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A Perspective on Malignancy in the Marrow

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Abstract

Malignancies that grow in the bone marrow cause a cascade of devastating consequences and are almost always fatal. For researchers to make significant headway in finding cures and treatments for these tumors and the subsequent devastation of cancer-induced bone disease, novel strategies and creative solutions will have to be considered. Great progress has been made in treating hematologic and solid tumor malignancies that ultimately affect the bone marrow, although it is also obvious that multi-disciplinary teams are required to ultimately win the war on cancers that affect the bone. In this perspective, we review recent advances in the identification of molecular and cellular targets in the bone marrow niche.

Keywords

Tumor; Bone Marrow Niche; Microenvironment; Bone Metastasis

Perspective

Cancers that grow in the bone marrow, including primary tumors (multiple myeloma) and bone metastatic cancers (such as breast cancer, lymphoma, thyroid and prostate cancer) are exceptionally difficult to treat. Targeting tumor cells directly in the bone marrow can be challenging due to their heterogeneous nature, their ability to evolve in response to drug treatments, and the drug-resistance often provided to them by the bone marrow microenvironment. Tumor cells often initiate a “vicious cycle” with local osteoclasts leading to osteolytic disease and punched-out lesions, which release growth factors and proteins stored in the bone to further fuel tumor growth. Targeting osteoclasts using bisphosphonates or RANKL inhibitors (denosumab) has proven useful at inhibiting bone loss, although results for survival or tumor burden are varied. However, to re-form lost bone and enhance

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the niche's promotion of hematopoiesis, targeting bone-building osteoblasts is now becoming feasible. For example we recently demonstrated that using an anti-sclerostin antibody rebuilds lost bone myeloma mouse models (Reagan et al. 2015). Others have also found that targeting the osteocyte, or osteocyte derived factors, has potential in healing fractures from myeloma (Delgado-Calle et al. 2016). Modulating the spectrum of epigenetic mechanisms and therapeutic applications of non-coding RNAs also has great potential. We also found that proteasome inhibitors can be used to target osteoblasts and increase bone formation, as well as kill myeloma cells and breast cancer cells, suggesting that repurposing of drugs across cancers may be a novel approach with minimal toxicities. (Swami et al. 2014; Jones et al. 2010). Strategies for restoration of a physiological balance between bone formation and absorption are becoming approachable.

The bone marrow adipocyte is under consideration as a novel cellular target in both myeloma and osteoporosis due to its endocrine and paracrine roles in skeletal biology and pathology (Reagan & Rosen 2015). In respect to the latter, we recently reported that the marrow adipocyte is unique and that it expresses high levels of RANKL, unlike peripheral adipocytes (Fan et al. 2017). Since RANKL is a potent stimulus of osteoclastogenesis, inhibitors that specifically target the marrow adipocyte may be a rational approach to prevent osteolysis. Alternatively, anabolic agents that target osteoblasts, such as PTH, also induce a shift in lineage allocation towards the osteoblast and away from the adipocyte (Fan et al. 2017). Although targeting angiogenesis has been a method for attacking solid tumors for decades, we are only now realizing that inhibiting vasculogenesis and/or angiogenesis in the bone marrow may also have therapeutic potential, especially since the progenitor to the bone marrow adipocyte may reside at or near the endothelial surface or vascular niche in the marrow where metabolic gradients may be operative (Reagan & Rosen 2015; Moschetta et al. 2014). New evidence also suggests that targeting the molecules on tumor cells that allow them to home specifically to bone marrow endothelial cells is a promising avenue for mitigating tumor metastasis to the bone (Glavey et al. 2014). Harnessing the power of the immune system by reactivating cells that have been suppressed by tumor cells, a field known as immuno-oncology, has been hugely successful for cancers outside the bone marrow. Due to the unique properties of the bone marrow microenvironment (Reagan & Rosen 2015), and the different modes of action of tumor cells in the bone marrow, checkpoint blockade inhibitors have not been as immediately successful in marrow malignancies as they have in other cancers such as lung cancer. However, this may change as researchers understand more about the mechanism of action of these drugs, and immune cell suppression of the tumor cells in the marrow. For example, daratumumab, a human IgG1k monoclonal antibody that binds CD38 (highly expressed on the surface of myeloma cells) has shown some success recently. It is believed to induce rapid tumor cell death through apoptosis, and multiple immune-mediated mechanisms, including complement-dependent cytotoxicity, antibody-dependent cellular phagocytosis and antibody-dependent cellular cytotoxicity (Costello 2017). As more is understood regarding immunosuppression for tumors in the marrow, more effective therapies targeting these pathways and cell types will be developed.

In summary, as we begin to understand the interactions between bone marrow cells and tumor cells, novel therapeutic targets are constantly being identified and screened for their clinical relevancy. Future directions will involve testing these potential candidate cells and

molecules in three-dimensional rather than two-dimensional models by capitalizing on advances in characterizing cellular “stemness” (Messier et al. 2016) and growing capabilities in tissue engineering and biomaterials basic research capacities for cancer and bone (Dadwal et al. 2016). Targeting the osteoblast as a means of improving skeletal mass and preventing osteolysis and fractures offers some real opportunities for future clinical trials. It is realistic to anticipate advances in capabilities for restoring competency to remodel bone that is compromised by cancer or cancer therapy.

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