PROSTATE CANCER

Molecular insights into bone metastasis

Advanced prostate cancer metastasizes preferentially to bone, and the resulting complications are the leading cause of death in affected men. Two new studies address the cascade of events that occur when prostate cancer cells spread to the skeleton, uncovering unique potential targets for treatment of this incurable disease.

The first study, led by Russell Taichman and published in *The Journal of Clinical Investigation*, yields evidence that prostate cancer cells localize to a niche in the bone marrow usually occupied by hematopoietic stem cells (HSCs). Once there, prostate cells compete directly with HSCs for niche support. The authors suggest that the complex interplay between metastatic cells and the niche microenvironment could provide a rich source of prospective drug targets.

Previous observations that disseminated prostate tumor cells have osteoblastic qualities and share the functional properties of HSCs led Taichman and colleagues to hypothesize that the metastatic process might be similar to the normal localization of HSCs to the niche. Bone marrow transplant studies in a mouse tumor xenograft model confirmed their idea. Moreover, by manipulating the size of the niche—genetically and hormonally—investigators found that metastatic cells could preferentially occupy the niche over HSCs. “What this means is that cancer cells specifically target, and function as molecular invaders of, the very home that HSCs depend on for their survival and function,” says Taichman. “What subsequently happens is that tumor cells take over the niche and drive HSCs out. This may be the reason patients often suffer from pancytopenia in the late stages of prostate cancer.”

Under normal physiological conditions, the niche regulates HSC proliferation and quiescence. Could the same mechanisms be hijacked by prostate cancer cells? The implications for understanding treatment failure are profound—if cells in the niche

are not proliferating, they will not be susceptible to standard chemotherapy. Furthermore, metastatic tumor cells might exist in a quiescent state within the bone for long periods of time before moving back into the bloodstream. This could explain why men can be disease-free for 5–10 years after receiving primary therapy before experiencing recurrence. “We are actively pursuing studies to determine if the HSC niche is able to induce a dormant state in metastatic tumor cells in the marrow and whether tumor cells or their niche can be targeted for chemotherapy,” Taichman concludes.

The second paper details how a team of researchers studying the PTEN signaling pathway identified a novel inhibitory protein interaction that seems to be lost in metastatic disease, and thus might be exploited therapeutically. *PTEN* is a well-known tumor suppressor gene with a strong link to advanced prostate cancer; a complete loss of *PTEN* has been reported in up to 60% of metastatic cases, compared with 2–20% of primary prostate tumors. In spite of this, *Pten* knockout mice have little metastatic potential, suggesting other factors must be important.

Using a variety of molecular and cellular techniques, researchers found that FOXO1 (a key downstream effector of PTEN) is a crucial negative regulator of the transcription factor RUNX2—an important player in the migration of prostate cancer cells to bone. Co-immunoprecipitation assays revealed the physical interaction between FOXO1 and RUNX2, while cell culture studies showed that FOXO1 could prevent cell migration and invasion mediated by RUNX2. “We demonstrated for the first time that FOXO1 binds directly to RUNX2 and inhibits its activity in prostate cancer cells,” says author Haojie Huang from Stony Brook University in New York. “Thus, FOXO1 functions as a node that connects the PTEN pathway with the RUNX2-mediated bone-relevant transcription program.”

Huang and colleagues propose a mechanism whereby the loss of PTEN frequently observed in advanced prostate cancer, and consequent inactivation of FOXO1, favor disease progression and metastasis via RUNX2. In such a model, inhibition of RUNX2 by FOXO1 would be lifted, permitting RUNX2-mediated gene transcription, leading to cell migration and invasion.

“Our immediate goal is to test whether crossbreeding of *Runx2* transgenic mice with *Pten* knockout mice leads to the development of prostate cancer bone metastasis. If so, this will be a useful model for further unfolding of the molecular mechanisms of prostate cancer bone metastasis and for the testing of metastasis-inhibiting drugs,” says Huang.

These findings suggest that significant steps are being made in the elucidation of how bone metastasis occurs, and inspire hope that directed treatment approaches might one day lead to more-effective management of advanced disease.

Sarah Payton

Original articles Shiozawa, Y. et al. Human prostate cancer metastases target the hematopoietic stem cell niche to establish footholds in mouse bone marrow. *J. Clin. Invest.* 121, 1298–1312 (2011) | Zhang, H. et al. FOXO1 inhibits Runx2 transcriptional activity and prostate cancer cell migration and invasion. *Cancer Res.* doi:10.1158/0008-5472.CAN-10-2603