Seminars in Cancer Biology 20 (2010) 85–92

Contents lists available at ScienceDirect

Seminars in Cancer Biology

journal homepage: www.elsevier.com/locate/semcancer

Review

Normal stem cells and cancer stem cells: similar and different

Mark Shackleton[a,b,*]

[a] Melanoma Research Laboratory and Department of Hematology and Medical Oncology, Peter MacCallum Cancer Centre, East Melbourne 3002, Australia
[b] Department of Pathology, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Parkville 3010, Australia

ARTICLE INFO

Keywords:
Stem cell
Cancer stem cell
Cancer progression
Self-renewal
Plasticity
Interconversion
Cancer regression

ABSTRACT

The functional capabilities of normal stem cells and tumorigenic cancer cells are conceptually similar in that both cell types are able to proliferate extensively. Indeed, mechanisms that regulate the defining property of normal stem cells – self-renewal – also frequently mediate oncogenesis. These conceptual links are strengthened by observations in some cancers that tumorigenic cells can not only renew their malignant potential but also generate bulk populations of non-tumorigenic cells in a manner that parallels the development of differentiated progeny from normal stem cells. But cancer cells are not normal. Although tumorigenic cells and normal stem cells are similar in some ways, they are also fundamentally different in other ways. Understanding both shared and distinguishing mechanisms that regulate normal stem cell proliferation and tumor propagation is likely to reveal opportunities for improving the treatment of patients with cancer.

1. Normal and cancer stem cells

The fields of stem cell biology and cancer biology share a common interest: how do cells proliferate? In stem cell biology, a major focus is on a specific type of cell proliferation called self-renewal that is characteristic of stem cells. Self-renewal enables stem cells to produce at least one progeny with a similar developmental potential [1,2]. Much has been learned about the mechanisms that regulate self-renewal of normal tissue stem cells.

One consistent observation in these studies has been the striking association between deregulation of stem cell function and carcinogenesis; many genes that promote self-renewal are also oncogenes and many genes that inhibit self-renewal are also tumor suppressor genes. These observations have led to the idea that some cancers originate in cells that have intrinsic self-renewal activity (i.e. stem cells) or in non-stem cells in which self-renewal is activated by oncogenic mechanisms. Studying normal self-renewal is thus important for understanding oncogenesis.

Distinct from the idea that cancers originate through activation of self-renewal mechanisms is the cancer stem cell (CSC) model of malignant propagation. The CSC model refers *not* to the cellular origin of cancers, but to the means through which established cancers propagate themselves [3,4]. In the CSC model, cancers are composed of functionally distinct cells: those with the potential for tumor formation and those that derive from tumorigenic cells and may even retain some proliferative activity, but have lost the potential to form tumors. Extensive evidence, presented in numerous previous reviews [1,3,5], indicates that at least some cancers follow a CSC model and contain tumorigenic cells as well as non-tumorigenic cells that derive from them.

Central to the CSC model is the idea that non-tumorigenic cells in a cancer derive from parent tumorigenic cells in a hierarchical and stable manner that parallels in concept the development of differentiated cells from stem cells in normal tissue development and homeostasis [6]. Indeed, the CSC model is so named because of this conceptual parallel. However, it is important to limit the conceptual links between normal tissue stem cells and tumorigenic cells in the CSC model, as these cells are fundamentally different in several important ways. Normal stem cells are notable for the vigilance with which their proliferation is controlled and for the care with which their genomic integrity in maintained. Tumorigenic cells are frequently distinguished by their lack of control of such processes. Identifying differences between normal stem cells and tumorigenic cancer cells is important for understanding how cancers progress and for translating advances in CSC biology into therapies that help patients.

2. Models of cancer propagation

Before considering similarities and differences between normal stem cells and tumorigenic cancer cells, it is worthwhile reviewing key concepts in the field of cancer propagation. Different models

Abbreviations: CSC, cancer stem cell; HF, hair follicle; HSC, hematopoietic stem cell; AML, acute myelogenous leukemia; CML, chronic myelogenous leukemia; Hh, Hedgehog.

* Correspondence address: Melanoma Research Laboratory, Peter MacCallum Cancer Centre, East Melbourne 3002, Australia. Tel.: +61 3 9656 5235; fax: +61 3 9656 1411.
E-mail address: mark.shackleton@petermac.org.

1044-579X/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.semcancer.2010.04.002

