REVIEWS

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Hepcidin and Its Role in Inflammatory Bowel Disease

Hepcydyna i jej rola w nieswoistych zapaleniach jelit

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Abstract

Anemia is one of the most common extraintestinal symptoms of inflammatory bowel disease (IBD). The pathophysiology of anemia in IBD is complex. It may be developed in the course of inflammation, intestinal bleeding or disorders of iron absorption. Hepcidin, discovered in the year 2000, is an endogenous peptide responsible for iron homeostasis. Recent data suggests that hepcidin is a major mediator of anemia and plays a central role in iron homeostasis and metabolism. This paper presents information about hepcidin structure and function, mechanisms of the regulation of the synthesis and current data about the role of this hormone in IBD-related anemia. Assessment of hepcidin levels in patients with IBD may become a key element in the treatment of anemia in the near future (**Adv Clin Exp Med 2013, 22, 4, 585–591**).

Key words: hepcidin, inflammatory bowel disease, anemia.

Streszczenie

Niedokrwistość to jeden z najczęstszych pozajelitowych objawów nieswoistych zapaleń jelit (n.z.j.). Patomechanizm niedokrwistości w n.z.j. jest złożony i może być związany ze stanem zapalnym, krwawieniem do światła przewodu pokarmowego lub zaburzeniami wchłaniania żelaza. Hepcydyna, odkryta w 2000 r., jest endogennym peptydem odpowiedzialnym za homeostazę żelaza. Obecnie uważa się, że hepcydyna jest głównym mediatorem niedokrwistości i odgrywa kluczową rolę w metabolizmie żelaza w ustroju. W artykule autorzy przedstawiają informacje o strukturze i funkcji hepcydyny, mechanizmach regulujących jej syntezę oraz bieżące doniesienia na temat roli tego hormonu w rozwoju niedokrwistości w n.z.j. Ocena stężenia hepcydyny u pacjentów z n.z.j. może stać się w najbliższej przyszłości kluczowym elementem w podejmowaniu decyzji terapeutycznych i leczeniu niedokrwistości (**Adv Clin Exp Med 2013, 22, 4, 585–591**).

Słowa kluczowe: hepcydyna, nieswoiste zapalenia jelit, niedokrwistość.

Inflammatory bowel disease (IBD) are chronic diseases of the digestive tract, with unknown etiology encompassing Crohn's disease (CD) and ulcerative colitis (UC). Typical clinical manifestations of IBD involve gastrointestinal symptoms, e.g. diarrhea, bloody stools, abdominal pain and a course with periods of flares and remissions. Additionally, a significant part of IBD patients suffers from extraintestinal manifestations (EM) affecting different systems and organs. Some of them are related to the disease activity, e.g. erythema nodosum and peripheral arthritis. The special meaning of the systemic complications like malnutrition and anemia, whose development is influenced by the frequency and time of duration of flares, must be emphasized [1, 2].

It should be highlighted that the most frequent extraintestinal manifestation in IBD patients is anemia. Anemia is diagnosed in 10–73% of CD patients and in 9–67% of UC patients [3]. On the other hand, due to its frequent occurrence, anemia in the course of IBD, especially in hospitalized patients, has not been considered a serious EM but rather as a part of the clinical manifestation of

disease which cannot be avoided [4]. Recently, diagnosis and treatment of anemia is in the focus of interest. It was shown, that therapy of anemia positively influences the quality of life, social well-being and cognitive function of IBD patients [5, 6].

Anemia in IBD has a complex background. It combines features of iron deficiency anemia (IDA) and anemia of chronic diseases (ACD). Recently published studies suggest that a protein named hepcidin may play a key role in the regulation of iron metabolism.

Hepcidin

Hepcidin was described independently by two research groups (Krause in 2000 and Park in 2001) [7, 8] which identified this substance in urine as an antimicrobial protein belonging to the defensins [9]. Initially it was named LEAP-1 (liver-expressed antimicrobial protein-1). However, due to the place of synthesis in the liver ("*hep*-") and antimicrobial features ("*-cide*") the name was finally changed to hepcidin.

