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COMMENTARIES

Bone Metastasis Targets The Endosteal Hematopoietic Stem Cell Niche

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Commentary on: Shiozawa Y, Pedersen EA, Havens AM, Jung Y, Mishra A, Joseph J, Kim JK, Patel LR, Ying C, Ziegler AM, Pienta MJ, Song J, Wang J, Loberg RD, Krebsbach PH, Pienta KJ, Taichman RS. Human prostate cancer metastases target the hematopoietic stem cell niche to establish footholds in mouse bone marrow. *J Clin Invest*. 2011 Apr 1;121(4):1298-312.

Bone is the most common site for metastasis, and is particularly the favorable site for prostate and breast cancer (1). However, the underlying cellular and molecular mechanisms remain elusive. Recent work published by Shiozawa and colleagues addresses this issue (2). While metastasized cancer cells and hematopoietic stem cells (HSCs) reside in the bone cavity, it remains largely unclear whether cancer cells compete with HSCs for the same niche during metastasis. Using a transplantation model of human prostate cancer to mice, Shiozawa *et al*. find that the endosteal HSC niche in the bone marrow is a direct target of prostate cancer dissemination. Prostate cancer cells competed with HSCs for occupancy of the HSC niche. In addition, engrafted prostate cancer cells were enriched with prostate cancer stem cells (CSCs). Also, cancer cells and HSCs shared the same mechanism to mobilize to the blood circulation. These findings suggest that the endosteal HSC niche plays a critical role in bone metastasis. Understanding the mechanism of cancer metastasis may provide important insight for therapeutic targeting that will be beneficial to cancer treatment.

The Endosteal HSC Niche

The endosteal bone surface is covered by bone-lining cells that include pre-osteoblasts and a specific type of macrophage (osteomacs) (3;4). Pre-osteoblasts are derived from mesenchymal stem cells and can differentiate into mature osteoblasts to form bone.

Recent studies of HSCs have revealed that the endosteal region is a niche that maintains quiescent HSCs and that N-cadherin-positive bone-lining pre-osteoblasts are one of the major components of this niche (5;6). Many adhesion molecules and signaling molecules have been reported to be involved in the maintenance of quiescent HSCs in the endosteal niche (7). Once HSCs are activated by extrinsic signaling, they will migrate from the endosteal niche and mobilize to the central marrow for circulation (8). Canonical Wnt signaling is one of the factors known to activate HSCs as well as to prompt bone-lining pre-osteoblasts to differentiate into mature osteoblasts (9).

Homing to the Endosteal HSC Niche

Almost all patients who die of prostate cancer have cancer metastasis to bone (10). However, it has not been clear whether cancer cells occupy the endosteal HSC niche during metastasis. In the current study

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by Shiozawa *et al*. (2), the authors co-transplanted human prostate cancer cells and HSCs to NOD/SCID mice. They observed that cancer cells competed with HSCs for engraftment to the endosteal niche. Considering previous reports that CSCs facilitate metastasis (11), it is probable that disseminated cancer cells in the endosteal HSC niche largely contain CSCs. Results from immunostaining showed that labeled cancer cells and HSCs co-localized to the endosteal niche. When the endosteal niche was expanded by parathyroid hormone, dissemination of cancer cells was increased in bone. In contrast, when the endosteal niche was reduced by the Col2.3Δ-TK system, dissemination of cancer cells was reduced. To examine the underlying mechanism by which cancer cells home and mobilize, the authors used AMD3100, an inhibitor of CXCR4/SDF1 signaling, to mobilize HSCs from the endosteal niche. When mice were pre-treated with AMD3100 prior to transplantation of cancer cells, engraftment of cancer cells was increased, indicating that cancer cells use the same niche that HSCs use.

