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Identification and relocation of osteo-metastocytes in the priming zone of the cancer terra-forming niche

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Overt tumor cell growth occurs in several cancers that arise in bone such as myeloma and those cancers that metastasize to bone such as breast, prostate, lung and thyroid. The initial spread of individual cancer cells to bone is commonly believed to occur in the marrow space providing a cancer permissive environment for overt cancer growth. However, the precise location of cancer cells that arise or metastasize in bone is unknown. Understanding the cellular and molecular mechanisms that govern arrival of cancer cells to the bone microenvironment may aid in accelerating future treatments and improve patient care. The aim of this work using preclinical models of myeloma was to identify and characterize the location of cancer cells arriving in bone within a few hours of arrival and establish whether removal of those cells to a different location reduced overt cancer growth. Data presented shows there are regions within bone that are permissive to single cancer cell colonization and not overt tumor growth. Conversely, we identify regions within bone that are both permissive to single cancer cell colonization and overt tumor growth. We show, for the first time, cancer cells arriving in overt cancer-permissive regions in bone almost exclusively home to bone surfaces and not deep in marrow as commonly believed. These cells are named "osteo-metastocytes" and they locate to within 40 microns of bone surfaces, a region called "the priming zone". Proximity of single cancer cells to the bone surface may be a key factor determining their potential for future growth. We demonstrate the feasibility of relocating 100% of individual cancer cells out of the priming zone by blocking bone-cancer cell interactions resulting in a reduction of overt cancer growth ($p<0.05$). This study shows factors that determine whether a normal healthy bone microenvironment is terra-formed into a cancer niche are derived at least in part from the bone surface. A rationale to study and target this region of bone in the early stages of cancer or reseeding of bone by treatment-resistant cancer cells following initial treatment to prevent relapse is presented.

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