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Article · September 2024

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Aplastic Anemia in HIV: Role of MicroRNA Signaling Pathways

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Abstract

Aplastic anemia (AA) is a severe hematological disorder characterized by the failure of bone marrow to produce adequate blood cells, leading to pancytopenia. In individuals with HIV, the pathogenesis of AA is exacerbated by HIV-induced immune dysregulation and the impact of the virus on hematopoiesis. Emerging research highlights the crucial role of microRNAs (miRNAs) in regulating various cellular processes, including hematopoiesis, immune responses, and inflammation. This review examines the involvement of miRNA signaling pathways in AA in the context of HIV, focusing on how miRNAs influence disease development and progression. MicroRNAs are small, non-coding RNA molecules that regulate gene expression post-transcriptionally. Dysregulation of miRNAs in HIV-infected individuals can contribute to the pathogenesis of AA by altering immune responses, promoting inflammation, and disrupting normal hematopoiesis. This review explores how specific miRNAs and their associated signaling pathways impact the bone marrow environment and contribute to the development of AA in the context of HIV.

Keywords: *aplastic anemia, HIV, microRNA, signaling pathways, hematopoiesis*

Introduction

Aplastic anemia (AA) is a severe hematologic disorder characterized by the failure of the bone marrow to produce adequate amounts of blood cells, leading to pancytopenia—anemia, leukopenia, and thrombocytopenia. This condition results in increased susceptibility to infections, bleeding, and fatigue. AA can be idiopathic or secondary to various factors, including autoimmune diseases, exposure to toxins, and infections. Among the secondary causes, HIV infection has emerged as a significant contributor to AA due to the complex interplay between the virus and the

hematopoietic system. HIV infection affects the immune system and can disrupt normal hematopoiesis in multiple ways. The virus directly targets and destroys CD4+ T cells, leading to immunodeficiency. This immune suppression can result in opportunistic infections and malignancies that further compromise bone marrow function. Additionally, HIV-induced chronic inflammation and immune dysregulation contribute to the development of AA by promoting autoimmune reactions against hematopoietic cells. The interplay between HIV-related immune changes and bone marrow pathology complicates the management of AA in these patients.[1-5] Recent research has identified microRNAs (miRNAs) as key regulators of gene expression and cellular processes involved in hematopoiesis and immune responses. MiRNAs are small, non-coding RNA molecules that modulate gene expression by binding to complementary sequences in mRNA, leading to their degradation or translational repression. These molecules play a crucial role in various physiological processes, including the regulation of hematopoietic stem cell maintenance, cell differentiation, and apoptosis. In the context of HIV and AA, miRNAs can influence disease progression by modulating these processes. The role of miRNAs in AA and HIV is an emerging field of research. Studies have shown that miRNAs can be differentially expressed in individuals with AA and those infected with HIV, suggesting a potential link between miRNA dysregulation and disease development. For instance, specific miRNAs have been implicated in the regulation of immune responses and inflammation, which are critical in the pathogenesis of AA. Additionally, miRNAs that regulate hematopoiesis can affect the bone marrow's ability to produce blood cells, further contributing to AA.[6-10]

MiRNAs such as miR-21, miR-150, and miR-155 have been implicated in immune modulation and inflammation, while others like miR-223 and miR-144 play roles in hematopoietic regulation. By studying these miRNAs and their target genes, researchers can gain a better understanding of how miRNA dysregulation contributes to AA in the context of HIV and identify potential therapeutic targets. MiRNA-based therapeutic strategies offer promising approaches for managing AA in HIV-infected patients. The ability to modulate miRNA expression with mimics, inhibitors, or other RNA-based therapies provides an opportunity to correct dysregulated pathways and restore normal hematopoiesis. For example, restoring the expression of tumor-suppressive miRNAs or inhibiting overexpressed oncomiRs could potentially improve disease outcomes. However, the development and application of these therapies require a thorough understanding of miRNA biology and their specific roles in HIV-related AA.[11-15] The integration of miRNA research with other omics technologies, such as genomics, transcriptomics, and proteomics, can further enhance our understanding of AA in HIV-infected individuals. Combining these approaches allows for a comprehensive analysis of the molecular landscape of the disease, helping to identify novel biomarkers and therapeutic targets. Continued research in this area is essential for advancing our knowledge and improving treatment strategies for AA in the context of HIV.[16-17]

