemical[49] and biological events[50]. Within this experimental framework, data obtained may support or contradict the hypothetical models, thereby shaping stage-defined biological models. Information obtained from these stage-specific stem cell studies will allow us to further explore the detailed mechanisms underlying the prospective roles of stage-specific molecules in stem cell development. Advances in our understanding of stem cell behaviour may extend application of stem cell transplantation, with stage-specific matching of normal stem cells and brain tumor stem cells. Advances in diagnosis and treatment of childhood cancers are expected to emerge from these coordinated stem cell studies, hopefully culminating in better cancer survival prognosis with a reduction in the risks of acute and late-stage adverse consequences of treatment.

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