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The Role of Iron Metabolism in the Regulation of Immune and Other Biological Functions

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Abstract

Recent observations have shown that there is a connection between iron metabolism andimmune functions, including the anticancer immunity. Both iron deficiency and overload may induce immunosuppression, even though for different reasons. Iron deficiency has been shown to be associated with a reduced secretion of IL-2 that plays a fundamental role in the regulation of the immune system, while iron overload may directly induce toxic effects on the immune cells. The main link between iron metabolism and the immunoinflammatory status is represented by hepcidin (HPC), a protein produced by liver. HPC inhibits the activity of ferroportin, the protein responsible for iron efflux into the blood, with a consequence iron intracellular accumulation and increase in ferritin levels. Then, the enhanced HPC production would be the main mechanism responsible for the anaemia of chronic diseases. The importance of the connections between iron metabolism and immune response is furtherly confirmed by the evidence that HPC production is under a cytokine control, since it is stimulated by the inflammatory cytokines, namely IL-6, and inhibited by IL-10, IL-2, erythropoietin, and hypoxia.

Keywords: Anaemia of chronic disease; Erythropoietin; Ferroportin, Hepcidin; Iron; Lactoferrin; Transferrin

Introduction

Recent experimental and clinical studies have shown that iron is not essential for the only haemoglobin production, but also for several other biological functions, mainly the immune responses [1]. Moreover, the researches performed during the last years have allowed a better definition of the different factors involved in iron metabolism. Iron entering the circulation depends on two main sources, consisting of macrophages that recycle iron from phagocytosed erythrocytes, and duodenal enterocytes that absorb iron from the intestinal lumen through the cell surface protein, the natural resistance-associated macrophage protein (NRAMP). Then, iron efflux into the blood from both macrophages and duodenal cells is realized by the iron transporter ferroportin (FPN), which is expressed on cell surface. Iron circulates into the blood complexed to transferrin (TF). Finally, iron is taken by the various cells through the transferrin receptor-type 1 (TFR1) that internalized iron into the cell. TFR1 activity is stimulated by IL-10 and inhibited by interferon-gamma. It has been also demonstrated the existence of a type 2 of TFR, the TFR2, that is mainly expressed by hepatocytes and monocytes, while TFR1 is mainly expressed by erythroid cells and monocytes. In any case, both TF receptors may bind and internalize the iron bound on transferrin by the endocytosis mechanism. In addition, in the last years, it has been demonstrated that iron metabolism is under a complex regulation, namely exerted by the liber peptide heptacidin (HPC). Other important factors involved in iron metabolism are represented by the ferrireductase, which transforms the trivalent iron from food in divalent iron to be transferred in the intestinal cells, the ferroxidase, also termedhephaestin, which converts the divalent iron to trivalent iron for the plasmatic transportation, since TF contain two-high affinity-binding sites for the trivalent iron [2].

The Physiological Role of Hepcidin and the Regulation of Its Secretion

HPC is a type II-acute-phase protein, mainly produced by liver, and it's most important function consists of the inhibition of FPN activity, with a consequent reduced iron efflux from both macrophages and duodenal cells into the blood, and a following iron intracellular sequestration, which allows an increase in ferritin intracellular concentrations. Conditions which enhance the demand for iron, including Iron deficiency and hypoxia, inhibit HPC production, with a consequent increase in FPN levels and activity. The inhibitory action of hypoxia on HPC secretion is mediated by the release of the hypoxia-induced factor-1 (HIF-1). Then, a negative correlation has been observed between HPC and FPN blood concentrations. In addition, HPC secretion has appeared to be under a complex cytokine and neuroendocrine regulation. In more detail, HPC secretion is stimulated by some inflammatory cytokines, in particular IL-6 [3], and in a less manner by IL-1beta [4], while the role of TNF-alpha is till controversial. The fundamental role of IL-6 in stimulating HCD secretion is furtherly confirmed by the evidence that a long-term treatment with an anti-IL-6 receptor antibody, such as tocilizumab, may inhibit HCD secretion and improve the anaemic condition [5]. On the other side, HPC may exert a direct inflammatory activity by stimulating the macrophage release of inflammatory cytokines, including IL-6 and TNF-alpha. Then, HPC and IL-6 would be connected by a positive feedback circuit. IL-22 has also appeared to promote HPC secretion [6]. On the contrary, HPC secretion is inhibited by the anti-inflammatory cytokine IL-10 [7]. HPC could be also inhibited by IL-2, since IL-2 cancer immunotherapy has been proven to decrease ferritin levels and enhance iron blood concentrations, with potential therapeutic efficacy in the treatment of anaemia of chronic diseases [8], and on the other side iron therapy has been seen to enhance IL-2 blood levels [9]. HPC secretion is also stimulated by the adipokine leptin, and in obese individuals, adipocytes themselves have appeared to produce HPC [10]. In contrast, vitamin D3 may inhibit HPC production, with a potential therapeutic activity in some forms of anaemia. In addition, because of the pro-inflammatory activity of HPC, the inhibition of HPC played by vitamin D could constitute one of the mechanisms responsible for its anti-inflammatory action, in addition to other mechanisms, such as the inhibition of IL-8 secretion [11], and the stimulation of TGF-beta production [12]. Testosterone has also appeared to inhibit HPC production. Finally, erythropoietin (EPO) may also inhibit HPC secretion, by contributing to enhance iron availability for haemoglobin synthesis and production [13]. Then, because of its fundamental role in iron metabolism, some understood anaemic conditions may today be explained as depending on alterations of HPC secretion, particularly in terms of abnormally enhanced HPC production.