Hepcidin is a protein hormone responsible for the regulation of the homeostasis of iron in the bodies of humans and other mammals. The hepcidin gene (HAMP) is located on chromosome 19 and encodes a preprohormone built of 84 amino acids which, under the action of convertases and proteases, is converted to a hormone containing 25 amino acids and 8 cysteine residues, exported outside of the cell and finally detected in serum and urine. Beside hepcidin, it is also possible to detect its 60-aminoacid prohormone in the urine and serum.

The main source of the synthesis of hepcidin is the liver. Additionally, expression of the HAMP gene was found (although smaller) in macrophages, adipocytes, renal tubular cells, the mucosa of the stomach, small and large intestine, muscles, heart and lungs. [9, 10]. Hepcidin circulates in the serum in free form or in combination with β-2 microglobulin and is eliminated mainly with the urine. There are also smaller, 20- and 22-aminoacide peptides detected in urine, which are most probably the products of degradation and do not play any significant role in the body [9].

Until recently, the concentration of hepcidin and its precursor was evaluated in serum as well as in urine. However, it must be highlighted that the concentration of the hormones in urine largely depends on kidney function. Additionally, it was recently shown that the local synthesis of hepcidin in the kidneys is also possible [10].

Currently there are three methods of assessment of the concentration of hepcidin: mass spectrometry (MS), radioimmunological assay (RIA) and immunoenzymatic (ELISA). However, further studies to standardize the evaluation of hepcidin concentration and to describe the normal range of values, which can be used in clinical practice, are needed [10–12].

Mechanism of the Action of Hepcidin

Hepcidin is responsible for controlling the amount of circulating iron, protecting its loss in the cells by mechanism of the connection with ferroportin [10, 13]. Hepcidin is a direct inhibitor of the protein responsible for the transport of iron beside the cells which store it. Reactions which follow the connection of hepcidin to ferroportin lead to the internalization and degradation of this protein in lysosomes. With the removal of ferroportin from the cellular membrane, hepcidin inhibits cellular export of iron which in consequence leads to a reduction in the plasma pool of this element. The mechanism described has a special meaning in the cells of the small intestine where it leads to the retention of iron in enterocytes and its removal from the body with the exfoliating intestinal epithelium. A similar situation appears in macrophages, which are the main source of iron for erythropoiesis, and as a consequence of ferroportin internalization, become a trap for iron, recovered in the mechanism of phagocytosis from erythrocytes.

Hepcidin decides about the amount of ferroportin, a transporter for iron on the cell membrane of enterocytes, hepatocytes, phagocytic cells in the liver and spleen, and the placenta. Additionally, the availability of ferroportin in the cellular membrane in the above-mentioned cells is also regulated in the mechanism independent from hepcidin and related to iron regulatory proteins (IRP). When the amount of iron in cells is low, the expression of ferroportin decreases, which leads to the limitation of iron export [14].

Hepcidin influences the development of anemia not only with the mechanism of the elimination of ferroportin but also due to the direct inhibiting of the proliferation of the erythropoiesis cells and their survival time [15].

Hepcidin Synthesis Regulation

Synthesis of hepcidin is variable and regulated by the level of iron in the body. HEMP gene expression is also affected by factors directly independent of the body iron stores such as inflammation and hypoxia [16, 17].

The consequence of increasing the pool of iron in the body is to stimulate the production of hepcidin in the liver, which results inter alia in the inhibition of the intestinal absorption of this element. In the pathways responsible for the transmission of signals to stimulate HAMP gene expression, many proteins such as the HFE protein (high Fe), transferrin receptor (TfR1, TfR2), bone morphogenetic protein (BMP), hemojuvelin (HJV) and transferrin are involved.

