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Anemia of Chronic Disease: Epidemiology and Pathophysiological Mechanisms – Literature Review

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Abstract-- Anemia of chronic disease (ACD), also known as anemia of inflammation (AI), is the term used to describe the hypoproliferative anemia. ACD was demonstrated in several conditions including systemic inflammation, acute and chronic infections of bacterial, viral, parasitic or fungal etiologies, cancer and hematological malignancies, chronic diseases such as chronic kidney disease and congestive heart failure, in addition to ageing, graft versus host disease after solid-organ transplantation, critical illness, and obesity. As a result of the possible different etiologies, the pathogenesis of ACD is complex with multiple pathways.

Although the relationship between anemia, chronic inflammation and iron was discovered decades ago, only recently did research describe the role of several pro-inflammatory cytokines, in addition to molecular pathways and the type II acute-phase protein hepcidin involving iron absorption and metabolism, helping in the understanding of new pathophysiological mechanisms which were not previously understood that can lead to ACD. Hence, our understanding of the molecular mechanism related to intestinal iron absorption and metabolism has improved significantly.

The pathophysiology of ACD is thought to be due to three main processes including a decreased erythrocyte survival that creates a demand for a mild increase in bone marrow production of erythrocytes, inability of the bone marrow to respond to the required increased demand due to an altered erythropoietin production or impaired ability to respond to erythropoietin by erythroid progenitor cells and alteration in iron stores' mobilization through increased uptake and retention of iron in cells of the reticuloendothelial system.

Lately, research advances including hepcidin's discovery contributed to our understanding regarding iron metabolism and pathophysiological mechanisms in ACD. However, future research remains essential in order to find potential therapeutic strategies, possibly targeting genes coding cytokines to discover optimal therapies in treating ACD more efficiently.

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1. INTRODUCTION

Anemia of chronic disease (ACD), also known as anemia of inflammation (AI), is the term used to describe the hypoproliferative anemia that was initially thought to be due to chronic infections, inflammation or malignancies. However, several other conditions were also found to be associated with ACD such as obesity, ageing, diabetes mellitus, kidney failure, congestive heart failure, critical illness, severe trauma and autoimmune disease (1). Due to the different possible etiologies, the pathogenesis of ACD is complex involving several pathways.

ACD which occurs mainly in hospitalized patients, is the second most common form of anemia following iron deficiency anemia (IDA) (2, 3). It is commonly defined as a mild to moderate, normochromic, normocytic anemia due to inadequate erythrocyte production, associated with low serum iron concentrations, normal-low transferrin levels despite preserved or even high macrophage iron stores in the bone marrow, in addition to normal or increased ferritin levels demonstrating high storage and retention of iron in the reticular endothelial system (RES) as well immune activation related factors (4). Moreover, reticulocytes are reduced expressing an underproduction of red blood cells (RBC). Furthermore, disproportionate reduction in erythropoietin levels and increased inflammatory markers such as C-reactive protein (CRP) can also be found in ACD (5). **Figure 1** illustrates the serum levels in ACD.

The relationship between anemia, chronic inflammation and iron was discovered decades ago (6). However, only recently did research describe the role of several pro-inflammatory cytokines, in addition to molecular pathways involving iron absorption and metabolism helping in the understanding of new pathophysiological mechanisms which were not previously understood that can lead to ACD. The

Figure 1. Serum levels in anemia of chronic disease.
CRP – C-reactive protein.

type II acute-phase protein hepcidin was recently identified, a peptide produced by the liver, as a central regulator of iron absorption in the intestines and macrophages iron recycling, leading to iron restricted erythropoiesis and ACD due to its exerted effects (7). Hence, our understanding of the molecular mechanism related to intestinal iron absorption and metabolism has improved significantly. It has been demonstrated that genetic disease associated with hepcidin deficiency can lead to hereditary hemochromatosis due to iron overload (8). On the other hand, an increase in hepcidin expression can cause anemia (9). Lately, significant progression in research evaluating hepcidin's role, mechanism of action and its association with inflammation has been reported (10).

Observing that the degree of ACD was related to the associated disease activity prioritized the search for mutual pathophysiologic mechanisms associating ACD with pathologies from different sources, while considering several immune and inflammatory response mediators (11-13). These include overproduction of cytokines including tumor necrosis factor alpha (TNF-α), interleukin 1 (IL-1) and interleukin 6 (IL-6) by macrophages, as well as interferon gamma (IFN-γ) by lymphocytes that have been linked to ACD (14-18). These cytokines in addition to hepcidin play a pivotal role in the inhibition of iron release from the marrow macrophages to the budding erythroid progenitors (19). Moreover, modulation of translation or transcription of genes involved in iron homeostasis can be induced through cytokines (20).