The Diagnostic Value of Hepcidin Blood Levels

HPC blood levels synthetise the status of iron metabolism, and its relation to the immunoinflammatory status of subjects. High levels of HPC have been found particularly in patients affected by anaemia of chronic disease (ACD), also termed as the anaemia of inflammation [14]. ACD may occur in pathologies characterized by an enhanced production of inflammatory cytokines, including advanced neoplasms, chronic infections, and autoimmune diseases, particularly in olde age, since aging is already characterized by an enhanced production of IL-17, which is released from The 17 lymphocytes, and stimulate the secretion of inflammatory cytokines by macrophages [15]. In contrast, low levels of HPC have been found in patients with anaemia due to iron deficiency, as well as in other conditions requiring an enhanced iron availability for haemoglobin production, such as hypoxia, as in the case of lung diseases. Moreover, the evidence of a decline in HPC levels has appeared to be a predictive marker for the response to EPO therapy in anaemic cancer patients. Abnormally high levels of HPC have been also seen in autoimmune pathologies as consequence of the altered cytokine secretion, and this evidence may explain the ACD, that may occur in autoimmunity. In fact, appositive correlation has been found between IL-6 and HPC blood levels in patients with chronic inflammatory diseases. On the same way,several histotypes of tumours, particularly in the metastatic disease, have appeared to be characterized by high HPC concentrations, but at present it is still unknown whether the enhanced HPC secretion may depend on the presence of tumour itself or on other concomitant conditions, such as the ACD, as well as HPC may exert a direct pro-tumoral action. Iron is also essential for the neoplastic cells. Then, from this point of view, HPC could promote cancer growth by inhibiting the activity of FPN, with a consequent promotion of iron accumulation into cancer cells. In fact, HPC expression is generally suppressed in cancer tissues. On the contrary, the block of TFR1 on cell surface of cancer cells could counteract the bound of iron-transferrin complex, and opposite tumour cell proliferation [16].

Iron and Immune Functions

Iron metabolism and immune system have appeared to be connected by reciprocal influences, since iron concentrations have been proven to influence the immune functions, and in turn the immune reactions may affect iron metabolism. Iron deficiency has been found to be characterised by low levels of IL-2, which become normal after iron supplementation [17]. In any case, despite the complexity of the problem and the controversial

results reported in the literature, it is possible to affirm that both iron deficiency and excess negatively influence the immune functions. Iron deficiency immunosuppresses because of the need of iron for all cell functions, including the immune cells. On the other side, iron overload also plays an immunosuppressive action, because of iron toxicity, due to the generation of reactive oxygen species (ROS), which allows an inflammatory status, and a consequent inhibition of the anticancer immunity, since macrophage-related chronic inflammation has appeared to suppress the immune reactions against cancer growth [18]. An important role in the regulation of iron-immune system interactions is played by HPC itself. In fact, HPC may directly influence the immune functions, in particular the defence against microbial pathogens by reducing the availability of iron,which is essential for the growth of pathogens, as wellas for the normal human cells. As far as immune cells are concerned, iron would be important particularly for T lymphocyte proliferation and differentiation, whereas its influence on B lymphocytes and autoantibody production is less evident [19]. In addition, it has been shown that the block of TFR with strategiessuch as the administration of anti-TFR monoclonal antibodies, has appeared to prolong the survival of allograft transplantation, and completely abrogate cytotoxic T lymphocyte response, by suggesting a fundamental role of TFR in mediating the immune reaction against organ transplantation. In fact, TFR expression has been proven to be up-regulated during T cell activation after its interaction with the antigen-major histocompatibility complex, and the expression of IL-2 receptor [20]. Then, TF and its receptor would be also involved in the maintenance of self-identity mechanisms. Moreover, at present, it is known that that the immune system and cytokine network are physiologically under a neuroendocrine central regulation, namely played by the pineal gland through its main hormone melatonin (MLT) [21], and brain opioid [22] and cannabinoid system [23]. However, no data are available about the possible existence of a neuroendocrine influence on HPC secretion. Then, at present it is still unknown whether the neuroendocrine system may influence the immune functions, as well as iron metabolism, at least in part through a modulation of HPC secretion.

The Activity of Lactoferrin

Lactoferrin (LF) is an iron-binding glycoprotein of the transferrin family, with particularly high concentrations in milk, but also in other secretions. It is also released from neutrophils in the presence of infections. LF plays a protective role in infections by locally sequestering iron, that is essential for bacterial proliferation, then by acting as an iron scavenger, but it does not supply the reticulocytes with iron. Moreover, recent studies would suggest an involvement of LF in then regulation of cytokine and chemokine secretions. In more detail, LF-induced iron sequestration has been proven to reduce the production of inflammatory cytokines,including TNF-alpha, IL-6, and IL-17, then by exerting an anti-inflammatory activity. Similar consideration may be suggested in the case of the neoplastic diseases, because of iron requirement by also tumour cells for theirgrowth.Moreover, LF has appeared to be essential for the maturation and differentiation of both Tand Blymphocytes, tostimulatedendritic cell functions as antigen presentingcells, ad stimulate IL-12 production by macrophages. Finally, LF has been seen to inhibit IL-5 secretion from Th2 lymphocytes [24], with potential therapeutic impact in the treatment of some forms of allergy, which is promoted by IL-5.

Conclusions

Until few years ago, iron was substantially taken into consideration for its importance in haemoglobin production. On the contrary, most recent researches have demonstrated that iron is involved in several other biological functions, namely the immune functionless. Since iron availability is mainly regulated by HPC, the main connection between iron metabolism and immune functionless could be represented by HPC itself.

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