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Publications 2023

OPEN ACCESS
ONLINE ISSN: 2992-5460
PRINT ISSN: 2992-6041

NEWPORT INTERNATIONAL JOURNAL OF RESEARCH IN MEDICAL SCIENCES (NIJRMS)

Volume 4 Issue 2 2023

https://doi.org/10.59298/NIJRMS/2023/10.1.1400

Hepcidin: The Gatekeeper of Iron in Malaria Resistance

*Emmanuel Ifeanyi Obeagu[1], Esther U. Alum[2,3] and Okechukwu P.C. Ugwu[3]

[1]Department of Medical Laboratory Science, Kampala International University, Uganda.
[2]Department of Biochemistry, Ebonyi State University, Abakaliki, Ebonyi State, Nigeria.
[3]Department of Publication and Extension, Kampala International University, Uganda.

*Corresponding authour: Emmanuel Ifeanyi Obeagu, Department of Medical Laboratory Science, Kampala International University, Uganda, emmanuelobeagu@yahoo.com, ORCID: 0000-0002-4538-0161

ABSTRACT

Malaria, a life-threatening disease caused by Plasmodium parasites, remains a global health challenge. Understanding the intricate dynamics between the host's iron regulation and the survival strategies of the parasites is crucial for the development of innovative antimalarial strategies. Hepcidin, a central regulator of iron homeostasis, has emerged as a key player in the host's defense against malaria. This comprehensive review explores the multifaceted roles of hepcidin in safeguarding the host from malaria infection. We delve into the molecular mechanisms of hepcidin regulation, its impact on iron availability, and its influence on the immune response. Furthermore, we discuss the complex interplay between hepcidin and Plasmodium species, revealing how the host's iron management influences the parasites' survival and pathogenicity. Additionally, we explore the therapeutic potential of targeting hepcidin and iron regulation in the context of malaria treatment. By unraveling the intricate web of hepcidin's functions as the "gatekeeper" of iron in malaria resistance, this review contributes to the development of novel strategies for combating this deadly disease.

Keywords: hepcidin, iron, malaria, inflammation

INTRODUCTION

Malaria, a formidable global health challenge, continues to exact a heavy toll on human lives, particularly in regions with limited resources and inadequate healthcare infrastructure. Plasmodium parasites, the causative agents of malaria, wield a cunning ability to adapt and persist within their human hosts [1-5]. Understanding the mechanisms that underpin the host's defense against these relentless invaders is a matter of paramount importance in the quest to develop effective strategies for preventing and treating malaria [4-9].

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PRINT ISSN: 2992-6041

At the heart of this battle is hepcidin, a small peptide hormone with a monumental role in regulating iron homeostasis. While hepcidin's involvement in maintaining the body's iron balance is well-documented, its multifaceted roles in the context of malaria resistance have recently come to the forefront of scientific inquiry. Hepcidin can be aptly described as the "gatekeeper of iron" in the host's response to Plasmodium infection [10]. The battle against malaria is ongoing, but with the insights provided by hepcidin's pivotal role, we find hope for more effective prevention and treatment strategies. As we embark on this journey through the intricate world of hepcidin, the gatekeeper of iron in malaria resistance, we aim to uncover the key to safeguarding the host from this relentless adversary [11].

Hepcidin: Molecular Pathways and Regulation

Hepcidin, a critical regulator of iron homeostasis, plays a central role in governing the body's iron balance. Its intricate regulation is influenced by a myriad of factors and pathways, ensuring that iron levels are maintained within the narrow range required for normal physiological functions. In this section, we will explore the molecular pathways and regulatory mechanisms that govern hepcidin production and its role in maintaining systemic and local iron homeostasis [12-20]. The synthesis of hepcidin is predominantly regulated at the transcriptional level through the HAMP gene. The HAMP gene is located on chromosome 19 and encodes prohepcidin, a precursor protein that is cleaved to produce the biologically active hepcidin peptide [21]. Prohepcidin undergoes proteolytic processing to generate mature hepcidin, which is subsequently secreted into the bloodstream. This mature peptide plays a pivotal role in regulating iron metabolism by controlling the expression and activity of the iron exporter, ferroportin [22].