In the present review, we shed the light on recently published research describing the epidemiology as well as the complex and intertwined pathophysiological mechanisms associated with ACD. We believe that this review is of great significance due to the potential therapeutic implications that are based on a better understanding of the pathophysiological pathways which can be targeted, therefore achieving a rapid resolution of anemia, in addition to reducing the associated morbidity and mortality as well as improving the patient's quality of life (21, 22).

2. EPIDEMIOLOGY

Although ACD is specifically common in hospitalized patients and is the second most common anemia globally following IDA, the exact prevalence remains unknown (18). It

is mainly due to infections and nutritional deficiencies. However, it remains challenging to distinguish the cause of ACD in subjects with inflammatory diseases because of the multifactorial and complex associated mechanisms. **Table 1** summarizes the common causes associated with ACD (18, 23).

Table 1. Underlying Common Causes in Anemia of Chronic Disease

Diseases Associated with Anemia of Chronic Disease
Infections (acute and chronic infections – viral, bacterial, parasitic, fungal)
Malignancies (hematological, solid tumors)
Systemic inflammatory disorder and immune-mediated diseases (rheumatoid arthritis, systemic lupus erythematosus and related conditions, vasculitis, sarcoidosis, inflammatory bowel disease)
Chronic disorders (congestive heart failure, chronic obstructive heart disease, chronic kidney disease)
Graft versus host disease after solid-organ transplantation
Anemia of the elderly
Obesity
Anemia of critical illness

2.1 Systemic Inflammatory Disorders

Systemic inflammatory disorders such as rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, vasculitis, systemic sclerosis or sarcoidosis can present with ACD. Several studies reported the prevalence of anemia in such conditions between 8 to 71% (18, 24-27). Moreover, the prevalence of anemia in rheumatoid arthritis patients was estimated to range between 33 to 60 % (28).

2.2 Infections

Acute and chronic infections of bacterial, viral including human immunodeficiency virus (HIV) infection, parasitic or fungal etiologies can lead to systemic inflammation and anemia which is linked to the severity of the disease with an estimated prevalence between 18 to 95% (18, 25, 29, 30).

2.3 Cancer and Hematological Malignancies

Although bone marrow infiltration by an abnormal cell population that is characteristic of hematologic malignancies such as lymphoma and multiple myeloma is more likely to lead to anemia, other solid tumors without bone marrow involvement can also cause anemia (31). Cancer-related anemia is usually multifactorial with different types of anemia such as ACD and IDA, in addition to causes including bone marrow infiltration as well as iron and vitamin deficiencies. The range of anemia in cancer patients is between 30 to 77% (18). The European Cancer Anemia Survey (ECAS) is a prospective study involving 15,367 European cancer patients with a follow-up period for up to 6 months (32). The study estimated the prevalence of anemia (hemoglobin <12 g/dL) at enrollment at 39.3%, which reached up to 67% during the survey follow-up. A recent prospective observational study involving 888 patients with different carcinoma types reported that anemic patients were 63.4%, while the degree of anemia was based on the severity of the cancer and performance status (33).

2.4 Chronic Disorders

Several chronic diseases including congestive heart failure and chronic obstructive pulmonary disease (COPD) can lead to ACD (34). Although chronic kidney disease (CKD) is mainly characterized by erythropoietin deficiency, it can also be associated with ACD (35-37).

2.5 Anemia of the Elderly

ACD accounts for approximately one-third of the anemia cases in the elderly. This is often due to associated concomitant inflammatory conditions or CKD (34). A recent study conducted on 191 consecutively hospitalized elderly subjects reported that ACD was found in 77% of the patients, out of which 71% had an acute infection, 17% had cancer, 16% had a concomitant renal failure and 16% had chronic infectious process or autoimmune inflammatory disease (38).

2.6 Graft versus Host Disease after Solid-Organ Transplantation

Several studies reported that patients that develop chronic rejection after solid-organ transplantation present with anemia ranging between 8 to 70% (18, 39, 40). A study conducted on 60 patients who were evaluated for 5 years following heart transplantation reported that 72% of the patients were anemic (41).

