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Malaria and Pregnancy: The Role of Placental MicroRNA in Disease Pathogenesis

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Abstract

Malaria in pregnancy poses significant risks to maternal and fetal health, particularly in regions where Plasmodium falciparum is endemic. The pathogenesis of placental malaria involves the sequestration of infected erythrocytes in the placenta, leading to inflammatory responses and impaired placental function. Recent research suggests that placental microRNAs (miRNAs) play crucial roles in mediating these pathological processes. Placental miRNAs are small non-coding RNAs that regulate gene expression and play critical roles in immune modulation and placental development. In the context of malaria infection, specific miRNAs are differentially expressed, influencing the immune response and contributing to the inflammatory milieu within the placenta. Key miRNAs, such as miR-146a, miR-155, and miR-210, have been identified as significant players in the regulation of cytokine production, immune cell infiltration, and trophoblast cell function. These miRNAs can either exacerbate or mitigate the inflammatory response, affecting pregnancy outcomes. Targeting placental miRNAs presents a promising therapeutic avenue for improving maternal and fetal health in malaria-endemic regions. However, challenges remain in ensuring the specificity and safety of miRNA-based interventions.

Keywords: *Malaria, Pregnancy, Placenta, MicroRNA, Pathogenesis, Plasmodium falciparum, Immune Response, Placental Malaria, miRNA Regulation, Maternal Health*

Introduction

Malaria in pregnancy is a major public health issue, especially in sub-Saharan Africa where Plasmodium falciparum is prevalent. Pregnant women are particularly susceptible to malaria due to changes in their immune system and the unique environment of the placenta. The consequences of malaria during pregnancy are severe, including maternal anemia, placental insufficiency, intrauterine growth restriction, preterm delivery, and increased risk of infant mortality. These

outcomes highlight the critical need for effective prevention and treatment strategies to protect maternal and fetal health. Placental malaria is characterized by the sequestration of Plasmodium falciparum-infected erythrocytes in the placental intervillous spaces. This sequestration is mediated by the interaction between parasite-derived proteins on the surface of infected erythrocytes and chondroitin sulfate A on the placental syncytiotrophoblast. This interaction initiates a cascade of inflammatory responses that disrupt normal placental function, impairing nutrient and oxygen exchange between the mother and fetus. Understanding the pathogenesis of placental malaria is essential for developing targeted interventions to mitigate its adverse effects. The immune system plays a pivotal role in the pathogenesis of placental malaria. The presence of infected erythrocytes in the placenta triggers an immune response characterized by the production of pro-inflammatory cytokines such as TNF-α, IFN-γ, and IL-10. These cytokines contribute to placental inflammation and damage, leading to impaired placental function and adverse pregnancy outcomes. The balance between pro-inflammatory and anti-inflammatory responses is crucial for maintaining placental health and ensuring a successful pregnancy.[1-10]

MicroRNAs (miRNAs) are small, non-coding RNA molecules that regulate gene expression at the post-transcriptional level. They bind to complementary sequences on target messenger RNAs (mRNAs), leading to mRNA degradation or inhibition of translation. MiRNAs are involved in a wide range of biological processes, including cell differentiation, proliferation, apoptosis, and immune responses. In the context of pregnancy, miRNAs play critical roles in regulating placental development and function, as well as modulating the maternal immune response to protect the fetus. The placenta is an immunologically unique organ that must balance the need to protect the fetus from maternal immune attack while defending against infections. Placental miRNAs contribute to this balance by modulating immune responses. Dysregulation of placental miRNAs can lead to abnormal immune activation and placental pathologies. For example, certain miRNAs can regulate the expression of cytokines and their receptors, influencing the inflammatory milieu within the placenta. This regulatory role is particularly relevant in the context of infections such as malaria, where the immune response must be carefully controlled to prevent excessive inflammation and tissue damage. Recent studies have identified specific miRNAs that are differentially expressed in placental malaria. These miRNAs are thought to influence the pathogenesis of the disease by regulating immune responses and placental function. For instance, miR-146a, miR-155, and miR-210 have been implicated in the inflammatory response to malaria infection. MiR-146a is known for its role in modulating inflammatory responses and is upregulated in placental malaria, potentially contributing to the regulation of pro-inflammatory cytokines. MiR-155 is associated with immune cell activation and is implicated in the heightened inflammatory response observed in placental malaria. MiR-210, often elevated in hypoxic conditions, may play a role in the placental hypoxia seen in severe malaria infections.[11-20]

