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RESEARCH HIGHLIGHT

Prostate cancer cells metastasize to the hematopoietic stem cell niche in bone

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The majority of men with advanced prostate cancer develop bone metastases as opposed to metastases at other sites.[1] It has been unclear why prostate cancer selectively metastasizes to and proliferates in bone. Recently, Shiozawa *et al.* delineated a mechanism that may account for the establishment of prostate cancer in bone.[2] Specifically, they identified that prostate cancer cells compete with hematopoietic stem cells (HSC) for the osteoblast in the HSC niche of the bone. Defining the mechanisms through which prostate cancer cells establish themselves in bone is critical towards developing effective therapeutic strategies to prevent or target bone metastases.

HSCs localize to the bone marrow microenvironment where multiple cells may contribute to the HSC niche.[3] However, the osteoblast has risen as a key cellular component of the HSC niche.[4] Several studies have provided strong support to the importance of the osteoblast in maintaining the HSC population including the observations that decreasing osteoblasts results in contraction of the HSC population,[5] whereas increasing osteoblasts results in expansion of the HSC population.[6] Osteoblasts regulate the HSC through several mechanisms. These include promoting chemotaxis to the HSC niche through production of CXCL12 (also known as stromal-derived factor-1), serving as a docking site for HSC in the endocortical bone microenvironment through production of vascular adhesion molecule-1[7] and annexin II,[8] and signaling the HSC to become quiescent through CXCL12.[9]

The concept that cancer cells can co-opt normal cellular activities has been previously demonstrated in the context of bone metastases. For example, the importance of CXCL12-mediated chemotaxis to drive cancer cells to bone, similar to the function on HSC to enter the bone marrow microenvironment, has been identified in multiple tumor types including breast cancer[10] and prostate cancer.[11] However, once in the bone marrow microenvironment, it was unknown where the tumor cells localize. Through several elegant experiments, Shiozawa *et al.* have now convincingly demonstrated that prostate cancer cells and HSCs occupy the same endosteal niche and furthermore that they compete with each other for niche occupancy on the osteoblast. Initially, they demonstrated that subcutaneous pre-implantation of mice with prostate cancer cells, but not non-metastatic transformed prostate epithelial cells, diminished the ability of HSC to engraft in an *in vivo* model of bone marrow transplant. This initial experiment provided the first indication that the prostate cancer cells compete with HSC for the HSC niche. They followed these experiments with direct evaluation of the prostate cancer cells' ability to compete with HSC for binding to osteoblasts both *in vitro* and *in vivo*. To perform this, they injected prostate cancer cells, which were irradiated to inhibit their proliferation, directly into the blood stream, and determined that they were able to inhibit HSC engraftment and marrow recovery in irradiated mice. Furthermore, using confocal and multiphoton microscopy, they demonstrated that HSC and prostate cancer cells colocalized at the osteoblasts in identical regions of the bone marrow. To provide further evidence of the importance of the osteoblast niche on development of bone metastases, they manipulated the niche volume. In these studies, they found that increasing the HSC niche through administration of a bone anabolic regimen of parathyroid hormone increased the metastatic burden, whereas decreasing the HSC niche through ablation of osteoblasts resulted in decreased metastatic burden. Additionally to ascertain the similarity in the niche occupation between HSC and prostate cancer cells, they explored if prostate cancer cells can be mobilized from the niche similar to HSC. They found two different factors that mobilize HSC from marrow: AMD3100, which blocks binding of CXCL12 to its receptor and granulocyte-colony-stimulating factor, both inducing an increase of circulating prostate cancer cells. Finally, the authors wanted to provide some clinical evidence for the competition between prostate cancer cells and HSC for the niche. Consistent with their concept of competition for the HSC niche, they found that men with metastatic disease had more circulating hematopoietic progenitor cells (derived from HSC) than men with only local prostate cancer.

These findings provide a new mechanism to account for the ability of prostate cancer cells to target and become established in bone. Importantly, they also suggest several significant clinical ramifications. A frustrating aspect of prostate cancer is that it is possible to subject a patient to prostatectomy with an apparent cure, but they develop bone metastases many years later. In context of the results presented by Shiozawa *et al.*, it is plausible to consider that prostate cancer cells are maintained in a quiescent state, similar to HSC, when they are in the HSC niche. This dormant state may allow prostate cancer cells to remain in the bone microenvironment for years until some event activates them or releases them from the niche. Another challenging aspect of prostate cancer bone metastases is that they appear protected from chemotherapeutics due to being sequestered in the bone microenvironment. The osteoblast-induced dormancy that occurs in the bone microenvironment could contribute to chemoresistance as most chemotherapeutic

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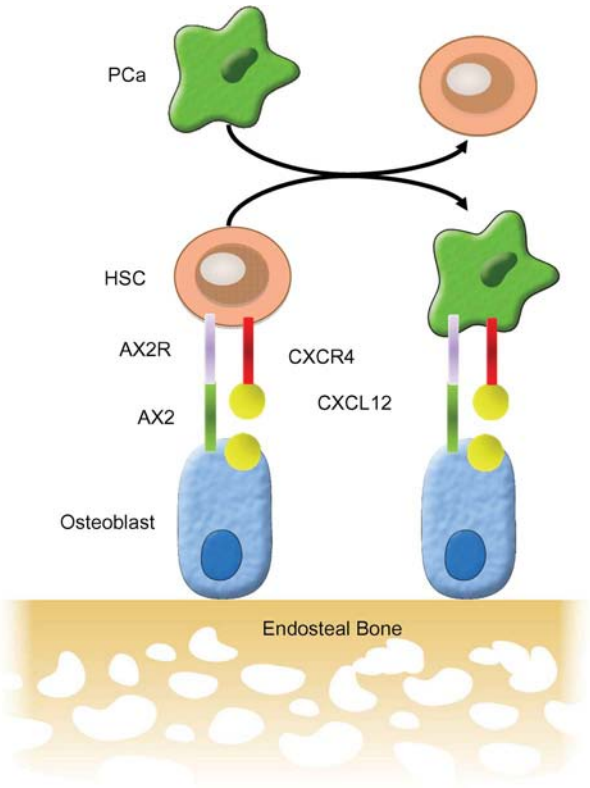

