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Review article

Anemia of chronic disease: A unique defect of iron recycling for many different chronic diseases

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ABSTRACT

Anemia of chronic disease (ACD) is frequently observed in patients with chronic diseases as a significant contributor to morbidity and mortality, which can aggravate the severity of symptoms of the underlying inflammatory status. The pathophysiology of ACD is multifactorial, including three mechanisms: shortened erythrocyte survival, impaired proliferation of erythroid progenitor cells, and abnormalities of iron metabolism. These mechanisms are "immune and inflammation"-driven, but several other factors, including chronic blood loss, hemolysis, or vitamin deficiencies, can aggravate anemia. All the abnormalities of iron metabolism observed in ACD can be explained by the effect of hepcidin upregulation. Hepcidin is a small liver peptide, that inhibits the cellular macrophage efflux of iron and intestinal iron absorption, binding to ferroportin and inducing its internalization and degradation. In ACD the synthesis of hepcidin is upregulated by increased inflammatory cytokines, causing the two main principal features: the macrophage iron sequestration and the iron-restricted erythropoiesis. ACD is the most complex anemia to treat. The recommended approach is the treatment of the underlying disease, which can lead to a major improvement or even resolution of ACD. Currently available treatments (transfusion, iron, and erythropoiesis-stimulating agents) can ameliorate anemia, but a considerable percentage of non-responders exist. On this evidence new treatment strategies might arise from the knowledge of the pathophysiology of ACD, in which hepcidin plays the central role. Prospective studies are needed to evaluate the safety and the efficacy of the new emerging treatments, which modulate hepcidin expression through different mechanisms.

1. Introduction

The terms anemia of chronic disease (ACD) or "anemia of inflammation" are used interchangeably to indicate an acquired condition that is commonly observed in the clinical settings of a wide variety of diseases, including infections, inflammatory conditions and malignancies (Table 1) [1,2].

ACD is the second most prevalent form of anemia after iron deficiency anemia (IDA) [3], and occurs in patients with chronic immune activation [2,4–6], mainly in hospitalized patients [7].

The incidence and prevalence of anemia increase with advancing age: up to 26.1% in men and 20.1% in women aged 85 years and over [8]. In this context low hemoglobin levels can be a marker of an underlying chronic disease even in absence of influence on health. Generally, the causes of anemia in the elderly can be divided into three groups: nutrient-deficiency anemia (34%), ACD (20%), and unexplained anemia (34%) [9,10]. Gastrointestinal blood loss is the primary cause of iron-deficiency anemia in older adults, even if anemia in the elderly is often not linked to a single cause, but generally related to several factors, including: chronic renal insufficiency, sex hormone deficiency, bone marrow failure and metabolic diseases. The cause of ACD in the elderly has not yet completely clarified and it seems more plausible that the oxidative stress that accompanies the evolution of our life is responsible of ACD [11]. Elderly individuals affected by ACD have a fivefold increase in mortality risk and hospitalization, as confirmed by a large prospective population-based study performed between 2003 and 2007 [12].

ACD is usually a mild-moderate (hemoglobin level 8–9.5 g per deciliter), normochromic, normocytic anemia, characterized by low iron and normal-low transferrin levels with normal or increased ferritin. The reticulocyte count is low as expression of underproduction of red cells, while the hypoferremia is due to acquisition of iron by the reticular endothelial system (RES). The consequence of decreased levels of serum iron is the reduction of transferrin saturation. If IDA and ACD coexist, transferrin saturation may be even lower. Ferritin levels are normal or increased in patients with ACD, reflecting increased storage and retention of iron within the RES, along with increased ferritin levels due to immune activation.

The anemia can become microcytic and tends to be more severe in presence of concomitant IDA. In this context the levels of the concentration of soluble transferrin receptor, a truncated fragment of the membrane receptor usually increased in iron deficiency, can be helpful [13].

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Table 1
The most common causes of ACD. The prevalence is estimated and shown as range. Modified from Weiss 2005 [1].

Disease	Prevalence (%)
Infections (acute and chronic)	18–95
Cancer (hematologic and solid tumors)	30–77
Autoimmune disorders	8–71
Chronic kidney diseases	23–50
GvHD after solid-organ transplantation	8–70

The correlation between chronic inflammation, anemia and iron was recognized over 50 years ago [14], but only in the last decade the antimicrobial peptide hepcidin has emerged as the key hormone regulatory of the iron homeostasis involved in causing the anemia in chronic diseases [15]. Since the identification of the iron regulatory hormone hepcidin, our understanding of the molecular pathway of iron metabolism has increased dramatically. Genetic defects leading to hepcidin deficiency cause iron overload associated with hereditary hemochromatosis [16]. Conversely, overexpression of hepcidin leads to severe iron deficiency and a fatal anemia in transgenic mice [17]. Substantial progress has been made recently into elucidating the mechanism of action of hepcidin, and the link between hepcidin and inflammation is now evident [15].

The prototypical type of ACD is the anemia observed in patients with rheumatoid arthritis (RA) [1,18]. Generally, the prevalence of anemia in chronic rheumatic diseases is high, and in RA the development of anemia is associated with more advanced stage of the disease [1,19], and is more common in women than in men [20]. ACD can be found also in children affected by the juvenile form of RA, called juvenile idiopathic arthritis, characterized by a systemic disease more than in patients with involvement of only single joints [19,21].

