Periostin: A Bridge between Cancer Stem Cells and Their Metastatic Niche

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Only a minority of cancer cells have the potential to initiate metastatic growth, but the factors that limit metastatic colonization remain mostly unknown. Malanchi et al. (2012) recently demonstrated that stromal periostin is crucial for metastatic colonization by regulating the interactions between breast cancer stem cells and their metastatic niche.

Tumor metastasis is the most common cause of cancer-associated mortality. To give rise to the outgrowth of metastatic tumors in a new organ microenvironment, cancer cells have to overcome various types of stresses and several rate-limiting steps (Bao et al., 2004). Most disseminated cancer cells are destroyed during metastasis formation and only a small subset of cancer cells are able to survive and colonize in a new environment. Specialized tumor microenvironments called metastatic niches are thought to be responsible for nurturing disseminated cancer cells from micrometastases to full macrometastases. Recent studies have shown that there may be a direct link between cancer stem cells (CSCs) and their metastatic niches. Identifying the limiting factors that regulate the properties of CSCs and their colonization of metastatic niches is therefore important for developing strategies to treat patients with metastatic tumors. In a recent issue of *Nature*, Huelsken and colleagues (Malanchi et al., 2012) provide new insight into how signals from the metastatic niche affect CSC self-renewal and metastatic colonization.

CSCs are a subpopulation of tumor cells that can drive tumorigenesis via their abilities to self-renew and differentiate, whereas their counterpart non-CSCs are not tumorigenic and are thought to not contribute substantially to tumor metastasis. Recently, distinct types of CSCs have been shown to determine tumor growth and metastatic activity in human pancreatic cancer (Hermann et al., 2007) and colorectal/colon cancer (Dieter et al., 2011; Pang et al., 2010). Using the MMTV-PyMT mouse breast cancer model, which has many characteristics similar to human luminal breast cancer and spontaneously metastasizes to the lungs, Malanchi et al. (2012) found that only the $CD90^+CD24^+$ CSC population from primary tumors or pulmonary metastases was able to produce lung metastases and initiate secondary metastases. This result, together with those from previous studies, supports the idea that only the CSC subpopulation is able to cause tumor metastasis and that selective expansion of CSCs is responsible for initiating metastasis.

Because the metastasis frequency is much lower than the number of injected CSCs, Malanchi et al. reasoned that specialized elements from the foreign microenvironment might govern metastatic colonization by affecting the maintenance and expansion of CSCs in metastatic sites. To explore the limiting factors that determine metastatic success, the authors analyzed potential niches in mammary gland, bone, skin, and intestine and identified *periostin* (*Postn*) as a stromal factor of normal stem cell niches. They demonstrated that POSTN is secreted by stromal αSMA^+VIM^+ fibroblasts in the lungs of metastasis-positive animals, but not by tumor cells. Furthermore, the authors found that while POSTN-knockout MMTV-PyMT mice show no differences in primary breast tumor volume and morphology compared with wild-type mice, they have a significantly decreased pulmonary metastasis potential, and the metastatic efficiency of POSTN-deficient tumor cells can be rescued in wild-type recipients. These data suggest that stromal POSTN acts as a key regulatory factor for lung metastasis of breast tumors. Interestingly, POSTN expression is induced in the lung stroma by infiltrating cancer cells. POSTN expression was increased in isolated primary lung fibroblasts treated with TGF-β3 or TGF-β2 or cocultured with tumor cells. Using a dominant-negative TGFβR2ΔTM, the authors found that blocking the action of TGF-β3 in tumor cells abrogates stromal POSTN expression and metastasis formation in lungs. Taken together, these results indicate that infiltrating tumor cells can educate stromal cells by secreting factors such as TGF-β3, which induces host stromal expression of POSTN to create a metastatic niche to support metastasis formation.

Investigating the underlying mechanisms of POSTN-induced metastasis, Malanchi et al. (2012) observed that POSTN-deficient tumor cells fail to form tumorspheres, but this phenotype can be rescued by adding POSTN protein to primary cultures. Furthermore, CSCs fail to initiate colony formation when cocultured with stromal cells isolated from $Postn^{-/-}$ lungs, but do form colonies with wild-type cells. $CD90^+$ CSCs have a tendency to preferentially localize adjacent to stromal niches in lung metastases, whereas the frequency of $CD90^+CD24^+$ CSCs in the rare pulmonary metastases in POSTN-deficient mice is reduced. Thus, stromal POSTN plays a key role in regulating CSC maintenance and expansion during metastatic colonization. To investigate how POSTN promotes stem cell maintenance and metastasis formation, Malanchi et al. (2012) analyzed the interactome of POSTN and found that

