Review Article

Medicine®

OPEN

Cancer stem cells

Role in tumor growth, recurrence, metastasis, and treatment resistance

Jenny C. Chang, MD[a,b,*]

Downloaded from http://journals.lww.com/md-journal by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 07/09/2024

Abstract

Cancer stem cells (CSCs) are a class of pluripotent cells that have been observed in most types of solid and hematologic cancers. CSCs have been shown in numerous cancer models to be involved in tumor development, cell proliferation, and metastatic dissemination, while possessing a capacity for sustained self-renewal. CSCs, which typically represent a small proportion of total cells of a given tumor, also exhibit resistance to chemotherapy and radiotherapy. Indeed, exposure to these treatments may promote "stemness" in nonstem cancer cells, which may explain why successful therapeutic reduction of tumor bulk will often fail to produce clinical improvement. Acquisition of stemness involves epithelial-mesenchymal transition (EMT), in which epithelial cells are transformed into a mesenchymal phenotype characterized by increased capacities for migration, invasiveness, and resistance to apoptosis. EMT may also contribute to metastasis by driving dissemination of mesenchymal CSCs to distant locations, whereupon the CSCs revert to an epithelial phenotype to support metastatic tumor growth. Several different approaches to treatment aimed at overcoming the intrinsic resistance of CSCs to conventional therapies are currently being developed. These include agents targeting tumorigenic pathways, such as JAK2/STAT3 and PI3K/mTOR, and immunotherapies, including vaccines and natural killer cells employed to induce a T cell response.

Abbreviations: 5-FU = 5-fluorouracil, CSC = cancer stem cell, CTC = circulating tumor cell, ECM = extracellular matrix, EMT = epithelial-mesenchymal transition, EphA3 = ephrin type-A receptor 3, FAK = focal adhesion kinase, HER = human epidermal growth factor receptor, IL-3R = interleukin-3 receptor, JAK/STAT = Janus-activated kinase/signal transducer and activator of transcription, MET = mesenchymal-epithelial transition, NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells, ROS = reactive oxygen species, TGF-β = transforming growth factor beta.

Keywords: cancer stem cell, CSC-targeting, epithelial-mesenchymal transition, metastasis, recurrence, resistance, tumor microenvironment

1. Introduction

Cancer stem cells (CSCs) describe a class of pluripotent cancer cells that behave analogously to normal stem cells in their ability to differentiate into the spectrum of cell types observed in tumors.[1,2] These characteristics of what is known as "stemness" allow for the growth of the primary cancer tumor as well as the development of new tumors.[1,2] CSCs may be identified via phenotypic surface markers (such as $CD34^+/CD38^-$ in leukemia stem cells), which has allowed for the observation of CSCs in most types of human cancer, including breast, brain, liver, lung, gastric, colon, prostate, pancreatic, and head and neck cancers, as well as multiple myeloma, leukemia, and melanoma.[2–6] In addition to their pluripotency, CSCs have been shown to be involved in fundamental processes of tumor development, cell proliferation, and metastatic dissemination, while possessing a capacity for self-renewal that make CSCs immortal.[2,7]

The qualities of stemness that define CSCs appear to be confined to a relatively small proportion of cancer cells, which are able to produce the diversity and heterogeneity of cancer cells that compose most of the tumor bulk. CSCs of several types of cancer may be markedly more tumorigenic than nonstem cancer cells.[1,2] CSCs are, however, generally resistant to chemotherapy and radiotherapy, meaning that despite these therapies successfully destroying a large proportion of the tumor bulk, the result may not be significant clinical improvement.[1] Taken together, the available data regarding CSCs indicate that they represent a rich source for understanding the development, and potential treatment, of a spectrum of cancer types. This article reviews the role of CSCs, as they are currently understood, with a particular focus on the role of CSCs in tumor growth, recurrence, metastasis, and treatment resistance.

1.1. Epithelial–mesenchymal transition and the acquisition of stemness

Epithelial-mesenchymal transition (EMT) refers to the process by which epithelial cells undergo several changes, including loss of polarity, which transitions the cells into a mesenchymal phenotype (Fig. 1).[8,9] The mesenchymal phenotype is associated with an increased capacity for migration, resistance to apoptosis, increased production of extracellular matrix (ECM) degrading

The author reports no conflicts of interest.

[a] *Cancer Center,* [b] *Institute for Academic Medicine, Houston Methodist Hospital, Houston, TX.*

[*] *Correspondence: Jenny C. Chang, Houston Methodist Hospital, Houston, TX 77030 (e-mail: jcchang@houstonmethodist.org).*

Copyright © 2016 the Author. Published by Wolters Kluwer Health, Inc. All rights reserved.

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially.