MicroRNAs and Their Biogenesis

MicroRNAs (miRNAs) are small, non-coding RNA molecules approximately 22 nucleotides in length that play a crucial role in the regulation of gene expression at the post-transcriptional level. These molecules exert their effects by binding to complementary sequences in messenger RNA (mRNA), leading to mRNA degradation or inhibition of translation. This regulation is critical for various physiological processes, including development, differentiation, and homeostasis, as well as in disease states such as cancer, cardiovascular diseases, and hematologic disorders. The biogenesis of miRNAs involves a series of well-defined steps that convert primary miRNA transcripts into mature miRNAs capable of regulating target mRNAs. The process begins in the nucleus, where miRNA genes are transcribed by RNA polymerase II into long primary miRNA transcripts (pri-miRNAs). These pri-miRNAs often contain one or more stem-loop structures and are typically several kilobases in length. The initial step of miRNA processing involves the cleavage of the pri-miRNA by the Drosha-DGCR8 complex, which removes the terminal loop and produces a shorter precursor miRNA (pre-miRNA) with a characteristic stem-loop structure.[18-23] The pre-miRNA is then exported from the nucleus to the cytoplasm by the Exportin-5 protein, a process that is essential for further maturation. In the cytoplasm, the pre-miRNA undergoes further processing by the Dicer enzyme, which cleaves the pre-miRNA into a double-stranded RNA duplex consisting of the mature miRNA and its complementary strand (the miRNA* strand). The duplex is then unwound, and the mature miRNA strand is incorporated into the RNA-induced silencing complex (RISC). The RISC complex, guided by the mature miRNA, binds to target mRNA sequences with partial complementarity, leading to mRNA degradation or translational repression. MiRNAs are known to regulate a wide range of biological processes by modulating the expression of their target genes. This regulation is highly specific, with each miRNA typically targeting multiple mRNAs, and each mRNA potentially being regulated by several miRNAs. The specificity and functional outcomes of miRNA-mediated regulation depend on the sequence complementarity between the miRNA and its target mRNA, as well as the cellular context and the presence of additional regulatory factors.[24-28] In the context of diseases such as aplastic anemia (AA) and HIV, miRNAs can influence the progression and pathogenesis by modulating key cellular processes. For example, miRNAs involved in hematopoiesis can affect the differentiation and proliferation of hematopoietic stem and progenitor cells, while those regulating immune responses can impact the inflammatory and immune landscape associated with HIV infection. [29-30]

Role of miRNAs in Hematopoiesis

Hematopoiesis is the intricate process of blood cell formation that occurs primarily in the bone marrow and involves the differentiation of hematopoietic stem cells (HSCs) into various blood cell types, including erythrocytes, leukocytes, and platelets. This tightly regulated process ensures a continuous supply of blood cells throughout an individual's life, balancing cell proliferation, differentiation, and apoptosis. MicroRNAs (miRNAs) are pivotal in this regulation, as they modulate gene expression involved in each stage of hematopoiesis.[31-32]

1. Regulation of Hematopoietic Stem Cells (HSCs): Hematopoietic stem cells (HSCs) are the progenitor cells capable of differentiating into all blood cell types. The maintenance and self-

renewal of HSCs are crucial for sustaining lifelong hematopoiesis. MiRNAs play a significant role in regulating HSC function by targeting genes that control stem cell maintenance and proliferation. For example, **miR-125a** and **miR-146a** are known to be involved in preserving HSC quiescence and preventing premature differentiation. Dysregulation of these miRNAs can lead to either stem cell exhaustion or the expansion of immature cells, contributing to hematological disorders.[33-34]

2. Influence on Cell Differentiation: As HSCs differentiate into various progenitor cells, specific miRNAs are essential for guiding this process. Different stages of differentiation are marked by changes in miRNA expression profiles. For instance, **miR-221** and **miR-222** are upregulated during the transition from myeloid progenitors to mature myeloid cells, promoting myeloid differentiation while inhibiting erythroid differentiation. Conversely, **miR-146a** and **miR-155** play roles in myeloid and lymphoid differentiation by targeting transcription factors and signaling pathways critical for lineage commitment.[35-36]

