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The Role Of Leptin And Adipokines In The Regulation Of Hemopoiesis

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Abstract: The article is devoted to the analysis of the role of leptin and other adipokines in the regulation of hematopoiesis. It is shown that bone marrow adipose tissue is an active component of the hematopoietic niche and affects the maintenance, proliferation and differentiation of stem and progenitor blood cells. Leptin and its receptor provide the production of key factors SCF and CXCL12 by mesenchymal stromal cells. Adiponectin and resistin are involved in modulating hematopoietic recovery after myelosuppression. Impaired adipokine secretion in obesity, aging, and malignant processes leads to niche dysfunction and changes in hematopoiesis efficiency. Understanding the molecular mechanisms of adipokine action opens up opportunities for developing new therapeutic approaches.

Keywords: Leptin, adipokines, adiponectin, resistin, visfatin, hematopoiesis, hematopoietic stem cells, bone marrow, bone marrow adipose tissue, regeneration.

Introduction: The scientific novelty of the work lies in the comprehensive analysis of the role of leptin and other adipokines in the regulation of hematopoiesis, the identification of the mechanisms of their interaction with the cells of the bone marrow niche and the systematization of data on the physiological and pathological consequences of their action, which allows us to consider adipokines not only as metabolic mediators, but also as potential biomarkers and targets for the treatment of hematopoietic disorders.

Hematopoiesis, the dynamic process of blood cell formation and differentiation, is supported by a rare population of hematopoietic stem cells (HSCs) residing in a specialized bone marrow microenvironment known as the hematopoietic niche. This niche provides a balance between quiescence and activation of HSCs, which is critical for their self-renewal and differentiation.

Previously, bone marrow adipose tissue was considered a passive structure, but recent studies have established its metabolic and secretory activity. Bone marrow adipocytes produce a wide range of biologically active molecules, including adipokines, cytokines, and growth factors, which directly and indirectly affect HSCs and their stromal microenvironment [1].

Particular attention is paid to leptin, a hormone that regulates energy balance. Its receptor (LepR) is expressed in the bone marrow, where LepR $^{+}$ mesenchymal Stromal cells (MSCs) are an important source of SCF and CXCL12 factors required for maintaining the HSC pool. Experimental data also indicate the ability of leptin to modulate the proliferation and differentiation of myeloid and erythroid precursors, as well as to influence the immune response. In addition to leptin, other adipokines, such as adiponectin and resistin, play a significant role in hematopoiesis. Adiponectin helps maintain the functional state of HSCs, while resistin, according to recent data, promotes the restoration of hematopoiesis after damage [2].

Disturbances in the secretion of these molecules caused by obesity, aging or oncohematological diseases can lead to disorganization of the bone marrow microenvironment and increase the risk of hematopoietic pathologies.

Therefore, studying the role of leptin and other adipokines is important for understanding the mechanisms of functioning of the stem niche and developing new therapeutic approaches to correct

hematopoietic disorders.

Leptin, a peptide hormone encoded by the LEP gene, is synthesized primarily by white adipocytes. Its concentration in the blood correlates with the volume of adipose tissue. The discovery of leptin in 1994 in a study of mutant ob/ob mice initially positioned it as a key regulator of energy metabolism [3]. However, subsequent scientific studies have revealed its multifaceted effects on immune responses, inflammation, angiogenesis, and, in particular, hematopoiesis [4].

The leptin receptor (LepR) belongs to the class I cytokine receptor family. There are several isoforms LepR (Ob - Ra – Ob - Rf), of which only the long form Ob - Rb has a complete intracellular domain capable of activating the JAK 2/ STAT 3 signaling pathway. Activation of LepR initiates the JAK 2/ STAT 3, PI 3 K / AKT and MAPK cascades, which ensures the pleiotropic effects of leptin on metabolic and cellular processes.

Of particular interest is the expression of LepR in the bone marrow. Unlike hypothalamic neurons, where LepR regulates energy balance, in the bone marrow it is expressed in a subpopulation mesenchymal stromal cells (MSCs). These LepR $^{+}$MSCs are the main source of stem cell factor (SCF) and chemokine CXCL 12, which are necessary for maintaining the hematopoietic stem cell (HSC) pool. Experiments in mouse models have shown that selective inactivation SCF or CXCL 12 in LepR $^{+}$ cells leads to disruption of HSC maintenance and a decrease in their functional activity [5].

In addition to the indirect effect via MSCs, there is evidence of a direct effect of leptin on hematopoietic cells. Under conditions of in In vitro, leptin stimulates the proliferation of colony-forming units of the granulocyte -macrophage (CFU - GM) and megakaryocytic series. Leptin has also been shown to participate in the regulation of erythropoiesis and the acceleration of hematopoiesis recovery after injury.