The mechanisms by which miRNAs regulate gene expression are complex and multifaceted. In the context of placental malaria, miRNAs can influence the pathogenesis of the disease through various mechanisms. For example, miRNAs can modulate the production of cytokines, altering the balance between pro-inflammatory and anti-inflammatory responses. They can also affect the survival and proliferation of trophoblast cells, which are critical for placental development and function. Additionally, miRNAs can influence the infiltration and activity of immune cells in the

placenta, impacting the overall inflammatory response to malaria infection. Given their regulatory roles, placental miRNAs represent promising therapeutic targets for mitigating the adverse effects of malaria in pregnancy. By modulating the expression of specific miRNAs, it may be possible to reduce placental inflammation, improve placental function, and enhance pregnancy outcomes in malaria-infected mothers. However, several challenges must be addressed to realize the therapeutic potential of miRNAs. These include ensuring the specificity and safety of miRNA-based interventions, as well as developing effective delivery methods to target the placenta without affecting other tissues.[21-25]

Placental Malaria: An Overview

Placental malaria is a severe complication of malaria in pregnancy, primarily caused by the Plasmodium falciparum parasite. This condition leads to significant adverse outcomes for both the mother and the fetus. Placental malaria is characterized by the sequestration of Plasmodium falciparum-infected erythrocytes within the intervillous spaces of the placenta. This sequestration is facilitated by the interaction between parasite proteins, such as VAR2CSA, and placental receptors like chondroitin sulfate A. This interaction causes the infected erythrocytes to adhere to the placenta, disrupting its normal function and triggering an inflammatory response. The presence of infected erythrocytes in the placenta triggers a local immune response. This includes the production of pro-inflammatory cytokines such as TNF-α, IFN-γ, and IL-10, which contribute to placental inflammation and damage. The recruitment and activation of immune cells, including monocytes and macrophages, further exacerbate the inflammatory response, leading to placental dysfunction and adverse pregnancy outcomes. Placental malaria significantly impairs the placenta's ability to facilitate nutrient and oxygen exchange between the mother and the fetus. The inflammatory response and the accumulation of infected erythrocytes cause structural and functional damage to the placenta. This can result in placental insufficiency, leading to fetal growth restriction, low birth weight, and preterm delivery. In severe cases, placental malaria can also lead to fetal loss and increased neonatal mortality.[26-30]

For the mother, placental malaria is associated with severe anemia due to the destruction of red blood cells. This anemia can lead to increased maternal morbidity and mortality, especially in regions with limited access to healthcare. Additionally, the chronic inflammation caused by placental malaria can have long-term effects on maternal health, including increased susceptibility to other infections and chronic diseases. The adverse effects of placental malaria extend to the fetus and neonate. Fetal growth restriction and low birth weight are common outcomes, increasing the risk of neonatal mortality and long-term developmental issues. Infants born to mothers with placental malaria are also at higher risk of malaria infection during infancy, further compounding the health challenges faced by these children. Diagnosing placental malaria can be challenging due to its often-asymptomatic nature in the mother. The gold standard for diagnosis is the histological examination of placental tissue, which can identify the presence of infected erythrocytes and inflammatory infiltrates. Other diagnostic methods include PCR and rapid diagnostic tests, though these may be less sensitive in detecting placental malaria compared to histology. Preventing and treating placental malaria involves a combination of strategies. Intermittent preventive treatment with antimalarial drugs during pregnancy (IPTp) is a key preventive measure recommended by the

