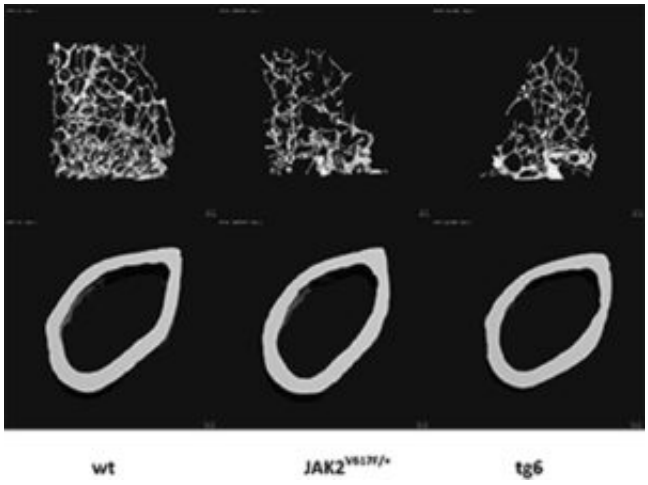
Osteoporosis and erythroid cells: is there a connection?

The skeleton is an extraordinary structure paramount not only for our movement but for multiple other functions as well. Bones are dynamic organs that continuously remodel through life in a process where mature bone is removed by specialized cells called osteoclasts and new bone is formed by another type of cells called osteoblasts. This circle of bone resorption, i.e. removal of old bone, and formation ensures bone strength and skeletal integrity. If an imbalance between these two tightly coupled processes occurs, bones will become brittle and fragile making them prone to fractures and their complications. This condition is called osteoporosis.



Three dimensional representative micro-computed tomography images of femurs from normal mice, indicated as wt, mice recapitulating the human polycythemia vera phenotype, indicated as JAK2V617F/+ and mice that constitutively overexpress erythropoietin, indicated as tg6. Top and bottom images depict different parts of femur; top images depict trabecular bone at distal metaphysis and bottom images cortical bone at mid diaphysis.

In the bone marrow, found inside our bones, an intricate network of cells and proteins works constantly to generate new, healthy red blood cells that circulate in the bloodstream. This happens by progressive maturation of progenitor erythroid cells; a process called erythropoiesis. These flexible cells take up oxygen from the lungs and deliver it to the tissues that use it to perform metabolic reactions necessary for our survival. This complex process is controlled by a key regulator, a hormone called erythropoietin, which is produced by the kidneys in response to oxygen levels in the blood and promotes red blood cell formation. When oxygen levels are low, the synthesis of erythropoietin and subsequently red blood cells will be increased and vice versa.

Polycythemia vera is a chronic disorder of the bone marrow characterized by increased and uncontrolled red blood cell production and low levels of erythropoietin. Patients suffering from

polycythemia vera were recently associated with a higher risk of fractures, although osteoporosis has not been well studied in this group. In addition, patients with certain types of chronic anemia have been reported to develop osteoporosis and fractures. Both of these diseases are characterized by expansion of erythroid cells; however, in anemias the production of red blood cells is low and erythropoietin is high. Furthermore, when erythropoietin was administrated in animal models researchers observed changes in bone mass.

In our study published in Osteoporosis International we aimed to better understand the effect of erythroid expansion on the bone by using two different mouse models; one that recapitulates the human polycythemia vera phenotype and another that constitutively overexpresses erythropoietin and produces a lot of red blood cells. Both of these mice have a high number of circulating red blood cells but different concentrations of erythropoietin. We first used an imaging technique, called micro-computed tomography that allowed us to assess the morphology and 3D structure of the bones from our two mouse models and compare it to normal mice. The results clearly show that both mice have bone loss of a similar degree. The fact that the mice suffered from osteoporosis led us to investigate how was bone remodeling affected. To do this we stained the bones and measured bone mass and the number of osteoblasts and osteoclasts relatively to the bone quantity. We found that the number of osteoblasts was decreased in both mice while no effect was seen in the osteoclasts. Next, we injected the mice at two different time points with a fluorescent dye that binds into newly formed bone and observed that the rate of bone formation was significantly decreased in both models.

Our study suggests that chronic expansion of erythropoiesis results in deceased bone formation and ultimately bone loss. These findings support the need for clinical research to evaluate the severity of osteoporosis in patients with polycythemia vera. Currently, erythropoietin is regularly prescribed, especially in patients with kidney failure, and illegally used by athletes. Future research is necessary to clarify the role of erythropoietin on bone remodeling.

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