Bone morphogenetic protein 6 (BMP6) plays a special role in regulation of the synthesis of hepcidin, dependent on the iron content in both the extracellular and intracellular form. After binding of this protein to a specific receptor on the surface of hepatocytes, it triggers a cascade of signals following which hepcidin gene transcription is stimulated. [18]. This pathway is modulated by a membrane protein called hemojuvelin (HJV), which enhances signal transmission from the BMP. The hemojuvelin expression within the cell membrane of hepatocytes and skeletal muscle is controlled by the serine protease, matriptase-2.

This enzyme, by cleaving to HJV, which is a cofactor for BMP-6, contributes to a decrease in the production of hepcidin. A mutation in the gene TMPRSS6, encoding protein matriptase-2, is the cause of iron-refractory iron deficiency anemia (IRIDA). Disorders in the synthesis of matriptase-2 cause increased expression of membrane HJV, which leads to excessive stimulation of hepcidin synthesis, resulting in a microcytic anemia with normal concentrations of iron in the body [19].

The regulation of the production of hepcidin, depending on the iron content in the body, is also affected by the previously-mentioned receptors TfR1 and TfR2, and HFE protein [20]. These receptors differ in location (TfR1 – most cells, TfR2 – mainly hepatocytes) and the degree of affinity for the transferrin-iron complex and HFE. Elevated concentrations of iron in the body trigger a series of complex reactions associated with these proteins, as a result of which, there is increased production of hepcidin in the liver. The mechanisms regulating the synthesis of hepcidin are shown in Figure 1.

Disorders in the production of hepcidin, resulting from mutations in genes involved in its synthesis, are a cause of hemochromatosis [21]. Both mutations in the HAMP gene, which is directly responsible for the synthesis of hepcidin, and the mutation of genes encoding proteins HFE, HJV and TfR2 lead to the occurrence of congenital hemochromatosis.

Hypoxia is a factor contributing to the inhibition of the production of hepcidin in the liver [17]. Hypoxia inducible factor 1 (HIF-1) is important in this mechanism, because its activity is dependent on the oxygen pressure in the body. In the case of hypoxia, increased HIF-1 activity releases a cascade of reactions that stimulate erythropoiesis and leading ultimately to the suppression of hepcidin production [22]. Erythropoietin, by binding to a specific receptor in the cell membrane of hepatocytes, also inhibits the expression of hepcidin. In addition, growth differentiation factor 15 (GDF15), secreted by erythroblasts in the final stage of erythropoiesis, suppresses hepcidin synthesis.

The most important factor in the synthesis of hepcidin, in the aspect of its relationship with anemia of inflammatory bowel disease, is the presence of inflammation. Inflammation is a factor stimulating the production of hepcidin and therefore reducing the circulating pool of iron in the body. The increase in hepcidin concentrations observed in the course of inflammation should be treated as a nonspecific defense mechanism aimed at restricting the availability of iron for microbial growth [23]. Anemia in chronic inflammation has a complex mechanism. Reactions caused by proinflammatory cytokines (TNF-α, IFN-α, IL-1 and IL-6) play a crucial role in infection and inflammation. The result of their actions is increased hepcidin synthesis, which leads to inhibition of intestinal iron absorption and sequestration in phagocytic cells. These cytokines also inhibit the proliferation of erythrocyte progenitor cells, worsening anemia. Interleukin 1 (IL-1) and interleukin 6 (IL-6) have a proven effect on HAMP gene expression and stimulating the synthesis of hepcidin [24]. This knowledge can be used in the near future for the treatment of anemia of chronic disease in patients with inflammatory bowel disease by the use of immunosuppressive drugs or biological therapy designed to suppress the production of proinflammatory cytokines. There are reports on the impact of the application of immunomodulator therapy for a significant improvement in the balance of iron in patients with IBD [25, 26]. In a study by Pastorelli et al., the authors did not comment on the importance of hepcidin, however it seems advisable to thinking that the use of biological treatment resulted in a normalization of inflammatory parameters, including a decrease in the level of proinflammatory cytokines and thus reduced hepcidin synthesis [25]. Bergamaschi et al. observed a stimulation of erythropoiesis in patients with anemia in the course of CD after applying a treatment with an anti-TNF-α antibody. The authors carried out only starting measurements of the prohepcidin concentration, which was higher in patients with ACD compared to the group with IDA [26]. The results of these reports confirm the need for further studies on this mechanism. Acknowledgment of the effect of