3. Regulation of Erythropoiesis: Erythropoiesis, the production of red blood cells, is a highly regulated process that involves the maturation of erythroid progenitors into functional erythrocytes. MiRNAs are key regulators of erythropoiesis by influencing the expression of genes involved in erythroid differentiation and function. For example, **miR-210** is upregulated in response to hypoxia and promotes erythrocyte maturation by targeting factors that inhibit erythropoiesis. **miR-144** and **miR-451** are also crucial in erythrocyte development, affecting cell survival and maturation.[37-38]

4. Regulation of Leukopoiesis: Leukopoiesis, the formation of white blood cells, is another critical aspect of hematopoiesis influenced by miRNAs. Specific miRNAs regulate the differentiation of various leukocyte lineages, including neutrophils, monocytes, and lymphocytes. **miR-155** is involved in the development of B and T lymphocytes by regulating genes associated with immune cell differentiation and activation. Similarly, **miR-223** is important for granulocyte maturation and function, and its dysregulation can lead to conditions such as neutropenia or myeloid malignancies.[39-40]

5. Role in Thrombopoiesis: Thrombopoiesis, the process of platelet production, is also regulated by miRNAs. **miR-150** and **miR-10a** have been shown to influence megakaryocyte development and platelet production by targeting genes involved in megakaryocyte differentiation and platelet release. Dysregulation of these miRNAs can result in platelet disorders, such as thrombocytopenia or thrombocytosis, which can have significant clinical implications.[41-42]

6. Impact of miRNA Dysregulation in Hematological Disorders: Alterations in miRNA expression are associated with various hematological disorders, including aplastic anemia, leukemia, and myelodysplastic syndromes. In aplastic anemia, for instance, miRNA dysregulation can affect hematopoiesis by modulating the immune response and bone marrow environment. For example, upregulation of **miR-21** and downregulation of **miR-223** have been observed in patients with aplastic anemia, reflecting disruptions in hematopoietic regulation and inflammation.[43-44]

miRNA Dysregulation in HIV and Aplastic Anemia

MicroRNAs (miRNAs) are crucial regulators of gene expression that impact various cellular processes, including immune responses and hematopoiesis. Dysregulation of miRNAs can have profound effects on health, contributing to the development and progression of diseases such as HIV and aplastic anemia (AA).[45]

1. miRNA Dysregulation in HIV Infection:

HIV infection leads to significant changes in the immune system, characterized by the depletion of CD4+ T cells, chronic inflammation, and immune activation. These changes are, in part, mediated by alterations in miRNA expression. Several miRNAs have been implicated in the pathogenesis of HIV infection through their roles in immune cell regulation and viral replication.

- **Immune Cell Regulation:** In HIV-infected individuals, miRNAs such as **miR-155**, **miR-146a**, and **miR-21** are often dysregulated. For instance, **miR-155** is involved in the regulation of immune responses and has been found to be upregulated in HIV-infected CD4+ T cells. This upregulation can contribute to immune activation and inflammation, exacerbating the disease. Conversely, **miR-146a** is a negative regulator of inflammation and its downregulation can lead to excessive immune responses and further immune dysfunction.[46-47]
- **Viral Replication:** miRNAs also influence HIV replication. For example, **miR-28** and **miR-32** can target viral mRNAs, modulating the efficiency of HIV replication. The balance between host-derived miRNAs and viral factors affects the progression of HIV infection and the development of related complications.[48]

2. miRNA Dysregulation in Aplastic Anemia:

Aplastic anemia is a condition characterized by the failure of the bone marrow to produce sufficient blood cells, leading to pancytopenia. The pathogenesis of AA involves both intrinsic defects in hematopoietic stem cells and extrinsic factors such as autoimmune responses. miRNAs play a significant role in the regulation of hematopoiesis and immune responses, and their dysregulation can contribute to the development of AA.[49]