Figure 1 Prostate cancer (PCa) competes with hematopoietic stem cells (HSCs) for the HSC niche. HSCs express annexin II receptor (AX2R) and CXCR4, the receptor for CXCL12. The chemokine, CXCL12, is produced by osteoblasts and induces chemotaxis of HSC to the HSC niche. The HSC docks onto the osteoblast, in part, through annexin II (AX2) binding to AX2R. PCa cells also express AX2R and CXCR4 which allows them to compete for binding to the osteoblast in the HSC niche inducing release of HSCs.

agents kill actively cycling cells. This suggests a clinical intervention in which mobilization of prostate cancer cells for the bone marrow microenvironment, as was done in the experimental models, could allow for sensitization of the prostate cancer cells to chemotherapy. Evidence for the effectiveness of this strategy in hematopoietic tumors has been demonstrated for both multiple myeloma[12] and acute myeloid leukemia[13] in which administration of AMD3100 induced their mobilization out of bone marrow and sensitized them to chemotherapy.

In summary, preventing and treating prostate cancer bone metastasis is an ongoing challenge. Defining novel strategies to target bone metastasis is crucial in order to make significant therapeutic gains. The results presented by Shiozawa *et al.* demonstrate that prostate cancer cells compete with HSCs for the HSC niche (**Figure 1**). This finding accounts for the observation that prostate cancer cells target bone and provides a mechanism to explain why bone metastases develop many years after an apparent cure. Furthermore, this report suggests a new therapeutic approach towards targeting prostate cancer bone metastases.

1 Shah RB, Mehra R, Chinnaiyan AM, Shen R, Ghosh D *et al*. Androgen-independent prostate cancer is a heterogeneous group of diseases: lessons from a rapid autopsy program. *Cancer Res* 2004; **64**: 9209–16.
2 Shiozawa Y, Pedersen EA, Havens AM, Jung Y, Mishra A *et al*. Human prostate cancer metastases target the hematopoietic stem cell niche to establish footholds in mouse bone marrow. *J Clin Invest* 2011; **121**: 1298–312.
3 Lymperi S, Ferraro F, Scadden DT. The HSC niche concept has turned 31. Has our knowledge matured? *Ann NY Acad Sci* 2010; **1192**: 12–8.
4 de Barros AP, Takiya CM, Garzoni LR, Leal-Ferreira ML, Dutra HS *et al*. Osteoblasts and bone marrow mesenchymal stromal cells control hematopoietic stem cell migration and proliferation in 3D *in vitro* model. *PLoS One* 2010; **5**: e9093.
5 Visnjic D, Kalajzic Z, Rowe DW, Katavic V, Lorenzo J *et al*. Hematopoiesis is severely altered in mice with an induced osteoblast deficiency. *Blood* 2004; **103**: 3258–64.
6 Calvi LM, Adams GB, Weibrecht KW, Weber JM, Olson DP *et al*. Osteoblastic cells regulate the haematopoietic stem cell niche. *Nature* 2003; **425**: 841–6.
7 Zhu J, Garrett R, Jung Y, Zhang Y, Kim N *et al*. Osteoblasts support B-lymphocyte commitment and differentiation from hematopoietic stem cells. *Blood* 2007; **109**: 3706–12.
8 Jung Y, Wang J, Song J, Shiozawa Y, Wang J *et al*. Annexin II expressed by osteoblasts and endothelial cells regulates stem cell adhesion, homing, and engraftment following transplantation. *Blood* 2007; **110**: 82–90.
9 Cashman J, Clark-Lewis I, Eaves A, Eaves C. Stromal-derived factor 1 inhibits the cycling of very primitive human hematopoietic cells *in vitro* and in NOD/SCID mice. *Blood* 2002; **99**: 792–9.
10 Müller A, Homey B, Soto H, Ge N, Catron D *et al*. Involvement of chemokine receptors in breast cancer metastasis. *Nature* 2001; **410**: 50–6.
11 Taichman RS, Cooper C, Keller ET, Pienta KJ, Taichman NS *et al*. Use of the stromal cell-derived factor-1/CXCR4 pathway in prostate cancer metastasis to bone. *Cancer Res* 2002; **62**: 1832–7.
12 Azab AK, Runnels JM, Pitsillides C, Moreau AS, Azab F *et al*. CXCR4 inhibitor AMD3100 disrupts the interaction of multiple myeloma cells with the bone marrow microenvironment and enhances their sensitivity to therapy. *Blood* 2009; **113**: 4341–51.
13 Nervi B, Ramirez P, Rettig MP, Uy GL, Holt MS *et al*. Chemosensitization of acute myeloid leukemia (AML) following mobilization by the CXCR4 antagonist AMD3100. *Blood* 2009; **113**: 6206–14.