The Role of Iron Status, Erythropoiesis, and Inflammation in Hepcidin Regulation

Hepcidin production is exquisitely sensitive to iron levels in the body. High iron levels stimulate the production of bone morphogenetic proteins (BMPs), particularly BMP6 and BMP2, which activate the SMAD signaling pathway. This pathway culminates in the transcription of the HAMP gene, leading to increased hepcidin synthesis [23].Erythropoiesis, the process of red blood cell production, is another key regulator of hepcidin. Erythropoietin (EPO), a hormone produced by the kidneys in response to tissue hypoxia, suppresses hepcidin production, allowing increased iron absorption to support red blood cell formation during anemia [24-31].Inflammatory signals, such as interleukin-6 (IL-6), play a pivotal role in hepcidin regulation. During inflammation, IL-6 induces hepcidin production via the JAK-STAT signaling pathway. This inflammatory response is part of the innate immune system's strategy to sequester iron away from pathogens, thereby limiting their growth [32-39].

The Impact of Hepcidin on Systemic and Local Iron Homeostasis

Hepcidin's ability to modulate systemic iron homeostasis ensures that the body can maintain iron levels within a narrow and physiologically relevant range. When iron is in excess, hepcidin levels increase, limiting dietary iron absorption and iron release from macrophages and hepatocytes into the bloodstream. Conversely, during iron deficiency, hepcidin production decreases, allowing for increased iron absorption to replenish iron stores [40]. Hepcidin also plays a crucial role in the regulation of iron within specific tissues. In the context of malaria, where iron sequestration can be a host defense strategy, local iron control in macrophages and other cells is essential to prevent Plasmodium access to iron sources [41]. Hepcidin's molecular pathways and regulatory mechanisms ensure the fine-tuned control of iron levels, enabling the host to respond to variations in iron status, erythropoietic demands, and inflammatory states. This dynamic regulation is a cornerstone of the host's defense against malaria and other pathogens, as it influences the availability of an essential nutrient to both host and parasite [42]. Hepcidin, a central regulator of iron homeostasis, exerts a significant influence on the host's immune response. Its role in modulating iron levels and the complex interplay between iron and immunity make hepcidin a key player in the host's defense against various pathogens, including Plasmodium species responsible for malaria.

Hepcidin's Effect on Innate Immune Cells

Macrophages and neutrophils are essential components of the innate immune system, actively participating in the defense against pathogens. Hepcidin's ability to regulate iron availability can influence the function of these cells. Elevated hepcidin levels can restrict iron availability, potentially impairing the antimicrobial activity of macrophages and neutrophils [43]. While iron is crucial for microbial growth, excessive iron can also be toxic due to the generation of reactive oxygen species (ROS). Hepcidin-mediated iron restriction may have dual effects on immune cells, limiting iron availability for pathogens while potentially protecting host cells from iron-induced oxidative damage [44].

The Influence of Hepcidin on Adaptive Immune Responses

T lymphocytes, including CD4+ and CD8+ T cells, play a central role in the adaptive immune response. Proper T cell responses are critical for the development of protective immunity against Plasmodium parasites. Hepcidin-mediated iron restriction may affect T cell proliferation, differentiation, and function, potentially influencing the host's ability to mount an effective antimalarial response [45].

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Hepcidin's regulation of iron levels can also impact the production of antibodies, a key component of adaptive immunity. Antibodies play a vital role in the host's defense against malaria by targeting Plasmodium antigens and preventing parasite invasion of host cells. Hepcidin-mediated iron restriction may affect the humoral immune response [46].

Implications of Hepcidin-Mediated Iron Regulation for Host Immunity during Malaria Infection

In the context of malaria, iron's dual role as a nutrient for the parasite and a potential driver of oxidative stress in the host creates a delicate balance. Hepcidin's role in iron regulation is central in maintaining this balance and optimizing the host's defense mechanisms [47]. Anemia, a common outcome of chronic inflammation, can compromise the host's ability to mount an effective immune response against malaria [48-52]. Excessive hepcidin production during inflammation, while serving as a defense mechanism to limit iron availability to pathogens, can also result in anemia of inflammation. This condition, characterized by decreased hemoglobin levels, can negatively impact the host's immune cells and overall resistance to the disease [53].Understanding the complex interactions between hepcidin, iron regulation, and the host's immune response is pivotal in the context of malaria resistance. Hepcidin's ability to restrict iron availability to both pathogens and the host's immune cells represents a double-edged sword that demands a delicate balance. The host's response to Plasmodium infection, influenced by hepcidin-mediated iron regulation, holds the key to more effective strategies for combatting malaria [54-58].