- **Hematopoietic Stem Cell Function:** In AA, miRNAs such as **miR-21** and **miR-146a** are often dysregulated. **miR-21** is associated with the inhibition of apoptosis and promotion of cell proliferation, and its upregulation in AA may contribute to the abnormal survival of hematopoietic cells. **miR-146a**, which is involved in regulating inflammatory responses, can be downregulated in AA, leading to increased inflammation and autoimmune damage to the bone marrow.[50]
- **Immune System Modulation:** The dysregulation of miRNAs involved in immune system regulation can exacerbate the autoimmune component of AA. For example, **miR-155** plays a role in the activation of immune cells and its overexpression can contribute to the

autoimmune attack on hematopoietic cells. Similarly, changes in miRNA expression can influence the production of cytokines and other inflammatory mediators, further impairing hematopoiesis.[51]

3. Interplay Between HIV and Aplastic Anemia:

In patients with both HIV and AA, miRNA dysregulation can have a compounded effect on disease progression. HIV-related immune dysfunction can exacerbate the autoimmune mechanisms driving AA, while AA can worsen the overall health status of HIV-infected individuals.

- **Compounded Dysregulation:** The presence of HIV can lead to alterations in miRNA expression that impact both the immune system and hematopoiesis. For instance, HIV-induced dysregulation of **miR-155** can contribute to both enhanced immune activation and suppression of hematopoietic stem cell function. Similarly, **miR-21**, which is involved in both HIV pathogenesis and AA, may influence disease severity by affecting both immune responses and bone marrow function.[52-53]
- **Therapeutic Implications:** Targeting miRNA dysregulation offers a potential therapeutic strategy for managing AA in HIV-infected patients. For example, restoring the balance of miRNAs involved in immune regulation and hematopoiesis could help mitigate the autoimmune damage in AA and improve overall disease outcomes. Additionally, understanding the specific miRNAs involved in both conditions can guide the development of targeted therapies aimed at correcting dysregulated miRNA pathways.[54-55]

miRNA Signaling Pathways in Aplastic Anemia

Aplastic anemia (AA) is a severe hematological disorder characterized by the failure of the bone marrow to produce adequate blood cells, leading to pancytopenia. The pathogenesis of AA involves a complex interplay of genetic, environmental, and immune factors. MicroRNAs (miRNAs) have emerged as crucial regulators of gene expression and cellular processes involved in hematopoiesis and immune responses. In AA, miRNA signaling pathways play a significant role in modulating the disease's progression and severity.[56-57]

1. Regulation of Hematopoietic Stem Cells (HSCs):

Hematopoietic stem cells (HSCs) are the progenitors of all blood cell types and their proper regulation is essential for normal hematopoiesis. In AA, miRNAs influence HSC function and maintenance through various signaling pathways.

- **miR-21 and miR-146a: miR-21** is known for its role in regulating cell survival and proliferation. In AA, **miR-21** is often upregulated, which can inhibit apoptosis and promote the survival of damaged HSCs, potentially contributing to the persistence of dysfunctional hematopoiesis. **miR-146a**, on the other hand, is involved in modulating inflammatory

responses. Its downregulation in AA can lead to excessive inflammation and autoimmune damage to HSCs.[58-59]

- **miR-150: miR-150** regulates HSC differentiation and maintenance by targeting genes involved in hematopoietic development. In AA, altered expression of **miR-150** can disrupt normal HSC function and contribute to the failure of blood cell production.[60]

2. Immune System Modulation:

The autoimmune component of AA is influenced by miRNA-mediated regulation of immune responses. Dysregulated miRNAs can affect the activation and function of immune cells, leading to the destruction of hematopoietic cells.

- **miR-155: miR-155** plays a critical role in immune cell activation and inflammation. In AA, increased levels of **miR-155** can enhance the activation of T cells and macrophages, promoting autoimmune responses against bone marrow cells. This miRNA also affects the production of pro-inflammatory cytokines, exacerbating the inflammatory environment in the bone marrow.[61-62]
- **miR-223: miR-223** is involved in regulating inflammation and myeloid cell differentiation. In AA, changes in **miR-223** expression can impact the inflammatory milieu and contribute to the autoimmune destruction of hematopoietic cells.[63]

3. Apoptosis and Cell Survival:

The balance between cell survival and apoptosis is crucial for maintaining normal hematopoiesis. In AA, miRNAs that regulate these processes can influence disease severity.