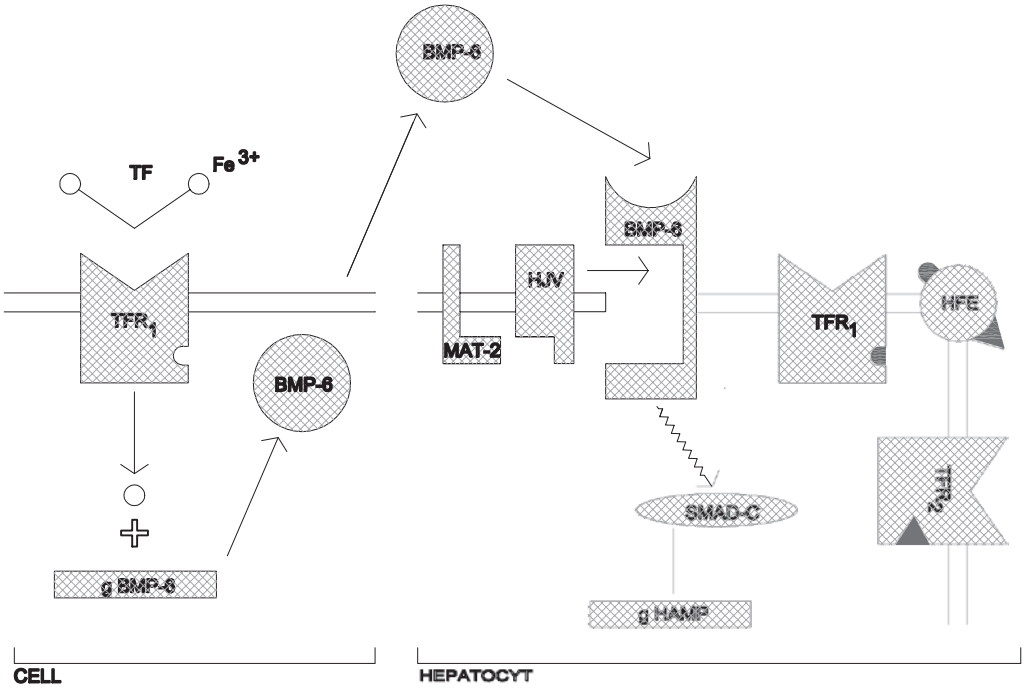

Fig. 1. Regulation of hepcidin expression. Synthesis of hepcidin is regulated by systemic iron availability. Iron transported in a complex with transferrin is binding to a transferrin receptor on a cell surface (TFR_1). This leads to iron internalization and stimulates expression of bone morphogenetic protein 6 gen (g BMP-6), the consequence of which is the synthesis of bone morphogenetic protein (BMP-6). Signal pathways associated with BMP-6 are modulated by hemojuvelin (HJV). On the surface of hepatocytes, HJV functions as a coreceptor for enhancing the signal transmission pathways for BMP. Matriptase-2 (MAT-2) located in the hepatocyte membrane can split HJV, which can lead to a decrease in hepcidin-production. Binding of BMP-6 to a specific receptor on the surface of liver cells (BMP-R) triggers a cascade of reactions involving signal proteins finally forming the SMAD complex (SMAD-C). SMAD-C translocates to the nucleus where it stimulates expression of the hepcidin gene (g HAMP). The HFE protein is present on the surface of hepatocytes and also has an impact on the synthesis of hepcidin. HFE is able to bind to various domains of the receptors for transferrin (TFR_1, TFR_2)