World Health Organization (WHO). In addition, the use of insecticide-treated bed nets (ITNs) and effective case management of malaria during pregnancy are crucial in reducing the incidence and impact of placental malaria. Treatment typically involves the use of safe and effective antimalarial drugs, tailored to the stage of pregnancy and the severity of the infection.[31-35]

Pathogenesis of Placental Malaria

Placental malaria, primarily caused by Plasmodium falciparum, represents a unique and severe manifestation of malaria that occurs during pregnancy. It involves the sequestration of infected erythrocytes within the placenta, leading to inflammation, placental damage, and adverse pregnancy outcomes. The hallmark of placental malaria is the sequestration of Plasmodium falciparum-infected erythrocytes in the placental intervillous spaces. This sequestration is mediated by the interaction between parasite proteins, particularly VAR2CSA, and specific receptors on the syncytiotrophoblast, such as chondroitin sulfate A (CSA). VAR2CSA binds to CSA with high affinity, allowing the infected erythrocytes to adhere to the placental surface and evade clearance by the spleen. The accumulation of infected erythrocytes in the placenta triggers a robust local immune response. This response is characterized by the production of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and interleukin-10 (IL-10). These cytokines contribute to the recruitment and activation of immune cells, such as monocytes and macrophages, which infiltrate the placental tissue. Pro-inflammatory cytokines play a pivotal role in the pathogenesis of placental malaria. TNF-α and IFN-γ promote the activation of immune cells and the production of other inflammatory mediators, exacerbating the local inflammatory response. Elevated levels of IL-10, which typically has anti-inflammatory properties, suggest a complex regulatory mechanism attempting to balance inflammation and immune modulation in the placenta.[36-40]

The inflammatory milieu in the placenta attracts various immune cells, including monocytes, macrophages, and T cells. These cells infiltrate the intervillous spaces and contribute to the local inflammatory response. Activated macrophages produce additional pro-inflammatory cytokines and reactive oxygen species, which can damage placental tissue and disrupt its normal function. The inflammation and immune cell infiltration in placental malaria led to structural and functional damage to the placenta. The integrity of the placental barrier is compromised, affecting its ability to facilitate nutrient and oxygen exchange between the mother and fetus. This can result in placental insufficiency, contributing to fetal growth restriction, low birth weight, and preterm delivery. Placental malaria is often associated with hypoxic conditions and oxidative stress. The sequestration of infected erythrocytes and the inflammatory response can reduce blood flow and oxygen supply to the placenta, leading to hypoxia. Hypoxic conditions further induce the expression of hypoxia-inducible factors (HIFs) and other stress-related proteins, exacerbating placental dysfunction and damage. Emerging evidence suggests that placental microRNAs (miRNAs) play a critical role in the pathogenesis of placental malaria. MiRNAs are small non-coding RNAs that regulate gene expression and modulate various biological processes, including immune responses and cell survival. Specific miRNAs, such as miR-146a, miR-155, and miR-210, are differentially expressed in placental malaria and may influence the inflammatory response and placental function. For instance, miR-146a is known to modulate the expression of pro-

inflammatory cytokines, while miR-210 is associated with hypoxia and oxidative stress responses. The pathological changes induced by placental malaria have significant implications for both maternal and fetal health. For the mother, placental malaria can lead to severe anemia and increased susceptibility to other infections due to the chronic inflammatory state. For the fetus, the impaired placental function can result in intrauterine growth restriction, low birth weight, preterm birth, and increased risk of neonatal mortality. Additionally, infants born to mothers with placental malaria are at higher risk of malaria infection during infancy.[41-45]