Medicine (2016) 95:S1(e4766)

Received: 6 July 2016 / Received in final form: 5 August 2016 / Accepted: 10 August 2016

http://dx.doi.org/10.1097/MD.0000000000004766

Downloaded from http://journals.lww.com/md-journal by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 07/09/2024

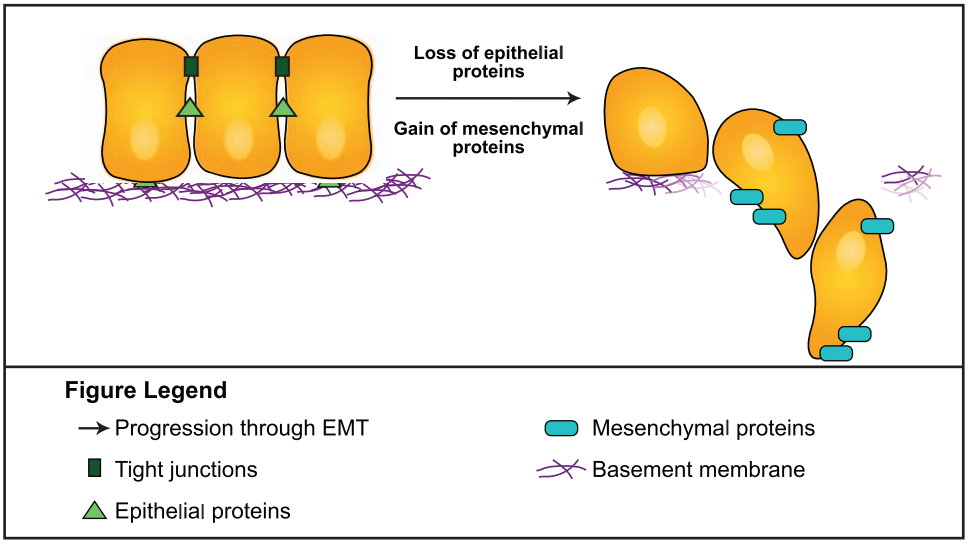

Figure 1. Epithelial-mesenchymal transition.[8,9]

enzymes, and increased proclivity for invasiveness.[9,10] The acquisition of the properties of stemness by cancer cells—that is, the transition from a nonstem cancer cell to a CSC—occurs via the process of EMT and the concurrent acquisition of an invasive mesenchymal phenotype.[3] Epithelial cells, which normally interact with the basement membrane, once transitioned into mesenchymal cells, migrate from the epithelial layer at the same time that the basement membrane undergoes degradation.[8,9]

In addition to its role in the development of stemness in cancer, EMT is involved in a variety of physiologic processes, including tissue repair and embryogenesis.[9,11] In embryogenesis, EMT operates at multiple stages, including the conversion of trophectoderm cells to promote invasion of the endometrium to anchor the placenta, and is subsequently involved in the differentiation of the mesendoderm into the mesoderm and the endoderm.[9] In tissue regeneration, a different type of EMT, type 2, responds to inflammation associated with tissue damage, and produces fibroblasts and other repair-related cells to reconstruct tissue.[9] In fact, there are 3 EMT subtypes categorized by their biological context: type 1 refers to EMTs related to embryo formation, implantation, and organ development; type 2 describes EMTs related to tissue regeneration, wound healing, and organ fibrosis; and type 3 are EMTs occurring in tumor cells that have already undergone genetic and/or epigenetic alterations. Although all 3 EMT types involve similar underlying biological processes, type 3 EMTs are those primarily relevant to CSCs and cancer progression, and produce outcomes significantly different from those observed in type 1 and 2 EMTs.[9]

Either exogenous expression of transcription factors that promote EMT induction or exposure to particular cytokines can spontaneously initiate the process in which cancer cells acquire CSC and mesenchymal phenotype properties.[12] With regard to breast cancer cells, ectopic expression of Twist, Snail, or FoxC2 transcription factors have been shown to induce EMT in human mammary epithelial cells, with spontaneous transformation into a mesenchymal phenotype, although without robust plasticity.[3] Interestingly, exposure of nonstem breast cancer cells to transforming growth factor beta (TGF-β) has been shown to produce mesenchymal/CSC-like cells with a high degree of plasticity, whereas removal or inhibition of TGF-β causes the cells to lose their mesenchymal/CSC-like characteristics, and to regain an epithelial and nonstem cell phenotype.[3]

EMT is, in fact, 1 side of a 2-way process, because epithelial and mesenchymal cells can move in either direction as a part of EMT or its reverse, mesenchymal-epithelial transition (MET).[9] Other pathways associated with the regulations of CSCs include Notch, Hedgehog, TGF-β, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and Wnt, which are associated with EMT induction, whereas human epidermal growth factor receptor (HER) and pathways involving bone morphogenetic proteins are associated with MET induction.[8] By undergoing EMT, and acquisition of a mesenchymal phenotype, CSCs are produced possessing characteristics that promote tumor progression, recurrence, metastasis, and resistance to therapy.[8]

1.2. Tumor growth

Although normal stem cells follow strict signaling pathways that direct differentiation into mature cells and govern self-renewal, dysregulation of such signaling can result in the formation of tumors.[13] Oncogenic hits, such as alterations occurring in the tumor microenvironment, or intrinsic alterations, such as APC/KRAS mutations, can also promote the initiation, expansion, and progression of malignancies.[1,14] Additionally, stromal fibroblasts secrete growth factors and inflammatory cytokines, including interleukin-8, an activator of the Janus-activated kinase/signal transducer and activator of transcription (JAK/STAT) 3 pathway, which is known to promote tumor initiation and cancer progression.[15]

The CSC model of development and differentiation can, to a large extent, account for the extraordinary heterogeneity, both of function and phenotype, present in many types of solid tumors and hematologic cancers.[7,16] The potential for multiple variations in manifestations of tumor propagation contribute to the observed heterogeneity of tumors (Fig. 2).[16] In its simplest manifestation, a single CSC may expand and differentiate into a tumor. Alternatively, multiple CSC pools may be present, each of which has the potential to develop into independent tumors. Activation of dormant CSCs—potentially dormant for years—may result in cancer recurrence at a later time. A secondary