Thus, leptin is a multifunctional adipokine that regulates hematopoiesis both indirectly, through modulation of the bone marrow stromal microenvironment, and through direct effects on hematopoietic progenitors.

Bone marrow adipose tissue (BMAT) secretes a variety of adipokines that play a key role in modulating the hematopoietic niche. Their effects can be either direct, affecting hematopoietic stem and progenitor cells (HSC / HSPC), or indirect, mediated through mesenchymal stromal cells (MSC), endothelium, monocytes/macrophages and metabolic milieu.

The effects of adipokines are context dependent: some enhance HSC exit from dormancy and promote repopulation after stress, while others provoke an inflammatory shift and shift hematopoiesis towards myelopoiesis.

Adiponectin has been identified as a factor that stimulates HSC growth. In experiments in in vitro and in In vivo it enhanced HSC proliferation and survival, which was shown through activation of the p38 MAPK signaling pathway [6].

Resistin, traditionally considered a proinflammatory factor, exhibits a positive effect on long-term repopulation in stressed hematopoiesis, for example, after chemo- or radiation damage, acting in an RXR - dependent mode [7].

Visfatin (NAMPT/Visfatin) has both intracellular (NAD synthesis) and extracellular effects, influencing the metabolism and functional state of niche cells [8].

The context-dependence of adipokine action is a critical aspect. Under physiological homeostasis, their signals support normal HSC function, whereas under pathological conditions (obesity, chronic inflammation) they can impair hematopoietic recovery. This duality makes BMAT and its secretome a promising but challenging target for therapeutic modulation aimed at correcting hematopoietic disorders.

Table 1 - Key adipokines and their effects on hematopoiesis

Adipokine	Source	Main effects on hematopoiesis	Proposed mechanisms
Adiponectin	BMAd, peripheral adipocytes	Stimulates HSC proliferation/maintenance; promotes exit from querescence during recovery	Activation of p38 MAPK in HSC; anti-inflammatory effect
Resistin	BMAd (RXR - dependent expression)	Positive regulation of long-term HSC repopulation under stress conditions	Activation of NF- κB /inflammatory pathways; modulation of niche under stress (ASH data/ preprint)

Visfatin (NAMPT)	BMAd, MSC, macrophages	Indirect effects on the monocyte-macrophage lineage and HSC niches	Regulation of NAD^+ metabolism; alteration of metabolic status of MSCs/macrophages
Chimerin (RARRES2), apelin, etc.	BMAd , stromal cells	Potential modulation of chemotaxis, angiogenesis and immune response	Alteration of endothelial and immuno-chemokine support of the niche (further evidence required)

Adipokines produced by bone marrow adipose tissue exert a complex effect on the hematopoietic niche, regulating its components and functions. These mechanisms can be classified into several key areas:

1. Direct effect on hematopoietic cells. Some adipokines can directly affect hematopoietic stem and progenitor cells (HSC/HSPC). For example, adiponectin stimulates HSC proliferation and their ability to repopulate. in vivo by activating the p38 MAPK signaling pathway. Similar proliferative effects for leptin have been described in a number of experimental studies, indicating its direct influence on the balance between cellular dormancy and HSC division [9].

2. Modulation of stromal components/ Adipokines affect mesenchymal stromal cells (MSCs), which are part of the hematopoietic niche. The $LepR^+$ MSC subset serves as the main source of important factors - SCF and CXCL12, which are required for the retention and maintenance of the HSC pool. Changes in the composition of the BMAT secretome can affect the expression of these factors, leading to changes in the number and function of HSCs [10].

3. Metabolic modulation. BMAT forms a local metabolic environment rich in lipids (triglycerides, free fatty acids), which can be directly used by HSC or change their metabolic programs. In addition, adipokine enzymes, such as NAMPT/ vistatin, regulate NAD^+-dependent processes, changing the energy status of niche cells and their ability to regenerate.

4. Immuno -inflammatory effect. And dipokines have pronounced immunomodulatory properties. Pro-inflammatory adipokines (resistin) can increase local inflammation, which shifts hematopoiesis towards myelopoiesis. In contrast, anti-inflammatory Adiponectin protects the niche from inflammatory degradation, promoting HSC restoration.

5. Effect on the vascular environment. Adipokines also influence endothelial cells, angiogenesis, and extracellular matrix composition, which is critical for the formation of the perivascular niche. By altering microcirculatory permeability and cytokine availability, adipokines indirectly modulate HSC behavior [11].