Role of MicroRNAs in Placental Function

MicroRNAs (miRNAs) are small, non-coding RNA molecules that play crucial roles in regulating gene expression. They are involved in various biological processes, including cell differentiation, proliferation, apoptosis, and immune responses. In the context of pregnancy, miRNAs are essential for proper placental development and function. miRNAs are transcribed from DNA as primary miRNAs (pri-miRNAs), which are then processed in the nucleus by the Drosha-DGCR8 complex into precursor miRNAs (pre-miRNAs). Pre-miRNAs are exported to the cytoplasm, where they are further processed by Dicer into mature miRNAs. These mature miRNAs are incorporated into the RNA-induced silencing complex (RISC), where they bind to complementary sequences on target messenger RNAs (mRNAs), leading to mRNA degradation or inhibition of translation. Through this mechanism, miRNAs finely tune the expression of numerous genes involved in critical cellular processes. Placental development is a highly regulated process that requires the coordinated expression of numerous genes. miRNAs play pivotal roles in this regulation by controlling the expression of genes involved in trophoblast differentiation, proliferation, and invasion. Trophoblasts are specialized cells that form the outer layer of the placenta and are crucial for its function. Specific miRNAs, such as miR-17-92 cluster, miR-21, and miR-34, have been shown to regulate trophoblast cell behavior, ensuring proper placental formation and function. The placenta acts as an immunological interface between the mother and the fetus, requiring a delicate balance between immune tolerance and defense against pathogens. Placental miRNAs contribute to this balance by modulating the maternal immune response. For example, miR-146a is known to regulate the expression of pro-inflammatory cytokines, helping to maintain an anti-inflammatory environment that is conducive to fetal development. Dysregulation of immune-related miRNAs can lead to abnormal immune activation, contributing to placental pathologies such as preeclampsia and intrauterine growth restriction (IUGR).[46-50]

Angiogenesis, the formation of new blood vessels, is essential for providing the growing fetus with nutrients and oxygen. Placental miRNAs are involved in regulating angiogenic processes. miR-210, for example, is known to be upregulated in hypoxic conditions and can modulate the expression of genes involved in angiogenesis. Proper regulation of angiogenesis by miRNAs ensures adequate blood supply to the placenta and fetus, supporting healthy fetal development. Placental miRNAs also play critical roles in the response to infections. In the case of placental malaria, specific miRNAs are differentially expressed and can influence the inflammatory response and placental function. For instance, miR-155 is associated with immune cell activation and is implicated in the heightened inflammatory response observed in placental malaria. Hypoxia, or low oxygen levels, is a common feature of various placental pathologies, including

preeclampsia and placental malaria. miR-210 is a well-known hypoxia-responsive miRNA that is often elevated in hypoxic conditions. miR-210 modulates the expression of genes involved in cell survival, proliferation, and metabolism, helping the placenta adapt to low oxygen conditions. However, prolonged hypoxia and dysregulation of hypoxia-responsive miRNAs can lead to placental dysfunction and adverse pregnancy outcomes. Given their regulatory roles, placental miRNAs represent promising therapeutic targets for addressing pregnancy complications. Modulating the expression of specific miRNAs could potentially improve placental function and pregnancy outcomes. For example, targeting miR-210 in cases of placental hypoxia might help mitigate the adverse effects of low oxygen levels on placental health. Similarly, modulating miR-155 and other immune-related miRNAs could help control excessive inflammation in placental infections like malaria.[51-55]

