

Leptin and its receptor in hematologic malignancies

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Abstract

Leptin is a cytokine which exerts highly pleiotropic activity serving as an important factor in the processes of fat tissue metabolism and energy expenditure regulation. In addition to that, it is involved in many processes involved in adaptive and innate immunity. Leptin biological activity strongly depends on its proper function and interactions with Ob-R receptor. It was shown, that leptin receptors are present on haematopoietic CD34+ stem cells, cell lines derived from erythropoietic, myeloid and lymphoblastic lineages, human leukemic blasts in acute myeloid leukemia, acute lymphoblastic leukemia and chronic myeloid leukemia as well as many other types of cancer cells. The broad variety of leptin biological actions make it a good target for research on cancer pathogenesis, including leukemias. Broadening of our knowledge concerning of leptin and its receptor on the hematopoietic system will give an opportunity to understand its relation to leukemia development.

Key words: leptin, leptin receptor, leukemias.

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Leptin, a key hormone regulating energy expenditure, stimulates proliferation of lymphocytes subpopulations and inhibits apoptosis in these cells. It also influences activation and differentiation of monocytes and macrophages as well as hematopoietic CD34+ stem cells. Leptin, both alone and in combination with various cytokines, induces normal myeloid and erythroid cells development [1, 2]. Moreover, leptin is produced by adipose tissue and bone marrow stromal cells forming essential part of bone marrow microenvironment, what indicate its active involvement in hematopoiesis [3].

The discovery of leptin receptor in hematopoietic cells led to the speculation that leptin may influence leukocyte development in bone marrow, and in consequence it may regulate physiological function of immune system. Some authors suggest that leptin is able to activate not only normal hematopoietic cells development by activation of receptors present on the surface of neighbor hematopoietic stem cells, but also, it may stimulate progenitor leukemia cells in a paracrine manner [4, 5].

In patients with acute leukemia the increased blood vessels density within bone marrow was observed [6, 7]. It was shown, that apart from hematopoietic cells growth pro-

moting activity including both normal and malignant cells, leptin is able to induce capillaries formation [8]. Administration of specific monoclonal antibody against Ob-R inhibits leptin binding to its receptor and reduces malignant cell mass in rats with acute promyelocytic leukemia. Moreover, the antibody causes the reduction of blood vessels density within the bone marrow microcirculation [9]. The antibody, because of the inhibition of leptin binding to its receptor, may influence signal transduction and reduce leptin activity. It signifies, that leptin biological activity strongly depends on its proper function and interactions with Ob-R receptor [10].

The studies performed on hematopoietic cells have shown the presence mRNA of both, long and short isoforms of leptin receptor, in various hematopoietic cells types. The transcription products encoding long and short forms of leptin receptor were found in yolk sac, fetal hepatocytes, bone marrow, spleen, hematopoietic progenitor cells CD34+ as well as in human hematopoietic cell lines Meg01 and HEL. In the studied cells, only long form of the receptor was able to fully transduce proliferation and differentiation signals to hematopoietic cell lines, what suggest that leptin influence regulation of hematopoiesis [1, 11].

Experimental data has shown that long, short or both isoforms are expressed by 68.2%, 59.1% and 45.4% patients with acute myeloid leukemia respectively, while in patients with acute lymphoblastic leukemia only low concentration of mRNA encoding short isoform was found [5].

In acute non-lymphoblastic leukemias the percentage of Ob-R positive cells does not change in comparison to the percentage of normal bone marrow granulocytic lineage. On the other hand, in children with acute lymphoblastic leukemias significant decrease in Ob-R expression in comparison to normal bone marrow was observed. The expression of short isoform of Ob-R may indicate the impairment in signal transduction in lymphoblastic leukemia cells, even if bone marrow leptin level is normal. It is possible, that anti-Ob-R monoclonal antibody used in the described study binds extracellular domain of short isoform of the receptor [12].

Long isoform of leptin receptor is expressed more often in primary acute non-lymphoblastic leukemia (ANLL) than in secondary ANLL and chronic myeloid leukemia (CML). In CML the receptor expression depends on clinical stage of the disease, and is much higher in immature blasts observed during blast crisis [5].

Not only normal hematopoietic cells but also leukemia cells are able to express functional receptors for various cytokines such as interleukins 3 (IL-3) and 6 (IL-6), granulocyte-macrophage colony stimulate factor (GM-CSF), granulocyte colony stimulate factor (G-CSF), macrophage colony stimulating factor (M-CSF) or stem cell factor (SCF). The cytokines are also able to regulate leukemia cell survival, proliferation and differentiation. Abnormal cytokine expression as well as their receptors expression can influence signal transduction disturbances in leukemia cells. It was shown, that leptin alone is not able to increase the expression of other cytokines receptors [1, 5]. Possibly, pro-inflammatory cytokines or growth factors, through the interaction with their receptors, modulate leptin receptor expression in various types of leukemia cells.

Leptin, in dose dependent manner, stimulates proliferation of human leukemia cell lines derived from myeloid cell lines such as MO7e and OCI/AML2. However, proliferative response of the described cell lines did not correlate with leptin receptor expression level.