2.7 Anemia of Critical Illness

A prospective, multiple center, observational cohort study of intensive care unit (ICU) patients involving 4,892 subjects across the United States demonstrated a reduction in mean hemoglobin levels despite receiving blood transfusions (42). Moreover, they reported that increased mortality and length of stay were independently predicted by a nadir hemoglobin <9 g/dL.

2.8 Obesity

A newly emerging area of interest is the intertwining of obesity and metabolic alterations, conditions that are associated with an increased prevalence worldwide, in addition to chronic inflammation with anemia (43, 44). It has been reported that obese subjects present with elevated levels of pro-inflammatory cytokines, acute phase reactants and increased iron-restricted erythropoiesis, possibly leading to anemia (45). A recently conducted cross-sectional study involving 947 consecutive bariatric surgery candidates demonstrated that 52.5% of the involved subjects presented functional iron deficiency defined by ferritin levels between 12-100 ng/mL for female subjects or 15-100 ng/mL for male subjects and serum CRP levels >3 mg/L (46). Moreover, a study involving 178 morbidly obese females selected for bariatric surgery reported the presence of iron depletion, suggesting that low-grade inflammation can possibly be a modulator of iron uptake and metabolism in obese subjects. Furthermore, they concluded that bariatric surgery can lead to an improvement in iron status and reduction in chronic inflammation (47).

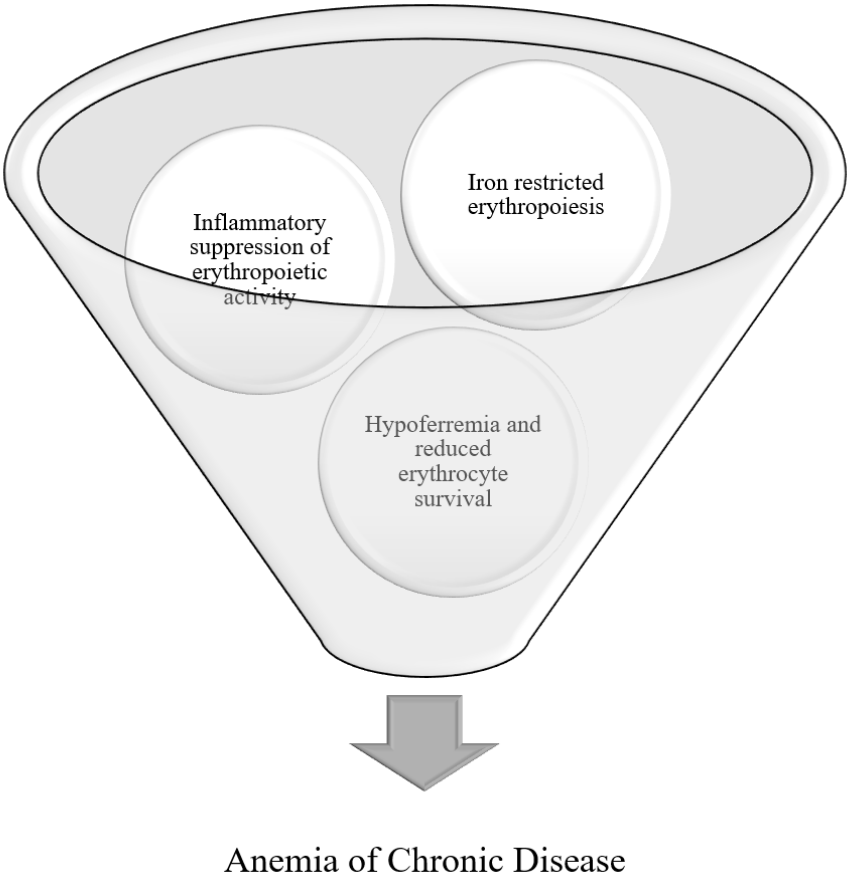

Figure 2. Pathophysiological mechanisms involved in anemia of chronic disease.

3. PATHOPHYSIOLOGY

Although ACD is caused by several complex and multifactorial pathways according to the etiology of the underlying disease, individual factors may also influence the progression of anemia. It is typically a result of immune activation resulting in iron balance dysregulation (10). The development of ACD is proposed to be due to three main processes as described in **figure 2** including a decreased erythrocyte survival that creates a demand for a mild increase in bone marrow production of erythrocytes, inability of the bone marrow to respond to the required increased demand due to an altered erythropoietin production or impaired ability to respond to erythropoietin by erythroid progenitor cells and alteration in iron stores' mobilization through increased uptake and retention of iron in cells of the reticuloendothelial system (13). In case of infection, it is thought that ACD results from the body's evolutionary defense mechanisms limiting the available iron for invading microbes.

