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**Abstract**

Bone marrow is organized in specialized microenvironments known as 'marrow niches'. These are important for the maintenance of stem cells and their hematopoietic progenitors whose homeostasis also depends on other cell types present in the tissue. Extrinsic factors, such as infection and inflammatory states, may affect this system by causing cytokine dysregulation (imbalance in cytokine production) and changes in cell proliferation and self-renewal rates, and may also induce changes in the metabolism and cell cycle. Known to relate to chronic inflammation, obesity is responsible for systemic changes that are best studied in the cardiovascular system. Little is known regarding the changes in the hematopoietic system induced by the inflammatory state carried by obesity or the cell and molecular mechanisms involved. The understanding of the biological behavior of hematopoietic stem cells under obesity-induced chronic inflammation could help elucidate the pathophysiological mechanisms involved in other inflammatory processes, such as neoplastic diseases and bone marrow failure syndromes.

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**Introduction**

Bone marrow is an animal tissue with one of the highest cell proliferation rates. It gives rise to components of all hematopoietic and immune system lineages. In humans, approximately $1 \times 10^{11}$ to $1 \times 10^{12}$ mature blood cells are produced daily, due to the division and proliferation of a population of hematopoietic stem cells (HSCs), with a unique capacity for self-renewal and multilineage differentiation. The organization of bone marrow in specialized microenvironments, the ‘marrow niches,’ is important for the maintenance of hematopoietic stem and progenitor cells, as...
well as their intramedullary localization and cell cycle phase. The majority of HSCs were originally believed to be quiescent, many studies have demonstrated that these cells are actually cycling, although very slowly, suggesting a state of dormancy. They are activated for more intense proliferation and differentiation under stress conditions, when demands are higher (i.e. during infection) or for replacement of cells eliminated by cell death. In fact, many progenitors already committed to specific lineages appear to cycle actively. This condition strengthens the idea that the proliferation of HSCs and their progenitors is regulated by factors external to the cell itself, which must involve the action of different niches. Osteoblasts, endothelial cells, macrophages and other more primitive mesenchymal cells exert, by mechanisms not yet fully elucidated, a direct effect on the control of hematopoiesis.

The identification and distribution of bone marrow niches has been the subject of intense scientific debate. For example, HSCs have been shown to be in direct contact with a population of osteoblasts, which delimit the bone marrow surface. Osteoblasts are characterized by their fusiform shape and high expression of N-cadherin, called SNO cells (spindle-shaped N-cadherin+ CD45- osteoplastic cells), which form the so-called 'endosteal niche'. Many HSCs are also close to the sinusoidal endothelium, suggesting that endothelial cells could also create clusters for HSCs (the vascular niche). Another recently discovered cell type that seems to play a key role in the maintenance of HSCs is the 'CAR cell' (CXCL12-abundant reticular cell), a small population of reticular cells expressing high amounts of CXCL12. CXCR4, the CXCL12 receptor, has been shown to be critical to maintain the HSCs pool and progenitor B cells in the bone marrow in direct contact with CAR cells, suggesting an important role of these cells in hematopoietic regulation.

Knowledge of the different rates of stem cell proliferation and their regulation by other cell types in homeostasis has raised questions regarding possible changes in these mechanisms and the relationship between infection and the hematopoietic niche along with HSC modulation. Factors such as the association between HSC exposure to toll-like receptor (TLR) ligands and osteoclasts maturation, in addition to higher bone marrow cellularity, mainly due to increased production of G-CSF by bone marrow cells in the obese group compared to controls. Moreover, mesenchymal stem cells (MSC) of HFD rats express considerably higher amounts of nuclear Factor kappa B (NF-kb) as well as tumor necrosis factor alpha (TNFα), IL-1 and IL-6, which can inhibit adipocyte differentiation of MSC thus shifting bone marrow differentiation towards osteoblasts. This mechanism could be responsible for niche alterations affecting marrow microenvironments and consequently destabilizing hematopoietic cell numbers and peripheral mobilization in the inflammatory state.

In humans, obesity is associated with a peripheral blood increase of white blood cell counts, correlating with increased levels of C-reactive protein and decreased IL-10. Disturbances in erythropoiesis have also been described, including anemia and alterations in iron homeostasis. Interestingly, increased levels of IL-6 and leptin induced by inflammation result in the release of hepcidin from the liver and adipose tissue. Hepcidin is an important regulator of iron homeostasis, inhibiting iron absorption by enterocytes and the sequestration of iron by macrophages that result in restricted erythropoiesis leading to mild/moderate anemia. Obesity is associated with high levels of hepcidin, independently of the presence of inflammation.
of liver alterations,27 suggesting that the anemia experienced by obese individuals may be secondary to the inflammatory status (anemia of chronic disease), in addition to the direct effects of cytokines on the proliferation and differentiation of erythropoietic progenitors.