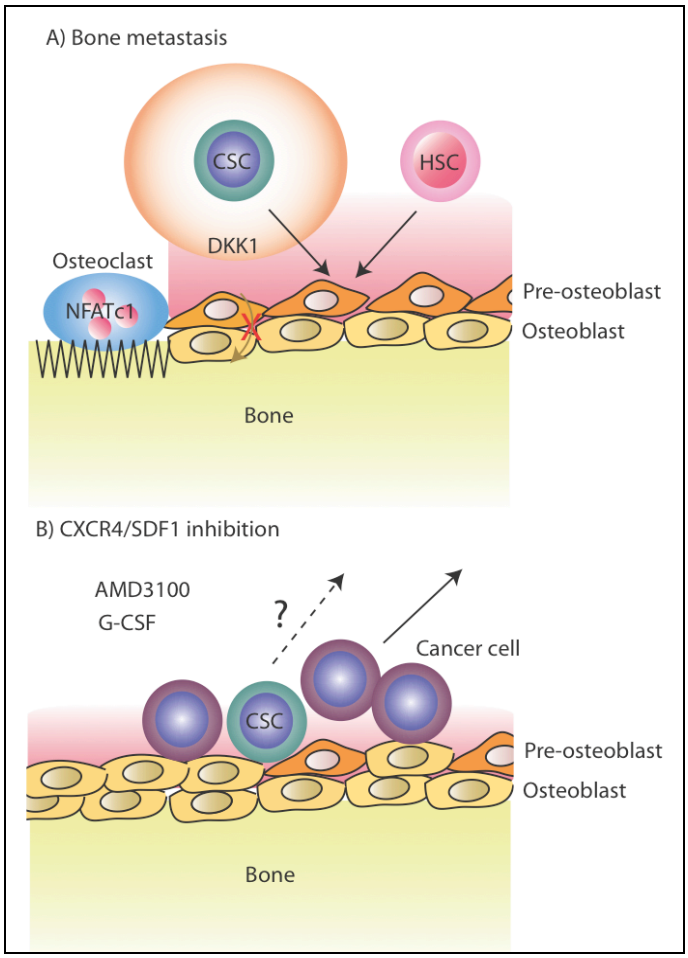

Fig. 1. A. Cancer stem cells (CSCs) and hematopoietic stem cells (HSCs) compete with each other to engraft to bone-lining pre-osteoblasts. CSCs express DKK1 to inhibit maturation of pre-osteoblasts to osteoblasts, which saves the quiescent stem cell niche for CSCs (featured in pink). In addition, NFATc1-mediated osteoclastogenesis leads to a breakdown of bone structure, causing the osteolytic feature of bone metastasis. Once CSCs are engrafted to the endosteal niche, they will propagate cancer cells. B. DKK1 expression is decreased and osteoblast maturation is enhanced. When CXCR4/SDF1 signaling is blocked by AMD3100 or G-CSF, cancer cells are mobilized from the endosteal niche. It is not clear whether CSCs are also mobilized from the niche.

Dickkopf-1 (DKK1) is one of the most frequently studied signaling molecules for cancer metastasis. Its expression is high in breast cancer, prostate cancer (in the early stages of metastasis), and multiple myeloma that metastasize to bone. DKK1 inhibits maturation of pre-osteoblasts via suppression of canonical Wnt signaling. It causes the breakdown of bone associated with NFATc1-mediated osteoclastogenesis. Once prostate cancer cells have disseminated to bone, DKK1 expression is decreased in cancer cells, allowing osteogenesis. The process opens more spaces for cancer cell metastasis (12) (Fig. 1A).

Dormancy at the Endosteal HSC Niche

Bone-lining pre-osteoblasts in the endosteal niche maintain quiescent HSCs through adhesion and signaling (7). Recent reports have revealed that leukemic stem cells (LSCs) reside in the endosteal niche and are also kept in a quiescent state. G-CSF treatment can activate these quiescent LSCs and facilitate their elimination in combination with chemotherapy (13). Interestingly, the current study by Shiozawa and colleagues showed that CD133+CD44+ cells enriching prostate CSCs were significantly higher in bone marrow 24 hours after transplantation. This observation is consistent with previous reports that CSCs facilitate metastasis (11). In addition, CD133+CD44+ prostate CSCs were more efficient than CD133-CD44- cancer cells in blocking engraftment of co-transplanted HSCs. Intriguingly CD133+CD44+ prostate CSCs expressed lower cyclin A1 and cyclin D1 in the qRT-PCR assay, suggesting slow cell-cycling of prostate CSCs. These observations indicate that the endosteal niche is the preferred targeting site for dormant prostate CSCs.

Mobilization from the Endosteal HSC Niche

The study by Shiozawa and colleagues also revealed that prostate cancer cells residing in the endosteal niche can be mobilized by AMD3100. This indicates that cancer cells also utilized CXCR4/SDF1 signaling for mobilization, the same molecular pathway inducing HSC mobilization. G-CSF is another reagent that mobilizes HSCs from the endosteal niche. G-CSF is known to suppress CXCR4/SDF1 signaling (14) and affect osteoblasts (15). When the researchers administered G-CSF to mice engrafted with prostate cancer cells, they observed mobilization of cancer cells in peripheral blood. It will be interesting to further test whether AMD3100 and G-CSF can mobilize CD133+CD44+ prostate CSCs from the endosteal niche (Fig. 1B).

Potential Therapeutic Utility

It is important to investigate how to target dormant CSCs in the endosteal HSC niche, as the niche may protect CSCs by keeping them from cycling. One possibility is to induce CSC mobilization by AMD3100 or G-CSF. It is also critical to further address whether mobilized CSCs are sensitive to chemotherapeutic drugs.

Conclusion

The study by Shiozawa *et al*. shows that prostate CSCs metastasize to bone and compete for the endosteal HSC niche. By seizing control of the same mechanism for HSC homing or mobilization, CSCs target and are further maintained in the endosteal niche. This finding may lead to potential new therapies for cancer cell metastasis to bone, including induction of cancer cell mobilization (*e.g.,* with AMD3100 or G-CSF) from the endosteal niche.

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