Cytokines and acute phase reactants are the molecular basis involved in ACD though exerting effects on the regulation of erythropoiesis and iron hemostasis. **Figure 3** describes how cytokines affect iron metabolism and erythropoiesis (19). Nevertheless, several other factors such as vitamin deficiencies, hemolysis, diseases and treatment-associated adverse events, in addition to age or gender can impact anemia development and progression (10, 48, 49).

3.1 Decreased Erythrocyte Lifespan

Decades ago, it has been demonstrated in human studies that transfused erythrocytes of patients with ACD present a normal lifespan if transfused to a normal recipient (23). However, transfusing normal erythrocytes to a patient with ACD was associated with a reduced lifespan suggesting an activation of macrophages leading to increased destruction of red cells.

Recent studies suggested several factors that can influence or lead to red cell survival shortening, a finding mainly present in an inflammatory setting. Increased macrophage activity is considered a minor influencing factor. However, erythrophagocytosis and hemolysis are suspected to play a critical role in the initiation of anemia in septic patients (34). Enhanced erythrophagocytosis by hepatic and splenic macrophages due to complement and antibody deposition on erythrocytes, as well as fibrin deposition causing mechanical destruction in the microvasculature and increased erythrophagocytosis because of macrophages activation are all factors that attribute to the shortening of the erythrocyte lifespan (50-52).

Moreover, immune cell activation and the production of various cytokines is induced by systemic inflammation. Lipopolysaccharide (LPS), IL-6 and interleukin-1β (IL-1β) are potent stimulators of hepcidin, the main regulator of iron hemostasis in the liver, while transferrin expression is

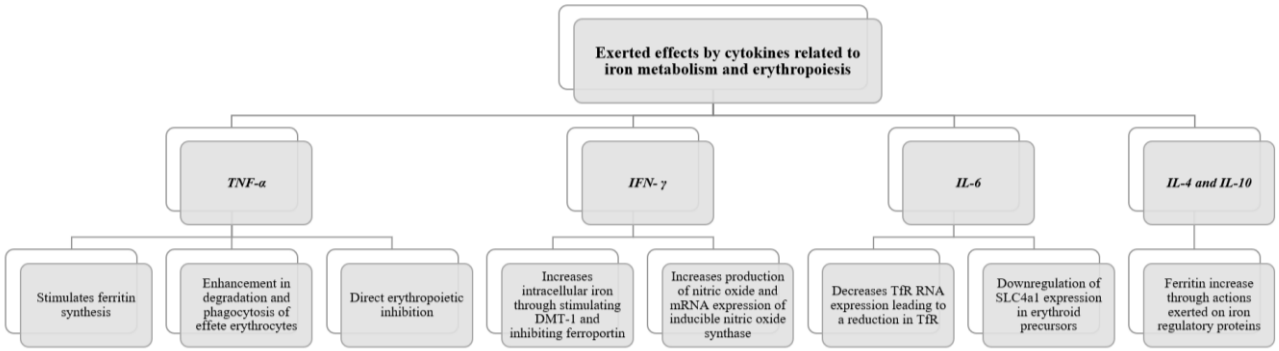

Figure 3. Exerted cytokine effects related to iron metabolism and erythropoiesis.
DMT-1 – Divalent metal transporter 1; **IFN-γ** – Interferon gamma; **IL-10** – Interleukin 10; **IL-4** – Interleukin 4; **IL-6** – Interleukin 6; **mRNA** – Messenger RNA; **TfR** – transferrin receptor; **TNF-α** – Tumor necrosis factor alpha.

reduced. Hepcidin leads to retention of iron in macrophages through degradation of ferroportin, the cellular iron exporter (34). Several cytokines including IL-1β, IL-6, IL-10, and interferon-γ (IFN-γ) enhance the uptake of iron by macrophages, in addition to increasing radical-mediated damage to red cells and macrophage ingestion. This process leads to efficient storage of iron due to a stimulation of ferritin production and inhibition of iron export through downregulation of ferroportin expression, resulting in hypoferremia and hyperferritinemia as typically seen in ACD (19, 53).