2. Pathophysiology

The pathogenesis of ACD is complex and multifactorial, linked to the underling chronic disease, but mainly due to alterations in iron balance, derived from the immune activation.

At least three major immune-driven mechanisms contribute to the development of ACD:

1. the reduction in the lifespan of erythrocytes;
2. the impaired proliferation of erythroid progenitor cells;
3. the increased uptake and retention of iron within cells of the reticuloendothelial system (RES) [1,3].

The molecular basis of ACD involves cytokines and acute phase proteins that affect the regulation of iron homeostasis and erythropoiesis, but several other factors, including hemolysis, disease and treatment-associated adverse events or vitamin deficiencies can also influence the development of anemia. In addition, the prevalence of anemia can be influenced by other factors not linked to the underlying disease, such as age or gender; and, in particular, an increased prevalence of multifactorial anemia is found in elderly patients [22,23].

2.1. The reduction in the lifespan of erythrocytes

The mechanism underlying the reduction in the lifespan of erythrocytes is the most difficult aspect in the pathophysiology of ACD to clarify.

In 1966 Cartwright and Wintrobe demonstrated a modest reduction of erythrocyte survival lifespan in ACD [2]. This reduction seems not due to an intrinsic defect of the red cell, as the survival of red cells from patients with ACD is normal when the red cells are infused into normal subjects. The underlying mechanism is not yet fully understood and probably other factors are involved and necessary to explain the degree of anemia. Most recently, it was suggested that elevated concentrations of inflammatory cytokines, such as interleukin-1 (IL-1), produced by activated macrophages as observed in patients affected by RA, could enhance the ability of macrophages to ingest and destroy red cells [24], particularly through a selective hemolysis of newly formed erythrocytes [25].

2.2. The impaired proliferation of erythroid progenitor cells

In ACD the proliferation and differentiation of erythroid precursors are impaired [6] for two main reasons: the reduced or impaired erythropoietin (EPO) production, and the inhibitory effect on bone marrow by inflammatory cytokines.

EPO is the most important erythropoiesis-inducing hormone. During inflammation EPO expression is decreased or inadequate for the degree of anemia [26,27]. The reduced level of EPO is at least in part due to the cytokine-mediated formation of reactive oxygen species (ROS), which in turn affects the binding affinities of EPO-inducing transcription factors and also damages EPO-producing cells. Studies *in vivo* have demonstrated that the injection of lipopolysaccharide (LPS) into mice results in reduced expression of EPO mRNA in kidneys and decreased levels of circulating EPO [28]. A reduced EPO activity can promote iron retention in the reticular endothelial cells because EPO and stressed erythropoiesis have been identified as important negative regulators of hepcidin production [29,30].

In addition, the overproduction of inflammatory cytokines, such as interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and interferon-γ (IFN-γ) [1] can influence the growth of erythroid burst-forming units and erythroid colony-forming units [6]. Interestingly, IFN-γ seems to be the most potent inhibitor, that can also reduce the responsiveness of erythroid progenitor cells to EPO decreasing EPO-receptors on erythroid progenitor cells [31].

Moreover, cytokines, including IFN-γ and TNF-α, may directly damage the erythroid progenitors by inducing the formation of labile free radicals, such as nitric oxide or superoxide anion [32], decreasing erythrocyte half-life and promoting erythrophagocytosis [33]. Patients with RA have reduced numbers of erythroid burst-forming units and hemoglobin levels, which inversely correlate with the circulating concentration of TNF [18,34]. Anti-TNF administration rescues erythroid-progenitor-cell proliferation and reduces apoptosis of these cells *in vitro* [35] and *in vivo* [34], confirming the correlation between TNF, anemia and defective erythropoiesis in patients with RA. Interestingly, in some patients with systemic lupus erythematosus (SLE), autoantibodies against EPO were detected in association with decreased circulating EPO levels and the development of anemia [36].

In addition, a possible role of hepcidin (see above) as inhibitor of erythroid colony formation *in vitro* has been demonstrated although the mechanisms are still undefined [37].

2.3. The increased uptake and retention of iron within cells of the reticuloendothelial system

The diagnostic feature of ACD is hypoferremia in the setting of adequate or increased iron stores [2] due to an impaired iron mobilization with an increased uptake and retention of iron within the cells of the RES. This diversion of iron from the circulation into storage sites of the RES leads to a limitation of the availability of iron for the erythroid progenitor cells and, as a consequence, to an iron-restricted erythropoiesis. The main actor involved in this pathophysiological mechanism is hepcidin.

2.3.1. Hepcidin

Hepcidin is a small liver peptide that acts as a systemic iron-regulatory hormone by regulating iron transport from tissue to plasma and it responds to body iron status, hypoxia and inflammation [15]. It was independently isolated from plasma by Krause et al. [38] and from human urine by Park et al. [39]. Since this peptide was mainly produced by hepatocytes and had antimicrobial effects, it was firstly termed liver-expressed antimicrobial peptide-1 (LEAP-1), and later hepcidin.