Hepcidina y anemia

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Iron is a central component of heme, iron-sulfur cluster-containing enzymes, and proteins involved in mitochondrial respiration, metabolic processes, hormone synthesis and DNA replication[1]. However, iron also catalyses the formation of toxic hydroxyl radicals, which can cause cellular damage. Therefore, tight regulation of iron homeostasis is needed to avoid both iron deficiency and overload.

Dietary iron is absorbed in the duodenum and transferred to the circulation, where most iron is used in the bone marrow for erythropoiesis. After a mean half-life of 120 days senescent erythrocytes are degraded by spleen macrophages and Kupffer cells with subsequent extraction of iron[2,3]. This re-utilisation of the metal meets 90-95% of the body's daily needs for iron while only 5-10% originates from the diet. The co-ordination of iron absorption and macrophage iron release is orchestrated by a small peptide known as hepcidin[4].

Hepcidin, also termed as the "iron-hormone" is mainly produced by hepatocytes in response to iron loading and inflammatory stimuli whereas its expression is reduced by iron deficiency, hypoxia and anaemia but also by sexual hormones or alcohol intake[1,4,5]. Hepcidin exerts its regulatory effects by binding to the only known cellular iron export protein, ferroportin, leading to ferroportin degradation and blockade of iron release from

macrophages or enterocytes. Accordingly, high hepcidin levels inhibit duodenal iron absorption and cause macrophage iron retention whereas hepcidin deficiency promotes ferroportin expression and increases circulating iron levels[4,6].

Alterations of hepcidin expression thus determine the availability of iron for erythropoiesis and centrally underlie the pathophysiology or the metabolic consequences of specific anemias.

Inflammation results in profound alterations of iron homeostasis, which are characterized by low circulating iron and increased ferritin levels, which frequently lead to the development of anemia , termed as anaemia of chronic disease (ACD)[7] or anemia of inflammation. ACD is thus found in patients with immunity associated diseases such as infections, cancer, auto-immune disease, congestive heart or renal failure[5]. However, recent evidence indicates a high prevalence of this anemia in patients with other chronic disorders, such as chronic obstructive pulmonary diseases, diabetes, obesity or congestive heart failure.

Three major pathophysiology pathways underlie the development of ACD which are all linked to iron homeostasis and inflammation.

First, inflammatory mediators and cytokines results in a diversion of iron trafficking and tissue iron distributions which results in iron limitation for erythropoiesis and subsequent development of anemia. Hepcidin, which can be induced by stimulation with inflammatory cytokines such as interleukin (IL)-1 or IL-6 but also LPS, is a central mediator of inflammation driven iron diversion[8]. Increased inflammation driven hepcidin levels then block iron re-circulation from macrophages but also dietary iron uptake by duodenal erythrocytes[6]. Iron homeostasis in the course of inflammation is further affected by hepcidin-independent but cytokines or lipopolysaccharide inducible mechanisms. Cytokines such as IL-1, IL-6, IL-10 or tumor necrosis factor (TNF) promote the uptake of iron into macrophages by different pathways including stimulation of erythrophagocytosis, and then increase iron storage and incorporation into ferritin[9-11]. The increased erythrophagocytosis is not only a consequence of immune driven expression of erythrocyte receptors such as Tim-4 on macrophages but also based on erythrocyte mediated damage and a subsequent reduction of erythrocyte half life which is hypothesized to result from inflammation driven radical formation[7,12]. In parallel, iron export via ferroportin is blocked transcriptionally and posttranslationally, either by interferon-gamma (IFNg) and LPS mediated blockade of ferroportin transcription as well as by degradation of ferroportin on the cell surface by circulating and macrophage derived hepcidin which acts in an autocrine fashion[4,9,13]. All these events lead to a blunted dietary iron absorption and iron retention in macrophages which is reflected by low circulating iron (hypoferremia) and normal or increased ferritin levels.

Second, inflammation negatively affects the formation and biological activity of the major red cell hormone erythropoietin. This is on the one hand due to reduced renal expression of the hormone caused by inhibitory cytokines such as TNF and IL-1 and, on the other hand, linked to reduced erythropoietin receptor expression on erythroid progenitors and limited availability of iron[14-16].

Third, cytokines and most specifically type I and II interferons, as well as inflammation inducible radicals inhibit the proliferation and differentiation of erythroid progenitor cells by multiple mechanisms including ceramid induced apoptosis, radical mediated cellular damage or suppression of heme biosynthesis. The reduced availability of iron and blunted activity of erythropoietin further contribute to dyserythropoiesis in the setting of inflammation[17,18].

Additionally, ACD can be aggravated by concomitant deficiencies in cobalamine, folic acid or vitamin D, the latter has been found to negatively affect hepcidin expression, thereby increasing circulating iron levels and ameliorating anemia. Moreover, renal insufficiency, hemolysis, bone marrow infiltration by parasites and tumor cells as well as side effects of medications and thus far poorly characterized polymorphisms in iron genes can contribute to the severity of anemia[19-21].

Because anemia results in hypoxia and impairment of organ functions a number of counterbalancing pathways are induced to correct anemia or to overcome iron retention in ACD. Reduced oxygen tension of the tissue induces the formation of erythropoietin in the kidney following activation and stabilization of hypoxia inducible factors (HIFs). The underlying mechanisms is hypoxia mediated inhibition of prolyl hydroxylases (PDH) which mediate rapid degradation of HIFs[22]. HIFs do not only stimulate erythropoietin production but

also increase duodenal iron absorption by inducing ferroportin expression, but HIF stabilization also negatively affects hepcidin formation which is mediated via HIF inducible erythropoietin production[23,24]. This is at least in part mediated by erythroferron, a recently identified bone marrow derived erythropoiesis inducible peptide, which blocks hepcidin expression in the liver and thus increases iron availability for erythropoiesis[25]. In addition, hypoxia stimulates the expression of platelet derived growth factor-BB which also inhibits hepcidin transcription, thereby increasing iron availability for erythropoiesis[26]. However, the definition of role of these factors for the pathogenesis of ACD and their therapeutic potential awaits further elucidation.