- **miR-21:** As mentioned earlier, **miR-21** can inhibit apoptosis by targeting pro-apoptotic factors. In AA, the upregulation of **miR-21** can contribute to the survival of damaged hematopoietic cells, which may lead to ineffective blood cell production.[64]
- **miR-34a: miR-34a** is known to regulate apoptosis and cell cycle arrest. Its dysregulation in AA can impact the balance between cell death and survival, affecting the overall functionality of the bone marrow.[65]

4. Regulation of Cytokine Signaling:

Cytokines play a key role in the pathogenesis of AA by modulating immune responses and hematopoiesis. miRNAs can influence cytokine signaling pathways, impacting disease progression.

- **miR-155 and Cytokine Production: miR-155** regulates the production of cytokines such as TNF-α, IL-6, and IL-1β. In AA, dysregulation of **miR-155** can lead to altered cytokine profiles, contributing to the autoimmune attack on hematopoietic cells.[66]

- **miR-146a and Inflammation: miR-146a** modulates inflammatory responses by targeting genes involved in cytokine signaling. Its downregulation in AA can result in increased production of inflammatory cytokines and further immune-mediated damage to the bone marrow.[67]

5. Epigenetic Regulation:

miRNAs also play a role in epigenetic regulation, which can impact gene expression and cellular processes relevant to AA.

- **miR-29: miR-29** is involved in regulating DNA methylation and histone modification. In AA, altered expression of **miR-29** can influence epigenetic changes that affect gene expression related to hematopoiesis and immune responses.[68]
- **miR-181a: miR-181a** affects the expression of genes involved in hematopoiesis and inflammation through epigenetic mechanisms. Its dysregulation in AA can contribute to disrupted blood cell production and immune dysfunction.[69]

6. Potential Therapeutic Targets:

and improve disease outcomes.

- **miRNA-based Therapies:** Restoring the expression of tumor-suppressive miRNAs or inhibiting overexpressed oncomiRs could offer therapeutic benefits in AA. For example, increasing **miR-146a** levels could help reduce inflammation and autoimmune damage, while targeting **miR-155** might mitigate excessive immune activation.[70]
- **Combination Approaches:** Combining miRNA-based therapies with other treatments, such as immunosuppressive agents or hematopoietic growth factors, could enhance therapeutic efficacy and address multiple aspects of AA pathogenesis.[71]

7. Integration with Omics Technologies:

Combining miRNA research with other omics technologies, such as genomics, transcriptomics, and proteomics, can provide a comprehensive understanding of AA.

- **Omics Integration:** Integrating miRNA data with genomic and proteomic analyses can help identify novel biomarkers and therapeutic targets. This holistic approach can elucidate the interactions between miRNAs, genes, and proteins involved in AA.[72]

Therapeutic Implications of miRNA-Based Strategies

MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression post-transcriptionally, and their dysregulation has been implicated in various diseases, including

aplastic anemia (AA). Given their pivotal role in disease pathogenesis, miRNAs represent promising targets for therapeutic intervention.[73]

1. Restoration of Normal Hematopoiesis:

One of the primary therapeutic goals in AA is to restore normal hematopoiesis. Dysregulated miRNAs that affect hematopoietic stem cell (HSC) function and differentiation can be targeted to ameliorate the disease.

- **miRNA Mimics:** Introducing synthetic miRNA mimics that restore the expression of downregulated or absent miRNAs can help reestablish normal gene expression patterns. For example, **miR-146a** is often downregulated in AA, leading to excessive inflammation and autoimmune damage. Administering **miR-146a** mimics could reduce inflammation and protect HSCs from immune-mediated destruction.[74]
- **miRNA Inhibitors:** Conversely, overexpressed or dysfunctional miRNAs can be targeted using miRNA inhibitors (antagomirs). For instance, if **miR-21** is upregulated and contributing to impaired hematopoiesis by inhibiting apoptosis, using inhibitors to block **miR-21** might enhance the apoptosis of damaged cells and improve marrow function.[75]

2. Modulation of Immune Responses:

Autoimmunity plays a significant role in the pathogenesis of AA, and miRNAs involved in regulating immune responses offer potential therapeutic targets.