Placental MicroRNAs in Malaria Infection

Malaria in pregnancy, particularly due to Plasmodium falciparum, poses significant health risks to both the mother and the fetus. The condition known as placental malaria involves the sequestration of infected erythrocytes in the placenta, leading to inflammation, placental damage, and adverse pregnancy outcomes. Recent research highlights the critical role of placental microRNAs (miRNAs) in modulating the immune response, inflammation, and placental function during malaria infection. Placental miRNAs are key regulators of the immune response during malaria infection. They modulate the expression of cytokines, chemokines, and other immune-related molecules, influencing the balance between pro-inflammatory and anti-inflammatory responses. This regulation is crucial in maintaining a controlled immune environment that limits tissue damage while combating infection. One of the most studied miRNAs in the context of placental malaria is miR-146a. It is known to play a pivotal role in regulating the inflammatory response. miR-146a targets several components of the Toll-like receptor (TLR) signaling pathway, which is activated in response to Plasmodium falciparum infection. By modulating this pathway, miR-146a helps to control the production of pro-inflammatory cytokines such as TNF-α and IL-6, thus mitigating excessive inflammation that can lead to placental damage. Another important miRNA in placental malaria is miR-155. It is associated with the activation of immune cells and the inflammatory response. During malaria infection, miR-155 expression is upregulated, contributing to the heightened inflammatory environment. While this response is part of the body's defense mechanism against the parasite, excessive inflammation can harm placental function and fetal development. Inflammation is a hallmark of placental malaria, driven by the accumulation of infected erythrocytes and the subsequent immune response. miRNAs play a crucial role in modulating this inflammatory milieu, influencing both the extent and nature of the immune response. miR-210 is a hypoxia-responsive miRNA that is often upregulated in placental malaria. Hypoxic conditions in the placenta arise due to the sequestration of infected erythrocytes, which disrupts blood flow and oxygen delivery. miR-210 modulates the expression of genes involved in cell survival, angiogenesis, and metabolism, helping the placenta adapt to low oxygen conditions. However, prolonged hypoxia and elevated miR-210 levels can contribute to placental dysfunction and adverse pregnancy outcomes. miR-223 is another miRNA implicated in the regulation of the inflammatory response during placental malaria. It modulates the activity of neutrophils and macrophages, key immune cells involved in the inflammatory process. By targeting specific

transcription factors and signaling molecules, miR-223 helps to fine-tune the inflammatory response, balancing the need to fight infection with the necessity of limiting tissue damage.[56-65]

The integrity and function of the placenta are critical for fetal development. miRNAs regulate various aspects of placental biology, including trophoblast proliferation, differentiation, and invasion. During malaria infection, dysregulation of these miRNAs can contribute to placental insufficiency and fetal growth restriction. miR-34a is involved in regulating trophoblast cell cycle and apoptosis. During malaria infection, changes in miR-34a expression can affect trophoblast survival and proliferation, leading to compromised placental structure and function. This dysregulation can impair nutrient and oxygen exchange, contributing to fetal growth restriction and low birth weight. miR-193b plays a role in trophoblast differentiation and invasion. In the context of malaria infection, altered expression of miR-193b can impact the ability of trophoblasts to invade the maternal decidua and establish a functional placenta. This can result in abnormal placental development and function, further exacerbating the adverse effects of malaria on pregnancy outcomes. Given their regulatory roles, placental miRNAs represent promising therapeutic targets for mitigating the adverse effects of malaria in pregnancy. Modulating the expression of specific miRNAs could potentially improve placental function and pregnancy outcomes in malaria-infected mothers. Anti-miR therapy involves the use of synthetic molecules to inhibit specific miRNAs. For example, targeting miR-155 with anti-miR molecules could help reduce excessive inflammation in placental malaria, protecting placental function and fetal health. Similarly, inhibiting miR-210 could mitigate the effects of hypoxia and oxidative stress on the placenta. Conversely, miRNA mimics can be used to restore the function of miRNAs that are downregulated during malaria infection. For instance, enhancing the expression of miR-146a could help control the inflammatory response and protect the placenta from excessive damage. This approach could be particularly useful in balancing the immune response to malaria infection while maintaining placental integrity.[65-70]

Therapeutic Potential of Targeting Placental MicroRNAs

MicroRNAs (miRNAs) are critical regulators of gene expression, influencing various biological processes including immune responses, inflammation, and cell survival. In the context of placental malaria, these miRNAs play significant roles in modulating the placental response to infection and maintaining its function. Targeting specific placental miRNAs holds promise as a therapeutic strategy to mitigate the adverse effects of malaria on pregnancy outcomes. Placental miRNAs are involved in regulating key processes that are disrupted during malaria infection, including trophoblast function, immune response, and inflammation. Dysregulation of these miRNAs can contribute to placental insufficiency, fetal growth restriction, and adverse pregnancy outcomes. By modulating the expression of specific miRNAs, it is possible to restore normal placental function and improve pregnancy outcomes in malaria-infected mothers. Anti-miR therapy involves the use of synthetic molecules called antagomirs or anti-miRs to inhibit the activity of specific miRNAs. This approach can be used to reduce the expression of miRNAs that are upregulated and contribute to the pathogenesis of placental malaria. miR-155 is upregulated during malaria infection and is associated with heightened inflammatory responses. Excessive inflammation can damage placental tissue and impair its function. Inhibiting miR-155 using anti-miRs can help reduce

