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Tumor microenvironment for cancer stem cells☆

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ABSTRACT

Tumor tissues consist of heterogeneous cancer cells including cancer stem cells (CSCs) that can terminally differentiate into cancer cells. Tissue-specific stem cells in normal organs maintain their stemness in a specific microenvironment, the stem cell niche; several studies have suggested that there are specific microenvironments that maintain CSCs in an immature phenotype. Cell types in a CSC niche vary from fibroblasts, to endothelial cells, immune cells, and so on; these non-cancer cells have been suggested to change their original features in the normal tissue/organ and to acquire a phenotype that protects CSCs from anticancer therapies. Therefore, to kill CSCs, we need to understand the cellular and molecular mechanisms involved in the maintenance of the immature phenotype of CSCs and in drug resistance.

Contents

1. Introduction

Adult stem cells in normal organs and tissues supply cells for terminally differentiated organs and tissues for a long time by their self-renewal activity, including symmetric and asymmetric cell division. Stem cells allow organs and tissues to maintain their function throughout lifetime [1]. The concept of cancer stem cells (CSCs) was first

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introduced in leukemia; however, the existence of CSCs has been reported in solid tumors as well as in hematopoietic malignancies [2]. The concept of stem cells has been easily accepted in the hematopoietic field because hematopoietic stem cells give rise to various hematopoietic lines through progenitors. However, the concept of CSCs in solid tumors has not been accepted easily, probably because of the obscurity of the definition of stem cell in normal solid organs. Normal stem cells have been identified in several organs; however, the pathway from stem cells to terminally differentiated cells through progenitors has not been precisely elucidated yet. In addition, although in normal organs stem cells are required to preserve organ function, cancer cells can proliferate and expand a tumor without CSCs. If CSCs do exist in tumors, do they develop stochastically by gene reprogramming or gene mutations caused by chromosomal instability upon exposure to severe unfavorable condition such as hypoxia and malnutrition? Recent publications have indeed demonstrated the existence of CSCs by showing their cell surface markers and their malignant behaviors, such as their tumorigenic, invasive, and metastatic abilities due to a very small number of cells [3]. Gene expression profiles in malignant cancer cells including CSCs showed that CSCs may possess an embryonic stem cell-like immature gene expression signature [4–6].

The localization of stem cells in normal organs has been identified, and it has been suggested that the interaction of niche cells with stem cells is critical for stemness maintenance [7]. As observed in normal organs, CSCs may localize at specific foci, and cell survival signals might be supplied by niche cells (Fig. 1). In order to cure cancer, we should regulate CSCs; however, CSCs have been suggested to show drug resistance by expressing several transporters [8]. Therefore, the regulation of the stem cell niche is a reasonable strategy to inhibit CSC survival. The main focus of this review is the identification of CSCs and of their niche in a variety of tumors and the regulation of the CSC niche.

2. Stem cell niche in normal organs and in cancers

2.1. Stem cell niche, a lesson from the bone marrow

The niche of hematopoietic stem cells (HSCs) in the bone marrow has been extensively characterized in mammalian organs. In embryos, HSCs proliferate in the intraluminal part of the arteries, such as the dorsal aorta and the omphalomesenteric arteries, and the vascular niche has been suggested to support HSCs [9,10]. We reported that Tie2, a receptor tyrosine kinase expressed on HSCs, is involved in the adhesion of HSCs to the endothelial cells (ECs) of the arteries through integrins activation [9]. On the other hand, two groups suggested that in the bone marrow HSCs frequently localize around the endosteum and that osteoblasts are components of the niche supporting HSCs [11,12]. One group showed that when bone morphogenic protein (BMP) signals were suppressed in osteoblasts, osteoblasts proliferation was induced [11], and the number of HSCs simultaneously increased. The other group induced proliferation of osteoblasts by the activation of the parathyroid hormone receptor, resulting in the increase of HSCs [12]. Taken together, these reports suggested that osteoblasts in the bone marrow may be components of the niche that regulates the number of HSCs. Tie2 activation through angiopoietin-1 produced by osteoblasts induces HSCs dormancy through a strong adhesion between HSCs and osteoblasts mediated by N-cadherin [11,13]. However, the involvement of N-cadherin has been questioned [14–17].

