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The role of cancer stem cells in cancer metastasis: New perspective and progress

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ABSTRACT

Recent studies have identified the important role of cancer stem cells (CSCs) in carcinogenesis and relapse. However, with respect to multistage cancer metastasis, the role of CSCs has not been well-defined. In several human cancers, data showed that some phenotypic subsets of CSCs were responsible for cancer metastasis. In this review, we surveyed recent advances in the role and mechanism of metastatic CSCs.

1. The basic procedure of metastatic cascade

Metastasis, frequently a final and fatal step in the progression of solid malignancies, encompasses several fundamental biological processes: cancer initiation, epithelial–mesenchymal transition (EMT), breach of the basement membrane barrier, neighbor invasion, intravasation, mesenchymal–epithelial transition (MET), extravasation, colonization and outgrowth of micrometastases and secondary cancer [1]. In fact, the evolution of metastatic cascade is a dynamic process influenced by unique cellular lineages, altered microenvironments, distinct anatomical restrictions and multiple genetic and epigenetic alterations [2].

A number of studies have attempted to address the question of cellular heterogeneity within cancer tissues and its implications for the selection of metastatic cancer cells. Luzzi et al. [3] traced the fate of B16F1 melanoma cells injected intraportally into murine livers. Although 80% of the injected cells survived and extravasated at day 3, only a small number of these cells (1 in 40) formed micrometastases, and only 1 in 100 micrometastases continued to grow into macrometastases, which suggested that the metastatic action of caner appears inefficiently.

2. Migrating cancer stem cells (CSCs)

Why so few cancer cells successfully navigate the multistep metastatic process? The precise nature of these cancer cells remains undefined. However, some properties of CSCs, a subpopulation of cells that display stem cell properties, mediate metastasis, and contribute to treatment resistance, suggest them as candidates for mediating metastatic progression. First, it is theoretically possible that only CSCs within cancer tissues have the ability to initiate and sustain cancer growth. Therefore, even if non-CSCs migrate (which is likely, given the number of cancer cells that can be detected in the blood), they would not be able to propagate into heterogeneously diverse metastatic lesions [4]. Furthermore, the inherent plasticity of stem cells makes CSCs more adaptable to survive in a foreign environment where growth factors and other signaling molecules are different from those in the primary caner site [4]. Also cellular plasticity in stem cells may facilitate EMT, which has been postulated as a key event during the early phase of cancer metastasis [5].

Brabletz et al. [6] firstly establish the hypothesis of migrating CSCs, which possess both an element of stemness and mobility. It is postulated that these cells undergo EMT at the invasive front of the

Abbreviations: CSCs, cancer stem cells; ALDH, aldehyde dehydrogenases; AdCC, adenoid cystic carcinoma; HCC, hepatocellular carcinoma; EMT, epithelial–mesenchymal transition; SDF-1, stromal cell derived factor 1; CXCR-4, chemokine C-X-C motif receptor 4; VEGF, vascular endothelial growth factor.

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primary cancer and migrate to colonize new tissues, where its acquired stemness to facilitate production of the cancer heterogeneity commonly observed in metastatic colonies [6]. The migrating cancer stem cell hypothesis is attractive owing to its integration of primary cancer initiation, progression and metastasis.

3. Metastatic capacity of CSC subpopulations characterized by different markers

Although CSCs have been identified in many types of cancer and the migrating cancer stem cell hypothesis has gained more attention in recent years, the issues that whether metastatic competence is inherent to all CSCs is still outstanding. Several studies have defined rare CSCs subpopulations which have distinct metastatic competence. Roberta et al. [7] identified a subpopulation of $CD26^+$ CSCs uniformly present in both the primary and metastatic tumors in colorectal cancer patients with liver metastasis. Furthermore, circulating $CD26^+$ CSCs were capable of forming metastatic growth in the liver after injected into mouse cecal wall. In patients without distant metastasis at the time of presentation, the presence of $CD26^+$ cells in their primary tumors predicted distant metastasis on follow-up [7].

Using a molecular tracking strategy, Dieter et al. [8] identified a types of extensively self-renewing longterm tumor-initiating cell (LT-TICs) with specific roles in cancer metastasis, which suggested the existence of a subpopulation of cancer cells with stem cell properties endowed with metastatic capacity on malignant progression in colorectal cancer.

Aldehyde dehydrogenases (ALDHs) are a group of enzymes that catalyze the oxidation of aldehydes [9]. Recent studies demonstrated that high level of ALDH activity could serve as a putative CSCs maker and its presence strongly correlates with tumor malignancy as well as self-renewal properties of CSCs in various human cancers. Intriguingly, evidences show that $ALDH^+$ human breast cancer MDA-MB-231 cells with stem-like properties are responsible for the bone metastasis [10]. Sun and Wang [11] found that a subpopulation of cells expressing high level of ALDH activity residing in human adenoid cystic carcinoma (AdCC) possessed enhanced invasive potential in vitro and highly metastatic capability in vivo, which suggesting $ALDH^+$ CSCs are responsible for mediating AdCC metastasis.

