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Cancer Stem Cells and Tumor Metastasis: First Steps into Uncharted Territory

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In several forms of human cancer, only a phenotypic subset of cancer cells, usually termed "cancer stem cells" (CSC), can initiate tumor growth when transplanted. In this issue of *Cell Stem Cell*, Hermann et al. (2007) analyze the relationship between CSC and tumor metastasis.

Tumor tissues have long been known to be composed of heterogeneous populations of cancer cells. Recently, a new wave of studies has begun to address whether distinct cancer cell subpopulations purified from the same solid tumor tissue are characterized by distinct functional properties. Remarkably, these studies have shown that, in several types of human cancer, only a phenotypic subset of cancer cells, usually a minority subset, is endowed with tumorigenic capacity, i.e., is capable to sustain the growth of a new tumor when injected in immunodeficient mice. This tumorigenic subset of cells is characterized by three main properties: (1) it expresses a distinctive repertoire of surface markers, which allows its reproducible and differential purification, (2) it is selectively endowed of tumorigenic capacity as opposed to all other subsets, and (3) it sustains the growth of heterogeneous cancer tissues, which recreate the full repertoire of cancer cell populations observed in the parent tumor, thus displaying two of the functional hallmarks of stem cells: self-renewal and differentiation. Based on these observations, the tumorigenic subset of cancer cells is currently defined the "cancer stem cell" (CSC) subset (Dalerba et al., 2007).

Among the most ominous properties of malignant cancer cells is their capacity to metastasize, i.e., to move from their primary tissue of origin and seed in a different anatomical compartment, where they sustain the growth of a secondary tumor lesion. Because CSC appear to be preferentially endowed with the capacity to self-renew, and thus to be responsible for the long-term maintenance of tumor growth, it has been predicted that they might be also primarily responsible for the formation of tumor metastases (Dalerba et al., 2007). This assumption, however, has not yet been addressed experimentally, and the relationship between CSC and metastasis remains obscure. In their present study, Hermann and colleagues tried to shed light on this fascinating research subject, using human pancreatic cancer as a model system (Hermann et al., 2007).

To characterize pancreatic CSC, the authors analyzed fresh human primary tumor tissues and showed that, in some patients, the capacity to form tumors after orthotopic injection in the pancreas of immunodeficient "nude" mice was restricted to a minority population of $CD133^+$ cells. Next, the authors used a human pancreatic cancer cell line and showed that the $CD133^+$ population of this cell line could be further subdivided into two subsets based on the expression of the CXCR4 molecule ($CD133^+/CXCR4^{neg}$ and $CD133^+/CXCR4^+$). Comparison of the tumorigenic capacity of bulk $CD133^+$ cells (containing a mixture of $CD133^+/CXCR4^{neg}$ and $CD133^+/CXCR4^+$ cells) and of $CD133^+$ cells depleted of the $CXCR4^+$ subset (i.e., $CD133^+/CXCR4^{neg}$) showed that both populations were equally capable to sustain tumor growth. Interestingly, however, depletion of the $CXCR4^+$ subset from bulk $CD133^+$ cells was able to abrogate the capacity of resulting tumors to form spontaneous metastases, at least in the short/medium term. A similar effect was obtained by pharmacological inhibition of CXCR4.

These observations have important implications, as they indicate that targeting of CXCR4 might be key to interfering with the spread of some pancreatic tumors. CXCR4 is the receptor for the CXCL12/SDF-1 chemokine and is involved in the control of leukocyte trafficking. There is ample evidence that CXCR4 can be directly expressed by cancer cells and regulates their migratory and metastatic properties (Balkwill, 2004; Muller et al., 2001). The present study, for the first time, demonstrates the role of CXCR4 in tumor metastasis by using a model where multiple phenotypic cancer cell subpopulations coexist in a dynamic equilibrium and where the tumorigenic and metastatic properties of distinct cell subsets, including CSC, can be tested independently, trying to chart their functional and hierarchical relationships.