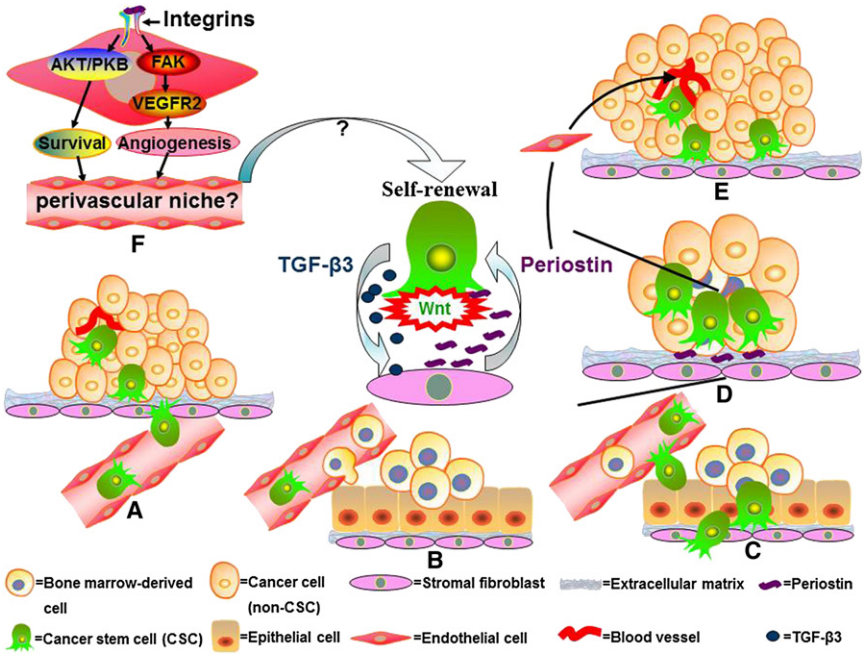

Figure 1. Periostin Mediates the Crosstalk between Cancer Stem Cells and Their Niche
Periostin (POSTN) plays an essential role in the crosstalk between cancer stem cells (CSCs) and their niche to permit metastatic colonization. (A) Tumor metastasis is initially triggered by cancer stem-like cells. (B and C) The premetastatic niche created by bone-marrow-derived cells is critical for tumor metastasis because it enhances the adhesion of infiltrating tumor cells. (D) Tumor-cell-secreted TGF-β3 educates the lung stroma to create a CSC-supportive niche by inducing the expression of stromal POSTN. POSTN recruits Wnt ligands, thereby augmenting Wnt signaling in CSCs, which promotes CSC self-renewal and metastatic formation. (E) POSTN promotes tumor metastatic growth by promoting both cell survival and angiogenesis. However, whether POSTN is involved in the formation of the premetastatic and perivascular niches, and thereby in the regulation of CSC maintenance and tumor metastasis, has not been characterized (C and F).

POSTN increases Wnt signaling by interacting with Wnt ligands, Wnt1 and Wnt3A. Interestingly, POSTN-deficient mice successfully form pulmonary metastasis under orthotopical MMTV-Wnt1 tumor cell transplantation. These results suggest that stromal POSTN bridges the gap between the metastatic niche and CSCs to create a CSC-supportive niche and promotes metastatic colonization by augmenting Wnt signaling pathway (Figure 1).

Interestingly, Bao et al. (2004) showed previously that overexpression of POSTN in human colon cancer cells can enhance the number and size of metastases in the liver, indicating that POSTN plays a critical role in establishing metastases in the liver microenvironment. These findings are consistent with the conclusion of Malanchi et al. (2012) that POSTN is a critical limiting factor during metastatic colonization. POSTN can also be secreted by bone-marrow-derived mesenchymal stromal cells and their derived cells (Coutu et al., 2008), and Kaplan et al. (2005) highlighted that the premetastatic niche created by bone-marrow-derived cells in secondary sites before the arrival of tumor cells can be a critical microenvironment for facilitating tumor metastasis, suggesting another potential site for POSTN involvement. Further investigation will no doubt increase our understanding of the role of POSTN in tumor metastasis in all of these locations.

The study from Malanchi et al. (2012) reinforces the notion that there may be functional similarities between matricellular proteins in regulating CSC stemness and metastatic niches. Osteopontin (OPN), tenascin C, and other matricellular proteins also promote tumor metastasis and modulate the maintenance and expansion of normal or cancer stem cells and metastatic niches (McAllister et al., 2008; Oskarsson et al., 2011; Ouyang et al., 2010). Whether and how these matricellular proteins regulate stemness of CSCs as metastatic niche components deserves a systemic evaluation.

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