A Brief Review on Cancer Stem Cells

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Abstract

More than a decade ago, the existence of a rare population with both stem cell-like properties and tumor initiating capability was first identified in acute myeloid leukemia and, subsequently, in several solid tumors. These populations with stem cell-like properties were termed ‘cancer stem cells (CSCs)’, indicating that only a subset of cancer cells were tumorigenic and able to initiate and produce the bulk of tumors, thus also termed ‘tumor initiating cells’. In this mini review on issues such as cancer stem cell markers, integrins, Matrix metallo-proteinases, chemokines and chemokine receptors are described to study the cancer stem cells associated metastasis. This review article, several mechanisms and signaling pathways of cancer stem cells during self-renewal and differentiation were mentioned.

Keywords: Cancer stem cells; Matrix metallo-proteinases; Chemokines and integrins

Introduction

Many studies performed over the past 30 to 40 years, when viewed collectively, have shown that the characteristics of stem-cell systems, the specific stem-cell properties described above, or both, are relevant to some forms of human cancer [1]. A minor subpopulation of cells in tumor samples has the capacity to initiate clonal growth in in vitro cultures or in in vivo transplant models which has perplexed researchers in the past. Two theories were proposed to explain this paradox. The stochastic theory suggested that all cancer cells are equally malignant but only clones that randomly possess favorable biological properties will grow upon transplantation. An alternative theory predicted that tumors are hierarchical like normal tissues and only the rare subpopulation of cells at the pinnacle of that hierarchy have the unique biological properties necessary for tumor initiation. The role of stem cells is now being addressed in many solid tissue cancers. In 1990s Irving L. Weissman, coined these stem cells, “Cancer stem cell”, stem cells arising through the malignant transformation of adult stem cells. These cancer stem cells are proposed to be the source of some or all tumors and cause metastasis/relapse of the disease state. Biologically distinct and relatively rare populations of “tumor-initiating” cells have been identified in cancers of the hematopoietic system, brain, and breast [2]. Cells of this type have the capacity for self-renewal, the potential to develop into any cell in the overall tumor population, and the proliferative ability to drive continued expansion of the population of malignant cells as shown in Figure 1. The discovery of cancer stem cells implores the question regarding the origin of these cells. Are they derived from normal stem cells with a cancerous phenotype? Or do previously differentiated progenitor cells with oncogenic mutations retain the ability to self-renew? A third theory hypothesizes that CSCs may come from a rare fusion event between stem cells and other cells. Figure 2 indicates the possible origin of cancer stem cells [3-5].

Markers for Cancer Stem Cells

They represent a tumour cell subpopulation, own typical stem cell properties as self-renewal and potential to differentiate and are possibly responsible for tumour growth. We have a lack of knowledge about the cells equipment of molecular markers that can be used for isolation and purification. One of the already established markers is the transmembrane-protein CD133. The role of CD133 as tumor stem cells marker is well depicted in the following Figure 3. All tested cancer samples has the capacity to initiate clonal growth in vitro cultures or in vivo transplant models.
floating spheres. Markers expressed on normal and cancer stem cells are shown in Table 1.

The following proteins play important role during cancer stem cell mediated differentiation, migration and metastasis of many cancer types.

**Integrins**

The integrins are a super family of cell adhesion receptors that bind to extracellular matrix ligands, cell-surface ligands, and soluble ligands. Figure 4 shows the role of integrins in cell-cell communication. Integrins are transmembrane αβ heterodimers and till date at least 18 α and 8 β subunits are known in humans, generating 24 heterodimers as shown in Figure 5.

