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INSIGHTS

Bone marrow runs the (bone) show

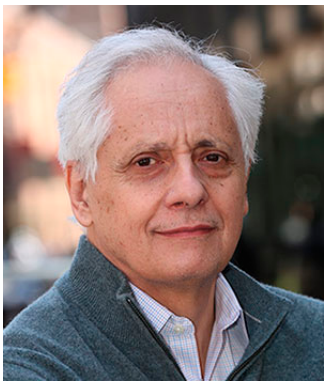
Gerard Karsenty

In this issue of *JEM*, a paper by Kim et al. (2021. *J. Exp. Med.* https://doi.org/10.1084/jem.20211872), asking a simple question through a remarkable alliance of human and mouse genetics, demonstrates that a prevalent hematological condition can lead to osteoporosis. This work is important by virtue of the quality of its results and its implication for the relationship between bone and its marrow.

Bone biology has for a long time lived in a semi-autarchy. Autarchy, because the attention of bone biologists has long focused, for good reason, on how bone-forming osteoblasts and bone-resorbing osteoclasts achieve their functions and talk to each other, as was surmised almost 40 yr ago (Rodan and Martin, 1982). It is also only a semi-autarchy because the constant alternation of bone resorption and bone formation, called bone modeling during childhood and bone remodeling past puberty, is influenced by hormones and neurotransmitters; these various regulations have also been, and continue to be, heavily studied because of their biological importance and, for some of them, their therapeutic ramifications (Khosla and Monroe, 2018; Wein and Kronenberg, 2018; Karsenty, 2006). But there is another influence that is sometimes overlooked. If bone is a landlord, then its primary tenant is the bone marrow. Yet despite their cohabitation, the complex dialog that takes place between landlord and tenant only began to receive the attention it deserves somewhat later than the endocrine regulation of bone (re)modeling. Nowadays, it is universally accepted that cytokines made by various cellular components of the bone marrow can and do affect bone (re)modeling (Fischer and Haffner-Luntzer, 2021). In this issue of *JEM*, Kim et al. (2021) substantially expand the scope of this burgeoning field that can be called osteo-hematology.

Clonal hematopoiesis of indeterminant potential, or CHIP, is a condition that was described relatively recently and that is defined by the presence of acquired somatic mutations in genes known to be mutated in myeloid malignancies in more than 2% of blood cells in individuals without any evidence of hematological malignancies. The incidence of CHIP increases with age, and affected individuals are at a higher risk than nonaffected ones of developing hematological malignancies and, most curiously, coronary heart disease (Steensma et al., 2015). What Kim et. al. (2021) did in this study was ask a novel medically relevant question regarding CHIP by considering a disease of the marrow in the context of bone. Since osteoclasts are cells of myeloid origin and are responding to several bone marrow–derived cytokines (Karsenty and Wagner, 2002), since bone and bone marrow are neighbors, if not landlord and tenant, and also since osteoporosis is an aging disease, could CHIP be a cause of osteoporosis? If this is the case, what would be the underlying mechanisms leading to this osteoporosis?

This question was addressed in a logical, clever, and rigorous manner that blended human genetics, mouse genetics, cell biology, and state-of-the-art molecular biology approaches. First, to set their work in a medical reality, the authors interrogated a large human genetic database, the UK Biobank, looking for a cohort of osteoporotic individuals. They then showed that within this large cohort they had identified, 6% of these patients exhibited somatic mutations in *Tet2* or *Dnmt3a*, the two most frequently mutated genes in CHIP. This allowed them to establish a first finding: the risk of incident osteoporosis was 1.44 times higher in individuals affected with CHIP than in individuals of the same age but without CHIP.



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Having established this firm foundation of their study in humans, the remaining part of this elegant paper was performed in the mouse. Since these two genes are the most frequently mutated genes in CHIP, the authors then performed transplantation of bone marrow obtained from mice with hematopoietic-specific deletion of *Tet2* or *Dnmt3a* into WT mice. In both cases, these transplantations did result in a low bone mass phenotype, the one triggered by

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transplantation of bone marrow cells coming from *Dnmt3a* mutant mice being the more severe. A histological and cell biological analysis established that this osteoporosis was due to an increase in bone resorption without any measurable decline in bone formation parameters. This part of the study validated their working hypothesis that CHIP, through somatic mutations in the hematopoietic compartment, can lead to osteoporosis.

The next phase of this study was composed of a series of cellular and molecular biology investigations designed to uncover the mechanism that could explain how a mutation of *Dnmt3* in the hematological compartment could influence bone resorption to such an extent that it leads to an overt osteoporosis phenotype. In this systematic and stepwise analysis, the authors first show that the increase in osteoclast number caused by the inactivation of Dnmt3a in hematological cells is not secondary to any molecular defect in the osteoclasts themselves. Rather, they showed that this molecular defect resides in the macrophage compartment, as is the case for atherosclerotic plaques (Fuster et al., 2017). What followed was a CRISPR/Cas9 screen performed in a *Dnmt3a*-null osteoclastic cell line generated that searched specifically for cytokine receptors that favor osteoclast-like cell differentiation. The focus on cytokine receptors was based on the reasonable assumption that during in vitro osteoclast differentiation, a portion of the culture contains undifferentiated myeloid cells capable of exerting a paracrine effect through various cytokines. This screen eventually led to the identification of the cytokine IL-20 as being secreted by *Dnmt3a*-null macrophages and able to induce differentiation of myeloid cells into osteoclasts. It is important to note here that, based on the use of an antibody, IL-20 had already been proposed 10 yr ago in *JEM* to be a regulator of osteoclast differentiation (Hsu et al., 2011). Thus, the work of Kim et al. (2021) provides a beautiful demonstration that IL-20 is indeed an osteoclastogenic cytokine in vivo; beyond this, it shows that just as bone cells affect hematopoiesis, hematopoietic cells in turn can affect bone remodeling (Raaijmakers et al., 2010; Kode et al., 2014). Altogether, and because of the arsenal of approaches it uses and the quality and number of experiments performed throughout, this is a compelling study linking one hematological disturbance to the emergence of the most frequent bone disease, osteoporosis.

No study is ever complete, and like every well-conducted investigation does and should do, this work immediately raises novel questions. For instance, given the influence osteoblasts can have on hematopoiesis, physiological and pathological (Calvi, et al., 2003; Kode et al., 2014), are we certain that osteoporosis or some forms of it do not, in turn, cause CHIP? Although the experimental arguments linking IL-20 to the *Dnmt3a* mutation–induced osteoporosis are strong, it will be important to determine the effect on bone mass of a myeloid cell–specific deletion of IL-20, or the effect of an osteoclast-specific deletion of its receptor. Likewise, is this pro-osteoclastogenic function of IL-20 specific to this molecule, or do other members of the IL-10 family of cytokines, which are present in the bone marrow microenvironment, share this property with IL-20 (Ouyang et al., 2011)? While these and other directions are undoubtedly promising, it remains that the present study is important because it asks a well-defined question of great biomedical importance and addresses it through the principle of causality in a most logical and rigorous manner. In doing so, it provides answers that are convincing and important insofar as they reveal a novel dimension to the relationship between bone and blood in the development of disease.

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