In the CD34+ cells obtained from normal bone marrow, high expression of mRNA encoding both long and short isoform of Ob-R was observed, however, the short isoform was more common. During the maturation of CD34-CD33+ and CD34-CD13+ promyelocyte cells, a significant decrease in short isoform expression and complete absence of long isoform expression were observed, what suggests that Ob-Rb expression decrease during progenitor cells maturation in bone marrow. On the other hand, in acute promyelocytic leukemias high expression of long isoform of Ob-Rb was observed [5].

In murine hematopoietic bone marrow cells culture leptin stimulated myeloid progenitor cells proliferation and showed significant synergy with stem cell factor (SCF) on

granulocyte-macrophage colony formation (GM-CFU) [13]. Whereas in *in vitro* studies on human myeloid leukemia cells leptin synergically or additively with other hematopoietic growth factors such as IL-1 β , IL-3, IL-6, TNF- α , GM-CSF and SCF stimulates cell proliferation (Fig. 1) [1, 5, 14]. In human CD34+ progenitor cells leptin stimulates granulocyte-macrophage colony formation either in the presence of or without erythropoietin [2].

Serum leptin concentration in ANLL adult patients is lower than in healthy subjects, nevertheless serum leptin together with locally secreted leptin is able to influence blasts characteristics [14].

Wex *et al.* [15] in the studies concerning leptin level in acute lymphoblastic leukemias in children at the moment of the diagnosis have shown significantly reduced plasma leptin level in bone marrow. Leptin concentration (measured in patients' blood) returned to the normal values after 33 days of chemotherapy, what was concordant with hematologic remission time. The above observations indicate the connection between tumor cells development and reduced leptin concentration.

Our research has also shown that in patients with childhood B- or T-cell lymphoblastic leukemia leptin level was significantly decreased in comparison to the control group. However, in the group of childhood ANLL patients, serum leptin level was comparable to the control group [12].

Low serum leptin level in patients with leukemia can be, in some ways, explained by the influence of hypoxia. Hypoxia is responsible for hypoxia-inducible factor 1 α (HIF-1 α) activation that in consequence leads to the inhibition of ob gene promoter [16]. The children with acute leukemias usually have low level of hemoglobin, what may cause tissue hypoxia and in consequence inhibit leptin synthesis.

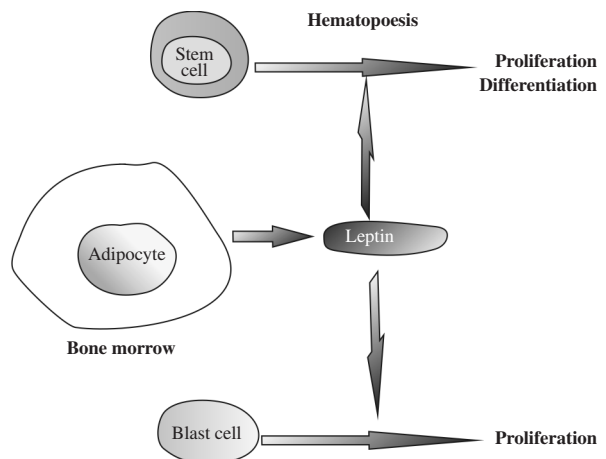


Fig. 1. A diagram of probable physiologic and pathophysiological function of leptin in hematopoiesis and leukemia [according to 1, 5]

Moreover, it was proved, that leptin gene expression is influenced by pro-inflammatory mediators, mainly acute phase cytokines: IL-6, TNF- α and IL-1 [17].

In cases of chronic inflammation caused by persistent increase in proinflammatory mediators' concentration in the organism, leptin level is decreased [17]. It can be an indirect cause of low leptin level in children with leukemias as hematologic malignancies cause the state of prolonged elevation of proinflammatory cytokines concentration, especially TNF [18].

The circulating leptin level can be regulated by hormone binding with its soluble receptor. Soluble leptin receptors circulate in the blood and are able to bind leptin with high specificity influencing concentration of biologically active, free leptin [19, 20].

The analysis of leptin concentration in bone marrow has shown that children with ANLL are characterized by significantly higher leptin level than the level observed in the control group [12]. High bone marrow leptin concentration in children with ANLL might be caused by synergistic activity of leptin with other cytokines and growth factors or by apoptosis inhibition in cancer cells. In children with lymphoblastic leukemia bone marrow leptin concentration was comparable to the control group.

Pro-inflammatory cytokines such as IL-1 β , IL-6, TNF and INF- γ inhibit leptin expression and secretion in bone marrow adipocytes [16] and in human subcutaneous adipocytes [15]. The cytokines are highly expressed in malignant cells, and hence may induce the inhibition of leptin concentration increase in neoplastic bone marrow.

Many authors described the relations between leptin receptor gene polymorphism and neoplastic disease development [21, 22]. It is suggested, that the studied polymorphism is related to signal transduction impairment from the receptor into the cell and can influence leptin receptor expression level in blast cells as well as the ability of the receptor to bind its ligand – leptin.

The relations between serum leptin level changes or leptin receptor expression and hematopoietic malignant cells proliferation in bone marrow are still a significant research problem. Understanding of the complex mechanisms underlying the described processes may contribute to the knowledge on etiology and development of both acute and chronic leukemias.

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