Ryc. 1. Regulacja ekspresji hepcydyny. Synteza hepcydyny podlega regulacji w zależności od ogólnoustrojowej puli żelaza. Żelazo transportowane w kompeksie z transferynę wiąże się na powierzchni komórki z receptorem dla transferyny (TFR1). Dochodzi do internalizacji żelaza i pobudzenia ekspresji genu białka morfogenetycznego kości (g BMP-6) następstwem czego jest synteza białka morfogenetycznego kości (BMP-6). Szlak sygnału związany z BMP-6 jest modulowany przez hemojuwelinę (HJV). HJV na powierzchni hepatocytów funkcjonuje jako koreceptor wzmacniając przenoszenie sygnału dla szlaku BMP. Matriptaza-2 (MAT-2) znajdująca się na powierzchni hepatocytów może rozszczepiać HJV, konsekwencją czego jest spadek produkcji hepcydyny. Przez związanie się BMP-6 ze swoistym receptorem na powierzchni komórek wątrobowych (BMP-R) zostaje wyzwolona kaskada reakcji z udziałem białek sygnałowych tworzących ostatecznie kompleks SMAD (SMAD-C). SMAD-C przemieszcza się do jądra komórkowego, gdzie stymuluje ekspresję genu kodującego hepcydynę (g HAMP). Na powierzchni hepatocytów znajduje się białko HFE, które również ma wpływ na syntezę hepcydyny. Białko HFE ma możliwość wiązania się z równymi domenami receptorów dla transferyny (TFR1 i THR2)

infection, and thus inflammation, to increase hepcidin production is the result of a study in which the authors have observed the effect of the injection of lipopolysaccharide (LPS) derived from the cell membrane of Gram-negative bacteria [27].

Hepcidin in Inflammatory Bowel Disease

The role which hepcidin may play in inflammatory bowel disease and IBD-related anemia has not been fully elucidated. Semrin et al. found out that the level of hepcidin in urine in CD was significantly higher in patients with active CD [28]. Level of hepcidin in urine positively correlated with a higher level of C-reactive protein (CRP) and interleukine-6 (IL-6) in patients with malabsorption of oral iron agents. Additionally, a higher level of prohepcidin in patients with active CD was observed. The level of the prohormone measured in serum correlated with Crohn's Disease Activity Index (CDAI), CRP and ferritin [26]. The concentration of prohepcidin was higher in patients with ACD as compared to patients with IDA, however

Table 1. Parameters of patients with IBD and controls compared with hepcidin/prohepcidin

Tabela 1. Parametry pacjentów z IBD i grupy kontrolnej porównane z hepcydyną/prohepcydyną

Publication (Publikacja)	Hormone (Hormon)		Studied group (n) (Grupa badana)			Statistical significance with (Istotność statystyczna z)
	ProHep.	Hep.	CD ChL-C	UC WZJG	HC ZO	
Semrin G et al. (2006) [28]	+	–	19	0	0	IL-6 p = 0.003 CRP p = 0.007
Arnold J et al. (2009) [29]	–	+	10	51	25	IBD/HC p = 0.005 IL-6 p = 0.0222
Bergamaschi G et al. (2010) [26]	+	–	22	17	29	IBD/HC p = 0.007 CRP p = 0.007 CDAI p = 0.033 sF p = 0.038
Nagy J et al. (2010) [31]	+	–	30	72	38	IBD/HC p > 0.05 CDAI p = 0.05 CRP p = 0.05
Kaya Z et al. (2010) [32]	+	–	15		14	IBD/HC p < 0.05 sF p = 0.001 ESR p = 0.02
Oustamanolakis P et al. (2011) [30]	+ (*)	+ (**)	51	49	102	IBD/HC p < 0.0001** p = 0.03* SCCAI p = 0.009** CDAI p = 0.09** sF p = 0.0008** CRP p = 0.004** p = 0.29*

ProHep. – prohepcidin, Hep. – hepcidin, CD – Crohn's disease, UC – ulcerative colitis, HC – healthy controls, IL-6 – interleukin-6, CRP – C-reactive protein, IBD – inflammatory bowel disease, CDAI – Crohn's disease activity index, sF – serum ferritin, ESR – erythrocyte sedimentation rate, SCCAI – Simple Clinical Colitis Activity Index.

