Prospective Isolation and Characterization of Metastatic Prostate Cancer Niche Cells in the Bone Marrow

Gunsagar S. Gulati[1,], Debashis Sahoo[2], Michael T. Longaker [1] , Irving L. Weissman [1], **Charles K. F. Chan [1]**

[1]Stanford University School of Medicine, [2]Department of Computer Sciences, UC San Diego

Background:
Previous studies have shown that colonization of bone by metastatic prostate cancer cells depends upon two components: (a) metastatic prostate cancer cells (MPCa) that initiate tumor expansion within the secondary site, and (b) various factors produced by the bone marrow niche that support MPCa invasion. However, little is known about the specific types of bone marrow stroma that constitute the MPCa-permissive bone microenvironment. We hypothesize that MPCas thrive in bones due to their ability to invade hematopoietic stem cell (HSC)-conducive marrow microenvironments, and co-opt factors normally produced for HSC maintenance to support their own growth.

Methods:
We developed new approaches to (a) identify new therapeutic targets in bone marrow stroma that allow for metastasis of prostate cancer to bone, and (b) determine whether antibodies against these targets, can effectively treat metastatic prostate cancer. Using novel computational platforms to mine a database compiled from transcriptomes of prospectively isolated bone marrow stromal cells, we identified many potential ligand-cognate receptor interactions between stromal cells, HSCs, and MPCa. To experimentally screen and validate these targets, we utilized a novel bone marrow niche assay, which allows us to genetically alter heterotypic bone stromal populations and monitor whether knocking out certain stromal factors affects prostate cancer metastases to bone.

Results:
We identified several novel pathways, including VEGF-C and Osterix, which are important for establishing both HSC and MPCa niches. We also identified CDCP1, or CUB Domain Containing Protein 1, a protein exclusively expressed on the surface of HSCs and MPCas that may have a potential role in mediating homing and engraftment to the bone marrow.

Conclusions:
Using a novel ectopic niche system, we identified novel skeletal stromal/progenitor populations that form the niches for both normal hematopoietic progenitors. The same niches could also be colonized by mPCa. To identify critical signaling pathways in both normal and mPCa niches, we conducted genetic studies of BM niches by transducing niche-forming stroma with lentiviral vectors. Gene silencing of factors necessary for endochondral ossification such as osterix and VEGFA and VEGFC inhibited formation of the niche and colonization by MPCa. We demonstrated that bone marrow stroma (SSC, CSP, 6c3+, Thy+) stimulates proliferation of MPCa cells and that CDCP1 is a candidate protein that promotes homing of metastatic prostate cancer cells to the bone marrow. CD47 blockade and CDCP1 opsonization promote phagocytosis of MPCSCs by mouse and human macrophages.

Conflicts of Interests:
None.

Funding Acknowledgements:
Prostate Cancer Foundation, Siebel Scholars, NIH K99/R00