**Matrix Metallo-Proteinases**

The conventional wisdom of the role of Matrix Metallo-Proteinases (MMPs) during tumor development is that they facilitate degradation of key ECM components, thereby assisting invasion of tumor cells into ectopic tissue compartments. Recent insights into ECM function during remodeling processes, and identification of many non-matrix substrates for MMPs, have implicated these enzymes as regulators of the cellular microenvironment and cellular functions during normal development and neoplastic progression, e.g., cell attachment, migration, cell proliferation, differentiation, survival, genomic (in) stability, angiogenesis, and malignant potential. Significantly, MMPs are expressed mostly by stromal cells and inflammatory cells, but act on the epithelial cells to regulate infiltrating inflammatory cells, regulates ECM degradation, apoptosis, cell recruitment, proliferation, bioavailability of VEGF and angiogenesis, and thus coordinate numerous events in developing tumors. The list of MMPs and their information is give below in the Table 2.
### Table 1: Markers expressed in normal and cancer stem cells in humans.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Cancer type</th>
<th>Normal stem cell markers</th>
<th>Cancer stem cell markers</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematopoietic</td>
<td>Leukemia</td>
<td>CD34+CD38-Thy1-Lin-</td>
<td>CD34+CD38-Thy1-Lin-</td>
<td>[4,7]</td>
</tr>
<tr>
<td>Breast</td>
<td>Mammary cancer</td>
<td>CD24\textsuperscript{high}</td>
<td>CD44\textsuperscript{high} ESA+Lin-</td>
<td>[5,6]</td>
</tr>
<tr>
<td>Brain</td>
<td>Brain tumor</td>
<td>CD133+Lin-</td>
<td>CD133+Nestin</td>
<td>[5,9]</td>
</tr>
<tr>
<td>Skin</td>
<td>Melanoma cancer</td>
<td>CD20-CD166- Nestin-</td>
<td>CD20+CD166+ Nestin+</td>
<td>[10,11]</td>
</tr>
<tr>
<td>Prostate</td>
<td>Prostate cancer</td>
<td>CD133+q2 β1\textsuperscript{h}</td>
<td>CD44+q2 β1\textsuperscript{h}CD133+</td>
<td>[13]</td>
</tr>
<tr>
<td>Tongue, Larynx, Throat and Sinus</td>
<td>Head and neck Squamous cell carcinoma (HNSCC)</td>
<td>CD44-</td>
<td>CD44+</td>
<td>[12]</td>
</tr>
</tbody>
</table>