Given that ACD is that prevalent, the question arises on the possible benefit resulting from anemia. Mainly, the inflammation mediated diversion of iron trafficking is considered to result from a defense strategy of the body to limit the availability of the essential nutrient iron to invading pathogens. Of note, recent evidence suggests that different regulatory mechanisms are activated following exposure of the organisms to circulating versus intracellular microbes[27]. While hepcidin mediated iron retention in macrophages appears to be beneficial to reduce the availability of this microbial nutrient for circulating bacteria[28], the opposite appears to be true for the host defense against intracellular bacteria residing within macrophages[29]. Hereby, macrophages increase iron export from cells via stimulation of ferroportin expression to reduce intracellular iron availability for microbes and thereby bypassing hepcidin mediated metabolic responses[30] whereas intracellular bacteria such as Salmonella stimulate hepcidin formation via estrogen receptor activation to secure a sufficient supply of iron for their growth[31]. Even the reduced activity of erythropoietin appears to exert beneficial immune-modulatory effects in the setting of infection, given that erythropoietin acts as an anti-inflammatory cytokine, and the reduced erythropoeitin availability in ACD results in promotion of anti-microbial host responses[32].

Thus, ACD is an immune driven disease, which mainly develops upon inflammation mediated mechanisms which have developed during evolution to limit the availability of the essential nutrient iron for invading pathogens or rapid proliferating tissues. This has to be kept in mind when treating ACD and when trying to overcome iron retention.

Based on our expanding knowledge on the central role of hepcidin in the pathophysiology of inflammatory anemia, attempts have been undertaken to indirectly or directly target hepcidin production. It is well known that treatment of the underlying disease and recurrence of inflammation often cures ACD. Accordingly, treatment of patients with different rheumatic diseases with the IL-6 antagonist toculizumab not only reduced IL-6 levels and disease symptoms but also reduced hepcidin levels and improved hemoglobin levels[33].

In addition drugs have been developed which either bind or neutralize hepcidin (antibodies, spiegelmers, anticalins) or block hepcidin formation by interfering with the hepcidin inducing signalling cascade[34-36]. Some of these drugs are currently in clinical phase I and II studies and the results of these studies in terms of their effects on the correction of ACD as well toward their impact on the disease underlying ACD are awaited.

However, before initiation of any treatment of anemia and specifically of ACD, a carefully diagnosis of anemia has to be performed not only to rule out other factors which contribute to anemia but also to define the degree of iron deficiency in this setting which can be functional or absolute. This is of importance because, depending on the underlying disease, 20-80 percent of patients with ACD can suffer from concomitant true iron deficiency originating from disease associated bleeding as in inflammatory bowel disease or based on iatrogenic (repetitive blood drawing, dialysis etc.) or physiological (menses) blood losses in association with an inflammatory disease[7]. This differential diagnosis is essential because patients with inflammatory anemia and absolute iron deficiency need iron supplementation which is mostly not indicated in patients with ACD alone. Because many laboratory markers are affected by inflammation, the determination of iron availability for erythropoiesis in this setting is often cumbersome. Several parameters including red cell indices, different iron metabolism parameters and combinations have been introduced with limited success as detailed elsewhere[37-39]. Thereby, hepcidin turned out to be a promising parameter for the iron needs for erythropoiesis because it appears that iron deficiency effectively reduced hepcidin formation thereby overcoming the stimulatory effect of cytokines in its expression[40,41]. Accordingly,

patients with ACD and true iron deficiency had significantly lower hepcidin levels than subjects with ACD alone[6]. Meanwhile, numerous methods for hepcidin determination have been introduced into clinical practice, thereby enabling its broad clinical use[5,42]. Prospective studies have to find out if hepcidin alone or in combination with other parameters (red cell indices) is a useful tool to correctly diagnose ACD patients and to choose the most appropriate therapy.

On the other site of the coin, hepcidin deficiency may cause harm in certain settings of anemia. Hepcidin reduction by erythropoietic factors is a counter-regulatory mechanism of the body to increase iron absorption and iron re-circulation from macrophages to increase the availability of the metal for the erythron in the setting of iron deficient anemia[43]. Hepcidin expression is thereby reduced by low circulating iron levels, but also by erythropoiesis derived factors such as GDF-15 or erythroferron[25,44], or hypoxia inducible proteins, such as PDGF-BB[26].

However, in subjects with insufficient erythropoiesis originating from hemoglobinopathies, tissue hypoxia and anemia erythropoietic similar signals which block hepcidin expression. This increases the circulating iron levels in the body, but iron cannot be utilized due to the defect in hemoglobin synthesis. As a consequence, such patients, including subjects with sickle cell anemia, thalassemia major or other congenital dyserythropoietic and inherited nonsyndromic sideroblastic anemias[14,45], develop severe iron overload over time.

Iron accumulating in tissues then catalyzes the formation of toxic radicals which results in cellular and tissue damage and organ failure over time, being a major factor contributing to in reduced life expectancy of such patients if not properly treated by iron chelators[46]. As an alternative to this treatment, it appears attractive to restore hepcidin function in order to avoid iron loading. Minihepcidins, which are small peptides, containing the ferroportin binding moieties of hepcidin, have been successfully used in experimental animal models and may hold promise as a new tool to treat such patients and to avoid life debilitating toxic iron accumulation[47].

Declaración de conflictos de interés:
El autor declara que no posee conflictos de interés.

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