Different models can be envisioned to explain for the observations of Hermann and colleagues (Hermann et al., 2007) (Figure 1). It is possible that two distinct subsets of CSC may coexist in the same cancer cell population: one with the capacity to self-renew ($CXCR4^{neg}$) and one with the capacity to self-renew and form metastases ($CXCR4^+$). To test this hypothesis, it will be necessary to test the tumorigenic capacity of purified $CXCR4^+$ cancer cells alone. If the $CXCR4^+$ subset proves to be tumorigenic, a second question would arise: what is the origin of $CXCR4^+$ cancer cells? Do they represent a distinct genetic subclone of CSC that arose as a result of additional DNA mutations

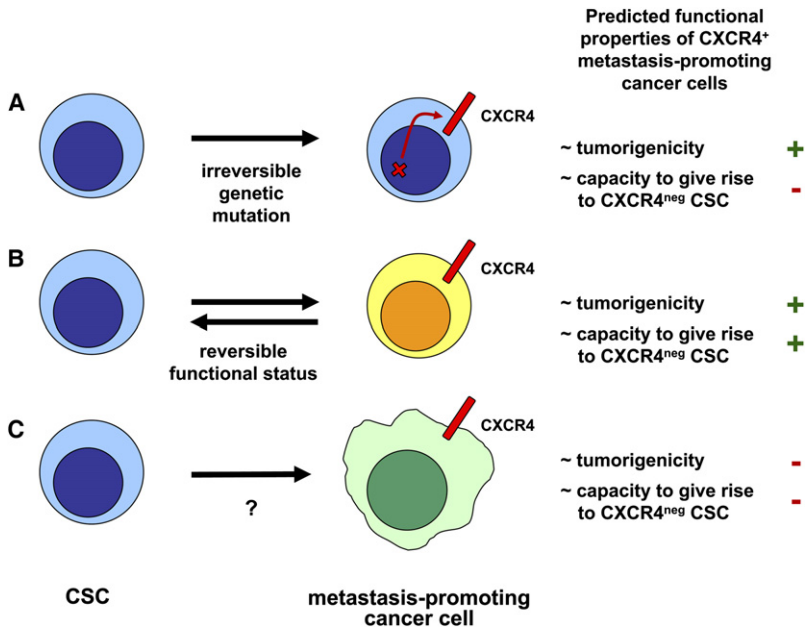

Figure 1. Possible Models to Explain the Origin of Metastasis-Promoting CXCR4$^+$ Cancer Cells

Three alternative models can be envisioned to explain the origin of CXCR4$^+$ cancer cells. In a first scenario (A), CXCR4$^+$ cancer cells might represent a genetic subclone of CSC, originated by accumulation of additional genetic mutations. In this case, CXCR4$^+$ cancer cells would retain the tumorigenic potential of CSC but would be unable to give rise to CXCR4^{neg} CSC subsets. A second possibility (B) is that CXCR4$^+$ cancer cells represent a reversible functional status of CXCR4^{neg} CSC. In this case, CXCR4$^+$ cancer cells would display both tumorigenic potential and the capacity to give rise to CXCR4^{neg} CSC subsets. A third theoretical scenario (C) envisions CXCR4$^+$ cancer cells as bystander players, unable to self-renew and sustain tumor growth by themselves but capable to promote metastatic dissemination, with a role similar to that of macrophages in several tumor model systems.

occurring after the first round of mutations that initiated the tumor (Figure 1A)? Or do they represent a CSC subset where induction of CXCR4 expression results from exposure to microenvironment stimuli (Figure 1B)? To distinguish between these possibilities, it will be necessary to analyze tumors originated from purified CXCR4^{neg} and CXCR4$^+$ cancer cells and evaluate whether or not they contain mixtures of CXCR4^{neg} and CXCR4$^+$ cells. It is also possible that CXCR4$^+$ cancer cells might be devoid of tumorigenic capacity but be endowed with a "facilitating" effect on the formation of metastases, a role somewhat similar to that of macrophages in many tumor model systems (Figure 1C) (Balkwill and Mantovani, 2001; Coussens and Werb, 2001). The answer to these questions, as well as the definition of the relative contribution of CXCR4 and other pathways in pancreatic cancer metastasis, awaits a more comprehensive analysis of pancreatic CSC isolated from multiple patients' fresh primary tissues.

Independently of the mechanisms underlying the prometastatic effect of CXCR4$^+$ cancer cells, the observations reported by Hermann and colleagues (Hermann et al., 2007) have interesting therapeutic implications, as they point to possible approaches to interfere with the metastatic capacity of malignant pancreatic tumors in vivo. Among them, one could list the pharmacological inhibition of the CXCR4 molecule (e.g., using small synthetic compounds, some of which already underwent phase I-II trials in human subjects) or the in vivo depletion of CXCR4$^+$ cancer cells (e.g., using anti-CXCR4 monoclonal antibodies). These approaches would not be designed to kill CSC or interfere with their growth but to block their dissemination. In the natural history of most human cancers, patients frequently undergo successful surgical resection of primary tumors but ultimately succumb to distant site metastases that develop later on. The possibility to "paralyze" tumors in a specific clinical stage could represent a significant addition to the oncologist's weaponry and gain time for patients with localized disease.

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