### Table 2: Description of matrix metallo-proteinases (MMPs).

<table>
<thead>
<tr>
<th>MMP</th>
<th>Name</th>
<th>Location</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMP1</td>
<td>Interstitial collagenase</td>
<td>secreted</td>
<td>Substrates include Col I, II, III, VII, VIII, gelatin</td>
</tr>
<tr>
<td>MMP2</td>
<td>Gelatinase-A, 72 kDa gelatinase</td>
<td>secreted</td>
<td>Substrates include Gelatin, Col I, II, III, IV, VI, X</td>
</tr>
<tr>
<td>MMP3</td>
<td>Stromelysin 1</td>
<td>secreted</td>
<td>Substrates include Col II, IV, IX, X, XI, gelatin</td>
</tr>
<tr>
<td>MMP7</td>
<td>Matrilysin, PUMP 1</td>
<td>secreted</td>
<td>Membrane associated through binding to cholesterol sulfate in cell membranes; substrates include: fibronectin, laminin, Col IV, gelatin</td>
</tr>
<tr>
<td>MMP8</td>
<td>Neutrophil collagenase</td>
<td>secreted</td>
<td>Substrates include Col I, II, III, VII, VIII, X, aggrecan, gelatin</td>
</tr>
<tr>
<td>MMP9</td>
<td>Gelatinase-B, 92 kDa gelatinase</td>
<td>secreted</td>
<td>Substrates include Gelatin, Col IV, V</td>
</tr>
<tr>
<td>MMP10</td>
<td>Stromelysin 2</td>
<td>secreted</td>
<td>Substrates include Col IV, laminin, fibronectin, elastin</td>
</tr>
<tr>
<td>MMP11</td>
<td>Stromelysin 3</td>
<td>secreted</td>
<td>MMP-11 shows more similarity to the MT-MMPs, is convertase-activatable and is secreted therefore usually associated to convertase-activatable MMPs. Substrates include Col IV, fibronectin, laminin, aggrecan, collagen, gelatin</td>
</tr>
<tr>
<td>MMP12</td>
<td>Macrophage metalloelastase</td>
<td>secreted</td>
<td>Substrates include elastin, fibronectin, Col IV</td>
</tr>
<tr>
<td>MMP13</td>
<td>Collagenase 3</td>
<td>secreted</td>
<td>Substrates include Col I, II, III, IV, IX, X, XIV, gelatin</td>
</tr>
<tr>
<td>MMP14</td>
<td>MT1-MMP</td>
<td>membrane-associated</td>
<td>Type-I transmembrane MMP; substrates include gelatin, fibronectin, laminin</td>
</tr>
<tr>
<td>MMP15</td>
<td>MT2-MMP</td>
<td>membrane-associated</td>
<td>Type-I transmembrane MMP; substrates include gelatin, fibronectin, laminin</td>
</tr>
<tr>
<td>MMP16</td>
<td>MT3-MMP</td>
<td>membrane-associated</td>
<td>Type-I transmembrane MMP; substrates include gelatin, fibronectin, laminin</td>
</tr>
<tr>
<td>MMP17</td>
<td>MT4-MMP</td>
<td>membrane-associated</td>
<td>Glycosyl phosphatidylinositol-attached; substrates include fibronectin, fibrin</td>
</tr>
<tr>
<td>MMP18</td>
<td>Collagenase 4, xcol4, xenopuscollagenase</td>
<td>secreted</td>
<td>No known human orthologue</td>
</tr>
<tr>
<td>MMP19</td>
<td>RAS1-1, occasionally referred to as Stromelysin-4</td>
<td>secreted</td>
<td>No known human orthologue</td>
</tr>
<tr>
<td>MMP20</td>
<td>Enamelysin</td>
<td>secreted</td>
<td>No known human orthologue</td>
</tr>
<tr>
<td>MMP21</td>
<td>X-MMP</td>
<td>secreted</td>
<td>No known human orthologue</td>
</tr>
<tr>
<td>MMP23A</td>
<td>CA-MMP</td>
<td>membrane-associated</td>
<td>Type-II transmembrane cysteine array</td>
</tr>
<tr>
<td>MMP23B</td>
<td>-</td>
<td>membrane-associated</td>
<td>Type-II transmembrane cysteine array</td>
</tr>
<tr>
<td>MMP24</td>
<td>MTS-MMP</td>
<td>membrane-associated</td>
<td>Type-I transmembrane MMP</td>
</tr>
<tr>
<td>MMP25</td>
<td>MTS-6-MMP</td>
<td>membrane-associated</td>
<td>Glycosyl phosphatidylinositol-attached</td>
</tr>
<tr>
<td>MMP26</td>
<td>Matrilysin-2, endometase</td>
<td>secreted</td>
<td>No known human orthologue</td>
</tr>
<tr>
<td>MMP27</td>
<td>MMP-22, C-MMP</td>
<td>Secreted</td>
<td>No known human orthologue</td>
</tr>
<tr>
<td>MMP28</td>
<td>Epilysin</td>
<td>Secreted</td>
<td>Discovered in 2001 and given its name due to have been discovered in humankeralinocytes. Unlike other MMPs this enzyme is constitutively expressed in many tissues (Highly expressed in tests and at lower levels in lung, heart, brain, colon, intestine, placenta, salivary glands, uterus, skin). A threonine replaces proline in its cysteine switch (PRCGVTD).</td>
</tr>
</tbody>
</table>

MMPs are important enzymes in the breakdown of extracellular matrix proteins.
Chemokines