6. Context dependence. The final effect of adipokines is determined by the physiological context. Under acute stress (chemotherapy, radiation), some of them can promote the restoration of hematopoiesis, whereas under chronic exposure (obesity, aging), their profile shifts towards proinflammatory factors, which disrupts hematopoietic homeostasis. Understanding these mechanisms is important for the development of therapeutic strategies for modulating the hematopoietic niche in various pathologies [12].

Adipokines and bone marrow adipose tissue (BMAT) perform both physiological and pathological functions in the regulation of hematopoiesis. Their effects on the hematopoietic system depend on the metabolic state of the organism and the physiological context.

Under normal conditions, adipokines and BMAT promote hematopoietic homeostasis:

1 . Maintenance of the HSC pool through the stroma. $LepR^+$ mesenchymal subset stromal cells (MSCs), as well as BMAT, is involved in the synthesis of SCF and CXCL 12. These factors are critical for the retention and survival of hematopoietic stem cells (HSCs) in their niche, ensuring a balance between dormancy and activation.

2. Recovery from acute stress. In conditions of acute myelotoxic injury (e.g. after radiation or chemotherapy), some components of the secretome BMAT may promote repopulation of the hematopoietic system. Several studies have shown that specific Adipokines such as resistin may improve long-term repopulation.

3. Metabolic replenishment. BMAT serves as a local source of lipids and other metabolically active molecules that support energy-dependent processes in HSCs and stromal cells, ensuring normal physiology.

Imbalance of adipokine secretion associated with pathological conditions leads to disruption of normal hematopoiesis:

1. Shift towards myelopoiesis. In obesity and chronic metabolic stress, the adipokine profile shifts towards proinflammatory molecules (e.g. resistin), which stimulates myelopoiesis and reduces the maintenance of long-lived HSCs. This is associated with a systemic

and local increase in proinflammatory cytokines.

2. Delayed recovery after injury. Excess adipocytes in the bone marrow are associated with a reduced ability to quickly restore hematopoiesis after myelotoxic injury, which has clinical significance, for example, in bone marrow transplantation.

3. Leukemia progression. Leukemic cells can "reprogram" surrounding adipocytes by using their free fatty acids and growth factors for survival and development of resistance to therapy. Thus, BMAT becomes part of the pathological niche that promotes oncogenesis.

of BMAT increases and the profile of secreted adipokines changes, which correlates with deterioration of the functional capacity of HSCs, the risk of clonal hematopoiesis and other hematological disorders.

Table 2 - Physiological and pathological effects of adipokines on hematopoiesis

Category	Consequences/phenotypes	Mechanisms / Markers
Physiology: Niche Support	quorescence /activation balance	LepR $^{+}$ MSC → SCF, CXCL12; local adipokines
Physiology: Recovery from Stress	HSC repopulation after radiation/ chemotherapy	BMAd - secret (contextual) - support/ inhibition .
Pathology: obesity, chronic inflammation	Shift to myelopoiesis ; immune system disorder	↑resistin/ visfatin , ↓ adiponectin ; proinflammatory cytokines
Pathology: Slow recovery	Slower recovery from myelosuppression	BMAd accumulation ; niche-support reduction (counter-data in models)
Pathology: Oncology support	Support of AML/MM growth; therapeutic resistance	Fatty acids → FABP4; adipokines reprogram the niche
Pathology: niche aging	Decreased HSC function ; clonal hematopoiesis	Increased BMAd ; change in adipokine profile (age)

Studying the mechanisms of action of adipokines on hematopoiesis opens up new prospects for the development of innovative therapeutic approaches in several key areas:

1. Hematopoietic stem cell transplantation (HSCT). Manipulation of adipogenesis or targeted modulation of individual adipokines (e.g., use of agonists or antagonists) may facilitate faster and more efficient repopulation after transplantation. Preclinical studies already support the potential of such approaches [13] .

2. Oncology (acute myeloid leukemia/multiple myeloma). The interaction of leukemic blasts with BMAT (bone marrow adipose tissue) is an important aspect of pathogenesis. Targeting these interactions, for example, blocking lipid transfer via the FABP4 protein, is considered a promising adjuvant strategy to standard chemotherapy.

3. Metabolic diseases and aging. Control of the systemic adipokine profile, in particular, reducing the level of proinflammatory factors and increasing the concentration of adiponectin, can serve as an auxiliary therapeutic strategy for normalizing hematopoiesis in obesity and age-related changes [14].

Thus, leptin and other adipokines play a complex, context-dependent role in the regulation of hematopoiesis. They affect hematopoietic stem cells both directly and indirectly, through modulation of the bone marrow stromal niche. These molecules change the metabolic and inflammatory environment, which is of great clinical importance. Disturbances in their work associated with obesity, aging, and oncohematological diseases can lead to dysfunction of hematopoiesis.

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