- **Immune Modulation:** miRNAs such as **miR-155** and **miR-223** are implicated in immune activation and inflammation. Targeting these miRNAs with specific inhibitors could dampen the autoimmune attack on hematopoietic cells and reduce the inflammatory environment in the bone marrow. For example, **miR-155** antagonists could be used to decrease the activation of T cells and macrophages, thereby alleviating the autoimmune component of AA.[76]
- **Restoration of Immune Tolerance:** Restoring the balance of miRNAs involved in maintaining immune tolerance could prevent the autoimmune destruction of hematopoietic cells. By targeting miRNAs that regulate regulatory T cells and other immune regulatory mechanisms, it may be possible to restore immune homeostasis and protect the bone marrow.[77]

3. Enhancing Hematopoietic Cell Survival and Proliferation:

MiRNAs that regulate cell survival and proliferation can be targeted to enhance hematopoietic cell function.

- **Anti-apoptotic Strategies:** In AA, overexpression of pro-survival miRNAs such as **miR-21** may lead to the persistence of damaged cells. Using miRNA inhibitors to target these

anti-apoptotic miRNAs could promote the elimination of dysfunctional cells and support the regeneration of healthy hematopoietic cells.[78-80]

- **Proliferative Support:** Conversely, miRNAs that inhibit cell proliferation may be targeted to promote the growth of hematopoietic progenitors. For example, if **miR-150** is downregulated and affecting HSC proliferation, restoring its levels could support the expansion of healthy hematopoietic cells.[81-82]

4. Combination Therapies:

Combining miRNA-based therapies with other treatments can enhance therapeutic efficacy and address multiple aspects of AA pathogenesis.

- **Synergistic Approaches:** Combining miRNA mimics or inhibitors with immunosuppressive agents or hematopoietic growth factors could offer synergistic effects. For example, using **miR-146a** mimics in conjunction with standard immunosuppressive treatments might provide a more comprehensive approach to managing autoimmune responses and improving hematopoiesis.[83-84]
- **Personalized Medicine:** Tailoring miRNA-based therapies to individual patient profiles based on specific miRNA dysregulation patterns could optimize treatment outcomes. Advanced miRNA profiling technologies can identify the most relevant miRNAs for each patient, guiding the selection of appropriate therapeutic interventions.[85]

5. Delivery Systems and Challenges:

Effective delivery of miRNA-based therapeutics is crucial for their success. Several delivery systems are being explored to enhance the stability and targeting of miRNA therapies.

- **Nanoparticle-Based Delivery:** Nanoparticles and liposomes can be used to deliver miRNA mimics or inhibitors specifically to target cells. These delivery systems can improve the stability and bioavailability of miRNAs, ensuring that they reach the bone marrow and exert their therapeutic effects.[86]
- **Challenges and Safety:** Ensuring the specificity of miRNA-based therapies and avoiding off-target effects is essential. Preclinical and clinical studies are needed to evaluate the safety and efficacy of these therapies, including potential side effects and long-term outcomes.[87]

Conclusion

Aplastic anemia (AA) is a complex hematological disorder characterized by the failure of the bone marrow to produce sufficient blood cells, resulting in severe anemia, thrombocytopenia, and leukopenia. The pathogenesis of AA involves both intrinsic defects in hematopoietic stem cells (HSCs) and extrinsic factors, including autoimmune responses and inflammatory processes.

MicroRNAs (miRNAs) have emerged as key regulators of gene expression and cellular function, playing a critical role in the development and progression of AA.

Dysregulation of miRNAs in AA affects various aspects of disease pathology, including HSC function, immune system modulation, apoptosis, and cytokine signaling. Specific miRNAs, such as **miR-21**, **miR-155**, and **miR-146a**, are involved in these processes and have been implicated in the disease's autoimmune and inflammatory components. By targeting these dysregulated miRNAs, it is possible to restore normal hematopoiesis, modulate immune responses, and enhance cell survival.

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Citation: Obeagu EI. Aplastic Anemia in HIV: Role of MicroRNA Signaling Pathways. *Elite Journal of Haematology, 2024; 2(9):* 17-32

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