Conditions associated with increased cytokine activation such as critical illnesses, acute infections or severe sepsis induce a rapid anemia within a few hours to days. This is a quick process, therefore, presuming its attribution to a deficient erythropoiesis is not supported. It was noticed that activated macrophages produce cytokines leading to increased concentrations, hence enhancing the capability of macrophages to ingest and destroy erythrocytes (54). This process is emphasized in newly formed erythrocytes through a process of selective hemolysis (55). Thereby, premature elimination of aging erythrocytes is present, possibly explaining the predominant young erythrocytes seen in ACD.

Despite our current understanding of factors attributing to the reduction in red cell lifespan including increased macrophage activity, massive erythrophagocytosis, selective hemolysis, pooling of erythrocytes and hemodilution, the exact underlying mechanism remains to be fully understood as other influencing factors are probably involved (34, 56).

3.2 Reduced Erythropoiesis

In a normal situation, the body would respond to an increased destruction of red cells causing a transient anemia by an enhanced erythropoietin production, consecutive to a compensatory increase in erythropoiesis. However, ACD represents an inflammatory suppression of erythropoietic activity through inadequate proliferation and differentiation of erythroid precursors that can be described by several mechanisms including an altered erythropoietin effect and limitation of iron via cytokines and hepcidin (57).

The first mechanism can be described by an impaired marrow response due to reduced or impaired erythropoietin production, the most crucial erythropoiesis-inducing hormone. During states of inflammation, a reduced or inadequate expression of erythropoietin has been reported for the degree of anemia (58, 59). Low erythropoietin levels can be partially attributed to the formation of cytokine-mediated reactive oxygen species (ROS), which exert their effect by altering erythropoietin-inducing transcription factors' binding affinities as well as damaging erythropoietin producing cells. Furthermore, a downregulation of erythropoietin mRNA in kidneys, in addition to reduced circulating erythropoietin levels were reported in vivo studies after injecting lipopolysaccharide into mice (60). Iron retention in the reticular endothelial cells is enhanced by lower erythropoietin activity, mainly due to the production of hepcidin negative regulators including erythropoietin and stressed erythropoiesis (10, 61). Moreover, it has been demonstrated that high-dose erythropoietin administration in patients with CRP levels > 50 mg/L wasn't associated with the same increase in hemoglobin levels as compared to patients with CRP levels < 50 mg/L (62).

It has been reported that during the process of increased erythropoiesis, erythropoietin and hypoxia downregulate the formation of hepcidin through inducing erythroferrone, hypoxia inducible factor 1, platelet derived growth factor-BB or matriptase-2 growth differentiation factor-15, leading to an increased supply of iron (63-67). Therefore, the reduction in available erythropoietin and its activity can cause a negative impact inducing several hepcidin blockers including erythroferrone. Hence, worsening the hepcidin-mediated erythroid limitation of iron and impairing erythropoietin signaling (68).

Another mechanism is attributed to inflammatory cytokines such as IL-1, IL-6, TNF- α and IFN-γ exerting their inhibitory effects on hypoxia-mediated stimulation of erythropoietin through the interference of mediated GATA-2 or HNF4 transcription or leading to erythropoietin producing kidney epithelial cells destruction, as well as on the bone marrow through influencing the development of erythroid burst-forming units and erythroid colony-forming units (18, 57, 69, 70). It has been implied that IFN-γ exerts the most potent inhibitory effects by reducing the responsiveness of erythroid progenitor cells to erythropoietin through downregulating erythropoietin receptor expression (71). IFN-γ has also been demonstrated to block the differentiation of erythropoietin

receptor expression on erythroid progenitors through the stimulation of PU.1 expression, reduction of red cell lifespan and promotion of the production, differentiation and activation of leukocytes (72).

Despite the numbers of erythropoietin receptors that don't seem to be altered in patients with inflammatory anemia, it is linked to a reduced efficacy of erythropoietin-mediated signaling which is inversely associated with IL-1 and IL-6 circulating levels (73). This indicates the inflammation-driven hyperresponsiveness of erythropoietin receptors (34). Nevertheless, recently, it has been suggested that a commonly associated finding with ACD, erythroid iron deficiency, causes a reduction in erythropoietin receptors through an impairment of transferrin receptor-2 mediated iron sensing present in erythroid cells. This process leads to a reduction in erythropoietin receptor expression by an iron-mediated downregulation of Scribble (74).

Furthermore, in cases of severe infection, the presence of anemia can be reported within a few hours to days in an acute setting. This anemia can't be entirely attributed to iron retention due to inflammation or inhibition of erythropoiesis that would usually require longer durations to develop. Finally, inflammation, an important characteristic of ACD can induce a state of relative erythropoietin resistance and cytokine release impairing the proliferation of erythroid precursors (4).