On the other hand, as observed in embryos, HSCs localize in the perivascular area of bone marrow sinusoids [18,19]. In the vascular

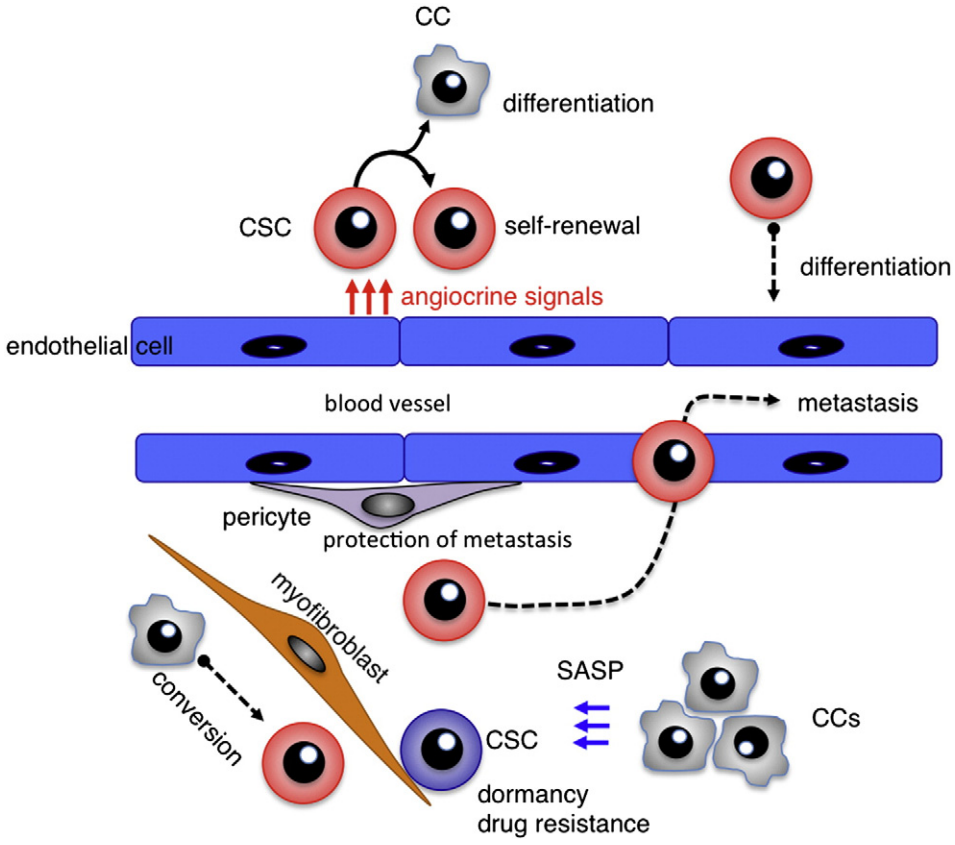

Fig. 1. Several cancer stem cell niches. Cancer stem cells (CSCs) frequently localize at perivascular areas. Endothelial cells produce several angiocrine factors and regulate stemness of CSCs or induce differentiation of CSCs into cancer cells (CCs). On the other hand, CSCs may support endothelial cell survival. In some tumors, CSCs may differentiate into endothelial cells and generate vascular cells as niche cells. The number of pericytes is low in the tumor microenvironment. Metastasis of CSCs may be blocked from pericyte-covered blood vessels, but pericytes may support stemness. Myofibroblasts induce malignant conversion of CCs into CSCs. Myofibroblasts in a hypoxic area support CSC dormancy. CCs differentiated from CSCs may also support stemness of CSCs by producing senescence-associated secretory phenotype (SASP) factors when senescence or apoptosis is induced by anticancer drugs.