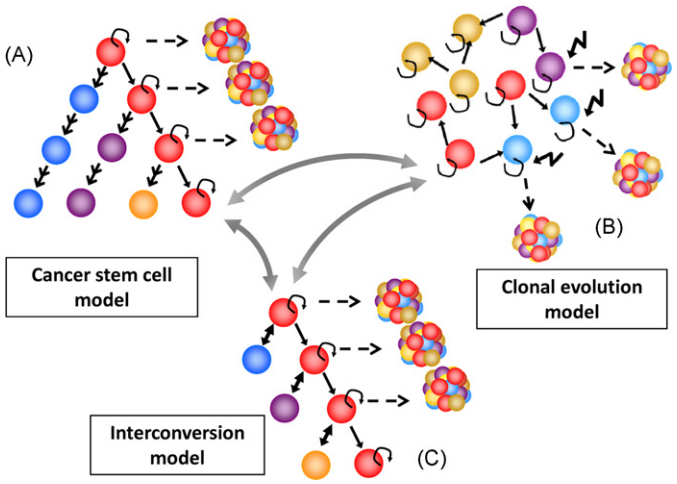

Fig. 1. Models of cancer propagation. (A) In the cancer stem cell (CSC) model, infrequent tumorigenic cells (colored red, renewal of malignant potential indicated by circular arrow) generate not only more tumorigenic cells but phenotypically distinct (non-red cells) non-tumorigenic cells in a manner which is stable and hierarchical (indicated by double-head arrows). (B) In the clonal evolution model, many phenotypically distinct cancer cells have malignant potential and some cells gain an advantage in disease-propagating ability by acquiring additional genetic mutations (indicated by jagged arrows). (C) In the interconversion model, although many cells have intrinsic malignant potential, cells can interconvert (indicated by two-way arrows) between actively malignant and relatively quiescent states which may be associated with phenotypic differences between cells. The large, central, two-way arrows depict the notion that these models are not mutually exclusive. Tumorigenic cells in the CSC model may undergo further genetic changes and/or may interconvert between more and less actively malignant states. Similarly, tumorigenic cells undergoing clonal evolution may transiently alter their malignant behaviour by interconversion. These changes may or may not result in a change in the predominant model of propagation that is used by a cancer. There is evidence that some cancers propagate predominantly according to a CSC model. Other cancers containing high proportions of cells with tumorigenic potential are likely to propagate predominantly by clonal evolution and/or interconversion.

are proposed to explain how established cancers propagate themselves. Classically, these include the CSC model, the clonal evolution model (also called the stochastic model) and the interconversion model (Fig. 1). Each of these models explains anecdotal and experimental observations that many cancer cells in tumors – just like cells in normal organs – are phenotypically and functionally heterogeneous.

The CSC model, outlined above, is fundamentally different from the other models in that it accounts for the possibility of irreversible loss of tumorigenic potential in some cancer cells through hierarchically determined mechanisms. In practice, tumorigenic cells in the CSC model should also be relatively rare in a cancer, as when these cells comprise a high proportion of cells there is little to be gained in considering them separately from the whole cancer. Furthermore, tumorigenic cells should be distinguishable from non-tumorigenic cancer cells in a way that makes their separation for independent evaluation possible. If tumorigenic and non-tumorigenic cells were unable to be separated, the CSC model would be neither useful nor testable. It is important in the study of any cancer to consider the possibility that it may follow a CSC model, as the identification, separation and study of rare populations of tumorigenic cells distinct from bulk populations of irreversibly non-tumorigenic cells will facilitate understanding of the mechanisms of progression of these cancers.

The clonal evolution model of cancer propagation [7–10] is based on the genetic instability of cancer cells. In the clonal evolution model, a high proportion of cancer cells has tumorigenic potential and individual cells gain an advantage in malignant behaviour over other cancer cells by acquiring additional genetic mutations (Fig. 1). Intratumoral genetic heterogeneity has been observed in several cancers [11–17]. This indicates that genetically divergent clones can arise from tumorigenic cells within a cancer and independently maintain malignant potential, although the degree and rate at which tumorigenic cells undergo genetic change is unknown and may be different for different cancers at different stages of disease progression. Clonal evolution also provides a basis for understanding genetic mechanisms of therapy resistance that can be acquired by cancer cells [18–21].

The interconversion model addresses the ability of tumorigenic cancer cells to interconvert between less and more actively malignant/proliferative states. Although direct evidence (i.e. the in vivo observation of malignant cells switching between different phenotypic and malignant fates in the same tumor) is lacking, intra-vital studies showing associations between Brn-2 expression, pigmentation and motility in melanoma cells within tumors strongly suggest that interconversion occurs [22]. Interconversion was recently proposed to explain differences between tumorigenic and non-tumorigenic cells in the CSC model, raising the notion that tumorigenicity can be contextual [23]. In fact, the possibility of two-way interconversion between tumorigenic and non-tumorigenic cells was never considered in the CSC model because this model only ever addressed the intrinsic potential of cancer cells to form tumors. A cell that is non-tumorigenic in one context but becomes tumorigenic in another context has by definition not lost tumorigenic potential. Such a cell is considered tumorigenic in the CSC model, as its lack of tumorigenicity at particular point in time is reversible, context dependent and not absolute.

3. Unifying model of cancer propagation

In the broad consideration of cancer propagation, the cancer stem cell model, the clonal evolution model and the interconversion model should not be thought of as mutually exclusive (Fig. 1). Cancers that follow a CSC model contain rare tumorigenic cells that may undergo clonal evolution and/or may interconvert between different states of malignant behaviour and therapy resistance. Examples of these cancers are myelogenous leukemias, in which there is evidence for hierarchical organization of tumorigenic and non-tumorigenic cells [24–28], and evidence that the tumorigenic cells are subject to ongoing genetic changes and epigenetic alterations [18,19,29] that help propagate the disease.

On the other hand, cancers with high proportions of tumorigenic cells may propagate primarily by clonal evolution and/or may contain cells that use reversible mechanisms to interconvert between more and less actively malignant fates. For example, human metastatic melanomas [30] and some mouse hematopoietic malignancies [31,32] contain high proportions of tumorigenic cells. These diseases thus do not appear to follow a CSC model characterized by rare tumorigenic cells. In the case of melanoma, extensive phenotypic heterogeneity may exist among cells in a tumor, despite the cells being similarly tumorigenic [30]. The basis of this heterogeneity is unknown, but likely to be in part determined by reversible epigenetic mechanisms. As above, melanoma cells may interconvert between various phenotypic and functional fates within tumors [22]. Additionally, genetic differences between melanoma cells could also explain the phenotypic heterogeneity of this disease, although genetic variation among melanoma cells has only been evaluated in a small number of genomic regions [17] and the full extent of genetic heterogeneity in melanoma, and indeed among cells in other cancers, remains unknown. The identification of genetic and epigenetic determinants of cancer cell phenotypes and cancer cell propagation is relevant and important regardless of the mode of disease propagation.