ML 22-06 (10/05/2022)

Front Oncol

. 2022 Apr 19;12:855188.
doi: 10.3389/fonc.2022.855188. eCollection 2022.

Bone Marrow-Derived Stem Cell Factor Regulates Prostate Cancer-Induced Shifts in Pre-Metastatic Niche Composition

Brittni M Foster[1], Lihong Shi[1], Koran S Harris[1], Chirayu Patel[1], Victoria E Surratt[1], Kendall L Langsten[1], Bethany A Kerr[1,2]
Affiliations expand

- PMID: 35515124
- PMCID: PMC9063312
- DOI: 10.3389/fonc.2022.855188

Free PMC article

Abstract

Skeletal metastasis is the leading cause of morbidity and mortality in prostate cancer, with 80% of advanced prostate cancer patients developing bone metastases. Before metastasis, bone remodeling occurs, stimulating pre-metastatic niche formation and bone turnover, and platelets govern this process. Stem cell factor (SCF, Kit Ligand) is increased in advanced prostate cancer patient platelet releasates. Further, SCF and its receptor, CD117/c-kit, correlate with metastatic prostate cancer severity. We hypothesized that bone-derived SCF plays an important role in prostate cancer tumor communication with the bone inducing pre-metastatic niche formation. We generated two cell-specific SCF knockout mouse models deleting SCF in either mature osteoblasts or megakaryocytes and platelets. Using two syngeneic androgen-insensitive murine prostate cancer cell lines, RM1 (*Ras* and *Myc* co-activation) and mPC3 (*Pten* and *Trp53* deletion), we examined the role of bone marrow-derived SCF in primary tumor growth and bone microenvironment alterations. Platelet-derived SCF was required for mPC3, but not RM1, tumor growth, while osteoblast-derived SCF played no role in tumor size in either cell line. While exogenous

SCF induced proangiogenic protein secretion by RM1 and mPC3 prostate cancer cells, no significant changes in tumor angiogenesis were measured by immunohistochemistry. Like our previous studies, tumor-induced bone formation occurred in mice bearing RM1 or mPC3 neoplasms, demonstrated by bone histomorphometry. RM1 tumor-bearing osteoblast SCF knockout mice did not display tumor-induced bone formation. Bone stromal cell composition analysis by flow cytometry showed significant shifts in hematopoietic stem cell (HSC), mesenchymal stem cell (MSC), and osteoblast cell percentages in mice bearing RM1 or mPC3 tumors. There were no significant changes in the percentage of macrophages, osteoclasts, or osteocytes. Our study demonstrates that megakaryocyte/platelet-derived SCF regulates primary mPC3 tumor growth, while SCF originating from osteoblasts plays a role in bone marrow-derived progenitor cell composition and pre-metastatic niche formation. Further, we show that both the source of SCF and the genetic profile of prostate cancer determine the effects of SCF. Thus, targeting the SCF/CD117 signaling axis with tyrosine kinase inhibitors could affect primary prostate carcinomas or play a role in reducing bone metastasis dependent on the gene deletions or mutations driving the patients' prostate cancer.