ProHep. – prohepcydyna, Hep. – Hepcydyna, ChL-C – choroba Leśniowskiego-Crohna, WZJG – wrzodziejące zapalenie jelita grubego, ZO – zdrowi ochotnicy, IL-6 – interleukina 6, CRP – białko C-reaktywne, IBD – nieswoiste zapalenia jelit, CDAI – Wskaźnik aktywności choroby Leśniowskiego-Crohna, sF – stężenie ferrytyny w surowicy, ERS – wskaźnik sedymentacji erytrocytów (OB), SCCAI – indeks aktywności klinicznej zapalenia jelita grubego wg Walmsleya.

the difference was not statistically significant. In another study, the authors showed that the level of hepcidin was lower in IBD patients (51 with UC and 10 with CD) than in healthy volunteers (n = 25) [29]. The level of hepcidin measured with RIA was lower when compared to healthy individuals, both in patients without anemia and patients with IDA. Moreover, a positive correlation between hepcidin level and IL-6 was demonstrated.

Recently, Oustamanolakis et al. showed that the serum level of hepcidin as well as prohepcidin measured with ELISA was significantly higher in IBD patients (49 with UC and 51 with CD) than in healthy individuals [30]. The mean level of hepcidin was significantly higher in IBD patients than in the control group. However, the level of prohepcidin was significantly lower in IBD patients as compared to healthy volunteers. Additionally, a negative correlation was shown of the level of hepcidin with hemoglobin but a positive correlation was seen with the level of prohormone. The level of hepcidin also correlated with CRP, ferritin and, in UC patients, with the index of activity of disease (SCCAI). There was no positive correlation of the studied hormones and CDAI. Such a relation, however weak, was shown in another study regarding UC patients and level of prohepcidin [31]. In the above-mentioned study, there was no statistically significant difference between the level of prohepcidin in the group of 102 IBD patients (72 UC and 30 CD) as compared to healthy volunteers.

The problem of hepcidin and prohepcidin in IBD was also studied in the child population [32]. In a study conducted on the group of 15 children with IBD, it was observed that the level of prohepcidin (measured using the ELISA method) was significantly higher than in healthy volunteers.

Additionally, the level of prohepcidin positively correlated with ferritin and erythrocyte sedimentation rate. These correlations are summarized in Table 1.

Animal studies also have an important role in the elucidation of the role which hepcidin may play in IBD [33, 34]. In a recently published study, the role of protein BMP-6 in the production of hepcidin was stressed [34]. In mice with colitis, an increase of the serum iron level and depression of the inflammatory process after administration of the substances inhibiting the action of BMP-6 was observed. Blocking of the main trace activating the expression of gene HAMP positively influences not only the amount of iron in the body but can also positively correlate with a decreasing of the inflammatory process. However, these findings require further study.

The authors concluded that hepcidin is a key hormone determining the availability of iron in the body. Elucidation of the mechanisms regulating the synthesis of hepcidin and its action on the cell level is an important step in the better understanding of iron metabolism. This hormone may play a role in diagnostic strategy in IBD patients with anemia but also in hemochromatosis development and iron deficiency anemia resistant to iron treatment. As an acute phase protein can participate in the lower availability of iron in the body and in the development of active inflammation in the mucosa.

Further studies are needed to establish the place of hepcidin assessment in IBD in clinical practice. It is possible that, in the future, a decrease of the level of hepcidin will be the preferred management aiming to improve intestinal iron absorption and its release from macrophages.

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