Bone Microenvironment-Suppressed T Cells Increase Osteoclast Formation and Osteolytic Bone Metastases in Mice

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ABSTRACT
Immunotherapies use components of the immune system, such as T cells, to fight cancer cells, and are changing cancer treatment, causing durable responses in some patients. Bone metastases are a debilitating complication in advanced breast and prostate cancer patients. Approved treatments fail to cure bone metastases or increase patient survival and it remains unclear whether immunotherapy could benefit patients. The bone microenvironment combines various immunosuppressive factors, and combined with T cell products could increase bone resorption fueling the vicious cycle of bone metastases. Using syngeneic mouse models, our study revealed that bone metastases from 4T1 breast cancer contain tumor-infiltrating lymphocyte (TILs) and their development is increased in normal mice compared to immunodeficient and T-cell depleted mice. This effect seemed caused by the TILs specifically in bone, because T-cell depletion increased 4T1 orthotopic tumors and did not affect bone metastases from RM-1 prostate cancer cells, which lack TILs. T cells increased osteoclast formation ex vivo and in vivo contributing to bone metastasis vicious cycle. This pro-osteoclastic effect is specific to unactivated T cells, because activated T cells, secreting interferon γ (IFNγ) and interleukin 4 (IL-4), actually suppressed osteoclastogenesis, which could benefit patients. However, non-activated T cells from bone metastases could not be activated in ex vivo cultures. 4T1 bone metastases were associated with an increase of functional polymorphonuclear and monocylic myeloid-derived suppressor cells (MDSCs), potent T-cell suppressors. Although effective in other models, sildenafil and zoledronic acid did not affect MDSCs in bone metastases. Seeking other therapeutic targets, we found that monocytic MDSCs are more potent suppressors than polymorphonuclear MDSCs, expressing programmed cell death receptor-1 ligand (PD-L1) in bone, which could trigger T-cell suppression because 70% expresses its receptor, programmed cell death receptor-1 (PD-1). Collectively, our findings identified a new mechanism by which suppressed T cells increase osteoclastogenesis and bone metastases. Our results also provide a rationale for using immunotherapy because T-cell activation would increase their anti-cancer and their anti-osteoclastic properties. © 2022 The Authors. Journal of Bone and Mineral Research published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: BONE METASTASIS; T CELLS; OSTEOCLAST; IMMUNOTHERAPY; IMMUNOSUPPRESSION; MDSC

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