CD133 is one of the most representative cancer stem cell markers. Woo et al. [12] found that CD133 high expressers in stage I lung adenocarcinomas (ADC) show a significantly higher risk of recurrence than CD133 low expressers. CD133 high expressers having strong proliferating activity and/or with vessel invasion show a higher risk of recurrence, which suggested the level of CD133 expression is an independent prognostic marker and its combination with proliferating activity and/or vessel invasion could have excellent prognostic value to predict postoperative recurrence in patients with stage I lung ADC.

Lingala et al. [13] co-stained hepatocellular carcinoma (HCC) specimens with anti-CD133 and anti-ALDH monoclonal antibodies, and found that doubly positive HCC cell clusters were co-localized in the areas adjacent to connective tissue and within invaded vessels, which suggested that $CD133^+/ALDH^+$ CSCs are highly metastatic.

4. EMT and MET in migrating CSCs

EMT and MET are recognized as critical events for metastasis of carcinomas. The former are responsible for degrading the surrounding matrix to lead the way of invasion and intravasation and the latter is important for cancer cells then enter the blood stream and reestablish colonies in the secondary sites [14]. Recent studies suggested that CSCs normally have characteristics associated with mesenchymal cells and also play a critical role in tumor initiation, growth, metastasis [15]. Migrating CSCs are located predominantly at the tumor-host interface and are derived from stationary CSCs through the acquisition of a transient EMT phenotype in addition to stemness [6]. EMT endows human mammary epithelial cells with CSCs-like properties which characterized by their $CD44^{high}/CD24^{low}$ phenotype [16] through up-regulating Mena, a member of the Ena/VASP family which plays a role in cell migration [17]. Intriguingly, many of circulating tumor cells expressing Mena display a mesenchymal phenotype which indicates EMT, and also acquired a breast cancer stem cell $CD44^+/CD24^-/Lin^-$ phenotype [18].

Vimentin (VIM) is related to EMT and also associated with cancer metastatic potential. Li et al. [19] demonstrated that human colorectal cancer $CD133^+$ SW480 single cell progenies (SCPs) are heterogeneous in invasion and metastasis. A few $CD133^+$ SW480 cells expressed VIM in the metastatic group SCP17 and SCP26, but the non-metastatic group SCP24 and SCP40 cells showed no VIM staining. Also, studies showed that in invasive CSCs, an epithelial marker E-cadherin was down-regulated, mesenchymal markers were up-regulated, and Transgelin which regulates EMT associated genes were over-expressed [20], which indicated some link exit between EMT and CSCs in tumor invasion and metastasis.

5. MicroRNAs, EMT and CSCs

Accumulating data suggested that upregulation of some microRNAs and downregulation or absence of some of them have been found in metastatic CSCs. Reduction of microRNA let-7 in breast CSCs increased in vivo tumorigenic and metastatic capability [21]. An additional example of potential role of microRNAs in metastatic CSCs was represented by miR-30. Over-expression of miR-30 in breast CSCs xenograft reduced lung metastasis, whereas blocking miR-30 expression enhanced metastasis in vivo [22].

Multiple microRNAs have been reported to be involved in EMT, which suggested that microRNAs might connect CSCs and metastasis through regulation of EMT [23]. EMT-inducer zinc finger E-box binding homeobox 1 (ZEB1) could enhance metastasis not only by promoting tumor cell mobility and dissemination, but also by maintaining a stem cell phenotype through inhibition of miR-200 family members, which is necessary for the formation of metastases from disseminated tumor cells.

6. Chemokines, CSCs and metastasis

To date, chemokines and their receptors have been known to play important roles in inflammation, infection, tissue injury, cardiovascular diseases, allergy, and malignant tumors [24]. Studies showed that chemokine receptors may potentially facilitate tumor dissemination at each of the key steps of metastasis [25]. The CXCR4/SDF-1 axis could mediate metastasis of the distinct subpopulation of CSCs. In the invasive front of human pancreatic cancer tissue, a distinct subpopulation of $CD133^+/CXCR4^+$ CSCs was identified to determine the metastatic phenotype of the individual tumor. Depletion of the cancer stem cell pool for these migrating CSCs significantly reduces the metastatic phenotype of pancreatic tumors, which indicates that a subpopulation of migrating $CD133^+/CXCR4^+$ CSCs is essential for tumor metastasis [26]. In the $CD133^+$ SW480 SCPs, which bear heterogeneous invasive and metastatic ability, CXCR4 expression was associated with stronger infiltrating and metastatic abilities, indicating that $CD133^+$ SCPs of SW480 cell line are prone to produce invasive and metastatic phenotypes and chemokines and their receptors are responsible for the recurrence and metastases of solid tumors [20].

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