In fact, studies involving patients undergoing bariatric surgery as treatment of obesity have clarified the fact that anemia in this population cannot be explained solely on the basis of iron availability and nutritional status.30,31 Drygalski et al. assessed 1125 obese patients before and after bariatric surgery for the prevalence of anemia and the depletion of body iron stores. The baseline incidence of anemia was higher than expected and increased significantly after surgery as the overall iron bioavailability improved significantly with pronounced weight loss, possibly following the reduction in inflammation.31 Gastric bypass surgery was also associated with a generalized decrease in the white blood cell and platelet counts, although not clinically important.32 These findings suggest that generalized suppression of hematopoiesis might occur after surgery, revealing a possible hyperproliferative state triggered by inflammation in obese patients.

Bioenergetic organization of stem cells in obesity

One of the striking features of the HSC niche is its low oxygen tension, yielding the term ‘hypoxic niche.’ This microenvironment of low O2 concentrations appears not only to be well tolerated by HSCs but also essential for keeping their self-renewal and differentiating properties.33-36

Through mitochondrial metabolism, O2 generates reactive oxygen species (ROS) that, at increased levels, lead to cell dysfunction and aging, disrupting tissue homeostasis. The aberrant production of low O2 concentrations appears not only to be well tolerated by HSCs but also essential for keeping their self-renewal and differentiating properties.33-36

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Increased AMPK after oxidative phosphorylation suppression is known to be transient. However, whether the maintenance of anaerobic conditions after normalization of AMPK could lead to the death of these cells, or whether any such mechanism would be only the initial part of an adaptive process by giving more advantage to these tissues, is not clear yet.45

An important mechanism of adaptation to hypoxia involves hypoxia-inducible factor 1 (HIF-1), a heterodimeric transcription factor composed of an O2-regulated subunit (HIF-1α) and a constitutional subunit (HIF-1β).46 The two subunits are present in all human and murine tissues and are activated by O2-dependent hydroxylases. The final action occurs primarily through modulation of transcription of other genes involved in the cell metabolism.47

Another event that appears to be important for adaptation to hypoxia is the exchange of the regulatory subunit of the cytochrome c oxidase from cyclooxygenase COX4-1 to COX4-2; the latter being activated by HIF-1. Other mitochondrial proteases are also activated by HIF-1, leading to enhanced degradation of COX4-1.48 This mechanism appears to be essential for the optimal function of cytochrome c oxidase in situations of hypoxia and to reduce ROS production.49

Recently, a mechanism to minimize cell damage caused by excess ROS production, dependent on the action of uncoupling proteins (UCP) has been elucidated. Part of the proton gradient used to drive the synthesis of ATP is deflected from the membrane back into the mitochondrial matrix, thereby reducing the emission of ROS, this transport is carried out by UCP ‘uncoupling’ the oxidative phosphorylation process.49 Three isoforms of UCP (UCP-1, -2 and -3) have been described and all appear to be activated by ROS molecules themselves, setting up a negative feedback loop.

Thus, we can speculate that obesity and its related deregulations in metabolism and inflammation may alter bone marrow niches and the energetic organization of marrow cells through pathways that have not been fully investigated until now.

Conclusion

Biologically, obesity is characterized by a state of chronic inflammation and its effects on the hematopoietic system, in particular on the stem cell compartment, are poorly understood. Therefore, further studies are needed to clarify the specific impact of this state at molecular and cellular levels, as well as the mechanisms involved. Long-term activation of hematopoietic stem cells during chronic inflammation may lead to the depletion of these cells or development of...
functional defects, such as those seen in aplastic anemia. Therefore, this area of research may also provide new evidence to understand other situations involving chronic inflammation, such as normal aging, neoplastic diseases and bone marrow failure syndromes.

The evaluation of the proliferative and self-renewal potential of hematopoietic cells, the cytokine and hematopoietic growth factor profiles of obese individuals and the bioenergetic organization of stem cells in obesity are some key points for future investigation.

**Conflicts of interest**

The authors declare no conflicts of interest.

**REFERENCES**