The Complex Interplay: Hepcidin and Plasmodium Species

The interaction between hepcidin, the master regulator of iron homeostasis, and Plasmodium species, the causative agents of malaria, is a multifaceted and intricate process. Hepcidin's role in governing iron levels within the host's body has significant implications for the survival strategies of the parasites. In this section, we delve into the complex interplay between hepcidin and Plasmodium species, shedding light on how hepcidin influences the pathogenesis of malaria and the strategies employed by the parasites for survival [59].Plasmodium parasites, particularly during the intraerythrocytic phase, depend on host iron stores for their survival and replication. Iron is a crucial nutrient for various physiological processes, including heme detoxification, DNA synthesis, and the production of proteins essential for the parasites' growth [60-64].Plasmodium parasites digest host hemoglobin to obtain heme, an essential source of iron. However, excess heme can be toxic to the parasites. To counteract this toxicity, Plasmodium has evolved detoxification mechanisms, allowing them to manage heme and utilize it as a source of iron [65-69].

Host Defense Mechanisms and Hepcidin's Role

Hepcidin, as the master regulator of iron homeostasis, can influence the host's iron management. By binding to ferroportin, the sole known cellular iron exporter, hepcidin triggers its internalization and degradation. This action effectively limits the export of iron from cells such as macrophages, hepatocytes, and enterocytes, reducing the availability of iron in the bloodstream [70]. Hepcidin-mediated iron sequestration creates a hostile environment for Plasmodium by restricting iron availability. By limiting iron access, the host can potentially inhibit the growth and survival of the parasites, thwarting their ability to propagate within the host [71]. Plasmodium parasites have evolved various mechanisms to counteract host defenses, including those related to hepcidin-mediated iron restriction. These adaptation strategies allow the parasites to circumvent the host's attempts to limit iron availability, ensuring their survival and propagation within the host's bloodstream [72]. Plasmodium species have evolved efficient antioxidant systems to cope with the oxidative stress associated with heme detoxification. These systems enable the parasites to neutralize reactive oxygen species (ROS) generated during heme catabolism [73].

Therapeutic Implications and Antimalarial Strategies

The intricate interplay between hepcidin, iron regulation, and Plasmodium species has unveiled potential therapeutic implications and antimalarial strategies. By targeting hepcidin and the host's iron management, researchers aim to develop innovative approaches to enhance the host's ability to combat malaria. In this section, we explore various therapeutic implications and strategies for malaria, leveraging the role of hepcidin as a central player in the host's defense [74].

Strategies to Target Hepcidin for Antimalarial Defense

One potential strategy is to develop therapeutics or vaccines that can induce the host to increase hepcidin expression in response to Plasmodium infection [75-78]. This would lead to a temporary reduction in serum iron levels, limiting iron availability to the parasites and potentially hindering their growth [78-82]. Hepcidin mimetics, synthetic molecules that mimic the actions of endogenous hepcidin, can be explored as potential antimalarial agents [75-78]. These mimetics could be administered to directly target ferroportin and limit iron export, effectively starving the parasites of this vital nutrient [78-82]. Iron chelation therapies, which involve the administration of iron-binding molecules, can help sequester iron within the host, making it less accessible to Plasmodium parasites. By limiting the parasites' access to iron, these therapies can inhibit their growth and replication [76-79].

Combining iron chelation therapies with conventional antimalarial drugs may offer a multi-pronged approach to treating malaria. Such combinations could target both the parasites directly and their iron acquisition strategies, potentially improving treatment outcomes.

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Vaccine Development and Hepcidin-Modulating Interventions

Strategies aimed at enhancing the host's immune responses, particularly those affected by hepcidin-mediated iron regulation, can be explored. This includes interventions to improve the function of immune cells, such as T cells and macrophages, by mitigating the impact of hepcidin-induced iron restriction. Vaccines that target Plasmodium antigens and enhance the host's immune response can be used in combination with hepcidin-modulating therapies. By bolstering the host's immunity, these vaccines may lead to improved antimalarial defense [77].

CONCLUSION

Hepcidin, the "gatekeeper of iron" in the host's defense against malaria, emerges as a pivotal player in the intricate battle against Plasmodium parasites. Hepcidin's multifaceted roles in regulating iron homeostasis, influencing the immune response, and shaping the host's defense strategies against malaria offer valuable insights and potential solutions in the battle against this devastating disease. As we continue to unravel the intricate host-parasite dynamics and refine our understanding of hepcidin's functions, we move closer to the development of more effective strategies for malaria prevention and treatment.

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OPEN ACCESS
ONLINE ISSN: 2992-5460
PRINT ISSN: 2992-6041

CITE AS: Emmanuel Ifeanyi Obeagu, Esther U. Alum and Okechukwu P.C. Ugwu (2023). Hepcidin: The Gatekeeper of Iron in Malaria Resistance NEWPORT INTERNATIONAL JOURNAL OF RESEARCH IN MEDICAL SCIENCES 4(2):1-8.
https://doi.org/10.59298/NIJRMS/2023/10.1.1400