3.3 Iron Restriction

A transitional step during heme synthesis involves the incorporation of iron into protoporphyrin IX, while zinc can act as an alternative protoporphyrin ligand (4). In case of iron deficiency, levels of incorporated zinc with protoporphyrin IX are elevated. Moreover, in ACD, levels of zinc protoporphyrin are elevated pointing out that insufficient amounts or iron are reaching to heme synthesis sites that would be utilized in the production of red cells causing zinc substitution (75). Furthermore, reduced sideroblast levels can also be seen in ACD.

Normally, approximately all the 20 to 25 mg of iron that enter the plasma are from recycling of macrophages' senescent erythrocytes, as well as iron storage in the liver. However, an inhibition of iron release from macrophages is present during inflammation (76-78). Moreover, only a small portion accounting for about 1 to 2 mg are retrieved from dietary iron. Despite the small amount of iron that is bound to transferrin which make up about 2 to 4 mg, iron in the plasma transits through this compartment with a turnover every few hours. Hypoferremia with normal or elevated iron stores is an important diagnostic finding in ACD which can be established within a few hours from inflammation onset (23). It is mainly due to the impairment in the mobilization of iron, in addition to increased iron retention and uptake within the RES which results in a shift of circulatory iron into storage sites. This leads to a condition where limited iron is available for utilization by erythroid progenitor cells and consequently iron-restricted erythropoiesis, mainly due to the role of the iron-regulatory hormone hepcidin that is induced by iron and inflammation and suppressed by tissue hypoxia (7, 79-81). Hepcidin is an essential amino acid required for normalization of the iron hemostasis process (82, 83). Hepcidin production by hepatocytes is positively regulated by iron stores and transferrin saturation, in addition to being negatively regulated by marrow erythroid activity (34, 63, 84). On the other hand, hepcidin deficiency is considered the main cause leading to hereditary hemochromatosis, a pathology associated with an altered iron absorption and release from stores (85-87).

Several changes in the mobilization and storage of iron can be induced by systemic immune activation, leading to iron storage in macrophages as well as reduced absorption of dietary iron. However, iron sequestration in macrophages is more critical for the iron cycle as more than 90% of daily iron needs for the synthesis of hemoglobin and erythropoiesis come from recycling of iron from senescent red cells by macrophages (84). Moreover, several cytokines are released by the immune system as a response to microbes, autoantigens or tumor antigens leading to an altered systemic iron metabolism.

It has been demonstrated that IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the hepcidin (88). Moreover, it has been reported that IL-6 was demonstrated to be a potent hepcidin inducer in hepatocyte cell cultures, predominantly through STAT3 (84). This essential role was confirmed in IL-6 deficient mice who weren't able to stimulate hepcidin as a response to turpentine inflammation (88). Moreover, IL-6 infusion in volunteer subjects was associated with an induction of hepcidin release and a simultaneous hypoferremia due to inhibition of iron release from macrophages (88). Therefore, IL-6 can be considered the main cytokine responsible for hypoferremia during inflammatory conditions. TNF- α was found to decrease the iron absorption in the duodenum in a hepcidin-independent manner (89). Moreover, IL-1, IL-6, IL-10 and TNF-α can stimulate iron storage in macrophages through different possible mechanisms including transferrin receptor–mediated endocytosis, divalent metal transporter 1, and increased iron acquisition by lactoferrin and lipocalin-2 (90). Furthermore, cytokines such as IL-1 and activin B can possibly induce the synthesis of hepcidin (91). However, their exact pathophysiological role remains unclear.

4. Conclusion and Future Directions

The interaction between inflammation, iron metabolism and erythropoiesis allowed us to have a better understanding regarding ACD which is considered to be a result of mildly decreased erythrocyte survival and iron sequestration which causes hypoferremia and reduced erythropoiesis, in addition to an inflammatory suppression of erythropoietic activity which is mainly due to several pro- and anti-inflammatory cytokines and hormones. Hepcidin is an essential amino acid required for the normalization of iron hemostasis.

Recent advances in the understanding of the pathophysiology in ACD may lead to several potential therapeutic strategies. Hepcidin's discovery significantly advanced our knowledge regarding iron metabolism, as well as provided potential new molecular targets. Moreover, future therapies should target genes coding cytokines involved in the pathophysiology of ACD. Furthermore, prospective, well-designed studies evaluating therapies associated with

improvements in morbidity and mortality are required in order to discover optimal therapies in ACD patients.

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