Chemokines are a family of chemoattractant cytokines (small proteins secreted by cells that influence the immune system) which play a vital role in cell migration through venules from blood into tissue and vice versa, and in the induction of cell movement in response to a chemical (chemokine) gradient by a process known as chemotaxis. In addition, chemokines also regulate lymphoid organ development and T-cell differentiation, mediate tumour cell metastasis, and have recently been shown to have a function in the nervous system as neuromodulators. In order for a cell to respond to a chemokine it must express a complementary chemokine receptor. Chemokine receptors belong to the vast family of G-protein coupled receptors (GPCRs): seven transmembrane receptors which bind extracellular ligands and consequently initiate intracellular signalling. When a chemokine binds its receptor a calcium signalling cascade is created, resulting in the activation of small GTPases [8-10]. This then has downstream effects such as activation of integrins (molecules involved in cell adhesion) and actin polymerisation, resulting in the development of a pseudopod (cellular projection), polarised cell morphology and ultimately cell movement. Chemokines are grouped and named according to their amino acid composition, particularly on the first two cysteine residues of a conserved tetra-cysteine motif. The CC and CXC chemokines form the two largest groups [10-13]. The molecules CX3CL1, XCL1 and XCL2 are also regarded as chemokines. In fact, the molecules expressed on a cell determine which tissue a cell will migrate into. For example, cells expressing the chemokine receptor CCR7 migrate to lymph nodes, where their ligands, CCL19 and CCL21, are expressed. Chemokines also regulate angiogenesis in the tumor microenvironment. The N terminus of several CXC chemokines contains three amino acid residues [Glu-Leu-Arg (ELR motif)], which precede the first cysteine amino acid residue of the primary structure of these cytokines [14,15]. CXCR4 is by far the most common chemokine receptor that has been demonstrated to be over expressed in human cancers. More than 23 different human malignancies, including breast cancer, ovarian cancer, melanoma, and prostate cancer, express CXCR4 [16]. Although CXCR4 can be expressed in a broad array of tissues, CXCR4 expression is low or absent in many normal tissues, including breast [17] and ovary [18]. Its sole ligand, CXCL12 is constitutively produced in multiple tissues, including those where metastases develop frequently (i.e., lung, liver, and bone).

Despite the increasing number of studies on genes and pathways involved in cancer “stemness”, factors in the tumor microenvironment that regulate CSCs, and how cancer cells, in turn, modify the niche by influencing their neighboring cells remain largely uncharacterized. Fibroblasts release a variety of growth factors, chemokines, and components of the extracellular matrix into the microenvironment and influence the differentiation and homeostasis of adjacent epithelia. Cancer-associated fibroblasts (CAFs) can promote cancer progression by modulating multiple components in the cancer niche to build a permissive and supportive microenvironment for tumor growth and invasion. The chemokines and their CXC members are given below in Table 3.

### Cancer Stem Cells Mediated Metastasis

Metastatic spread of cancer cells from the primary tumors to distant vital organs, such as lung, liver, brain, and bone, is responsible for the majority of cancer-related deaths [19]. Cancer stem cells are likely to play essential roles in the metastatic spread of primary tumors because of their self-renewal capability and their potential to give rise to differentiated progeny that can adapt to different target organ microenvironments [20]. Investigating the metastatic behavior of cancer stem cells (CSCs) is critical for the development of more effective therapies to prevent or delay the progression of malignant diseases.

### Conclusion

Tumorigenic contribution of CSCs is still not fully uncovered. This is in part explained by the presence of heterogeneous population due to the lack of exact definition of CSC population. However, many evidences suggest that CSCs are actively recruited into tumor site, and contribute to tumor microenvironment as either themselves or as the tumor-associated fibroblasts. They directly or indirectly regulate tumor cell proliferation, differentiation, immune tolerance, angiogenesis, metastasis and drug resistance through the interaction with numerous cytokines and growth factors as well as providing niche to the cancer cells in cooperated with ECM. To study the above-mentioned list of the contents in cancer stem cells it is important to maintain a database. Such a database on cancer stem cells will surely help not only the researchers but also clinicians for the development of pharmacotherapeutics.

### References


