



Are Cancer Stem Cells Responsible for Cancer Recurrence?

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Local recurrence or distant organ metastasis are the major causes of cancer mortality [1,2]. Conventional treatments, including surgery, chemotherapy, and irradiation, do not consistently prevent cancer recurrence [3,4]. Thus, an alternative therapeutic approach is needed. Recent evidence indicates a specific cell population of cancer stem cells or tumor initiating cells (jointly CSC) exists in various cancers that may be identified by cell surface markers, such as CD133, CD44, aldehyde dehydrogenase 1 (ALDH1) enzyme expression, or side population. However, the specific and exclusive CSC marker(s) are dependent on the type of cancer [5,6]. CSCs are similar to normal stem cells in that they have the ability to self-renew while producing differentiated daughter cells [7] however, they are resistant to conventional treatments [8,9]. It has been reported that CSC activation or education is in part orchestrated by the surrounding microenvironment [10]. Thus, in addition to conventional cancer treatments, targeting the CSC population may be essential to prevent recurrence or metastasis.

According to the hypothesis, CSCs that metastasize to the lymph node are stimulated by the lymph node microenvironment. Lymph node stromal cells, including follicular dendritic cells, prime and support these therapy-resistant cancer cells, and promote extra-nodal metastasis, through soluble factors such as chemokine (C-X-C motif) ligand 12 (CXCL12) [11,12]. Most solid tumor *in vivo* studies generate human tumor xenografts from immunodeficient mice, a foreign microenvironment for human cancers. It was shown that as few as 100 purified CSCs could initiate tumors in immunodeficient mice [5]. It is unclear whether this phenomenon is in fact due to the presence of CSC or rather represents a selection of cells surviving a foreign environment; in syngenic animals, a dominant cell population rather than rare CSC seems to sustain many tumors [13]. To test the hypothesis, *in vitro* and *in vivo* models must establish a humanized tumor microenvironment. Such a method was reported in breast cancer studies, where an orthotopic xenograft model was established in which both the stromal and epithelial components of the reconstructed mammary gland were of human origin, providing the proper environment for the development of human mammary epithelium [14]. We reported similar humanized tumor microenvironment models for follicular lymphoma and colon cancer [11,12]. In these models, co-inoculation of human stromal cells with cancer cells recreates a humanized microenvironment similar to a

lymph node. Our data shows that the humanized microenvironment is essential for CSC to form tumor in immunodeficient mice, selectively supports CSCs survival from chemotherapeutic drugs, and enhances drug-resistant CSC tumor formation through CXCL12 and CXCR4 signaling. Evidence has also shown that AMD3100, a small molecule inhibitor of CXCL12/CXCR4 signaling, can reduce the migration of follicular lymphoma cells towards stromal cells, and can inhibit cancer cell tumorigenesis, supporting that AMD3100 disrupts the CSC niche and makes the CSC more susceptible to chemotherapy [15]. To eliminate cancer recurrence, an adjuvant therapy regimen is required to target CSCs and their supportive stromal environment.

In conclusion, not all cancer cells constituting a tumor are the same; a small population of CSC exists [16]. Cancer poses a problem not only with its cancer cells, but also in its involvement with a microenvironment that specifically supports CSCs. Thus, the CSC population is responsible for recurrence and metastasis with the help from its stromal environment [17,18]. Therefore, combination treatment with chemotherapy drug in conjunction with other therapies, such as stromal/CSC signaling-targeted therapy may effectively keep cancer in remission [19].

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Received: June 12, 2012 Accepted: June 13, 2012 Published: June 15, 2012

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