Temporal/Spatial Transcriptomic analysis of Normal and Neoplastic Stem Cell Niches.

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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 have established a technique to determine the three dimensional architecture of the immediate cellular microenvironment surrounding hematopoietic stem cells (HSC) and also metastasizing prostate cancer cells in the bone marrow. The new method combines several innovative procedures including a way to isolate 10-30 cell aggregates from the bone marrow containing HSCs or mPCas using a microfludic FACS sorter that is capable of low-shear sorting. This technique is applicable for analyzing a wide variety of normal stem cell and tumor immuno-microenvironments. From our initial analysis we have identified CDCP1 as a surface protein that may play a key role in trafficking both normal HSCs and mPCas to the bm niche and we are developing several strategies to target CDCP1 expressing mPCas for immune therapy.

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 3D niche analysis 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.

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