inflammation, protecting the placenta from damage and improving fetal outcomes. Preclinical studies have shown that targeting miR-155 can effectively modulate immune responses and reduce inflammation in various disease models, supporting its potential as a therapeutic target in placental malaria. miR-210 is a hypoxia-responsive miRNA that is upregulated in placental malaria due to the hypoxic conditions induced by the sequestration of infected erythrocytes. Elevated miR-210 levels can contribute to placental dysfunction and adverse pregnancy outcomes. Anti-miR therapy targeting miR-210 can help mitigate the effects of hypoxia and oxidative stress on the placenta, improving placental function and fetal health. Studies have demonstrated the efficacy of anti-miR-210 in reducing hypoxia-induced damage in other contexts, highlighting its potential therapeutic benefits in placental malaria.[71-75]

miRNA mimics are synthetic molecules designed to restore the function of miRNAs that are downregulated during malaria infection. By enhancing the expression of these miRNAs, it is possible to counteract the dysregulation caused by the infection and improve placental health. miR-146a is known to regulate the inflammatory response and maintain immune homeostasis. During placental malaria, the expression of miR-146a may be dysregulated, leading to excessive inflammation. Using miRNA mimics to enhance miR-146a expression can help control the inflammatory response, protecting the placenta from damage and improving pregnancy outcomes. Research has shown that miR-146a mimics can effectively reduce inflammation in various disease models, supporting their potential use in placental malaria. miR-223 plays a role in modulating the activity of neutrophils and macrophages, key immune cells involved in the inflammatory response during malaria infection. Enhancing the expression of miR-223 using miRNA mimics can help fine-tune the immune response, reducing excessive inflammation and protecting placental function. Preclinical studies have demonstrated the effectiveness of miR-223 mimics in regulating immune responses and reducing inflammation, making them a promising therapeutic option for placental malaria. Effective delivery of miRNA-based therapies to the placenta is crucial for their success. Several strategies are being explored to achieve targeted delivery and maximize therapeutic efficacy. Nanoparticles offer a promising approach for delivering miRNA-based therapies to the placenta. These particles can be engineered to encapsulate miRNA mimics or anti-miRs and protect them from degradation in the bloodstream. Additionally, nanoparticles can be functionalized with ligands that target specific receptors on placental cells, enhancing their uptake and ensuring localized delivery. Preclinical studies have shown that nanoparticle-based delivery systems can effectively deliver miRNA therapeutics to the placenta, supporting their potential use in placental malaria. Viral vectors, such as adeno-associated viruses (AAVs), are another strategy for delivering miRNA-based therapies. These vectors can be engineered to carry miRNA mimics or anti-miRs and target placental cells. Viral vectors offer high transduction efficiency and sustained expression of therapeutic miRNAs, making them a powerful tool for treating placental malaria. However, concerns about immunogenicity and safety need to be addressed before clinical application.[76-89]

Conclusion

The therapeutic potential of targeting placental microRNAs (miRNAs) in the context of malaria infection represents a novel and promising approach to addressing the adverse effects of this

condition on pregnancy outcomes. Placental malaria, driven by Plasmodium falciparum, leads to significant complications including inflammation, placental dysfunction, and adverse fetal outcomes. miRNAs, as crucial regulators of gene expression, play pivotal roles in modulating these processes, influencing immune responses, inflammation, and placental function. Research has demonstrated that specific miRNAs, such as miR-155, miR-210, miR-146a, and miR-223, are involved in various aspects of placental pathology during malaria infection. These miRNAs regulate inflammatory responses, hypoxia, and trophoblast function, impacting overall placental health and fetal development. By targeting these miRNAs with anti-miRs or mimics, it is possible to correct dysregulated pathways, reduce excessive inflammation, and restore normal placental function.

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