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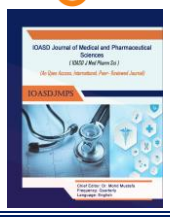

Unveiling the Molecular Mechanisms of Erythropoietin in HIV Pathogenesis: A Review

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ABSTRACT

Erythropoietin is a glycoprotein hormone traditionally recognized for its central role in regulating erythropoiesis. Increasing evidence, however, highlights its pleiotropic effects in immunity, inflammation, and cellular protection, which are particularly relevant in the pathogenesis of human immunodeficiency virus infection. Anemia remains one of the most common complications of HIV and is often linked to impaired EPO production or resistance to EPO signaling, exacerbated by chronic inflammation and viral-induced bone marrow suppression. Beyond hematopoiesis, EPO modulates immune responses, attenuates oxidative stress, and exerts anti-apoptotic effects through key pathways such as JAK2/STAT5, PI3K/Akt, and MAPK. These mechanisms may mitigate immune cell loss and tissue damage but can also inadvertently support viral persistence by protecting infected cells. Recombinant human EPO has shown clinical benefits in correcting HIV-associated anemia, yet its broader therapeutic implications and potential as a biomarker remain insufficiently explored. This review examines the molecular mechanisms by which EPO influences HIV pathogenesis, integrating insights into hematopoietic dysfunction, immune modulation, oxidative stress, apoptosis, and viral dynamics. A deeper understanding of these mechanisms could expand the therapeutic landscape of HIV care, positioning EPO as both a treatment adjunct and a marker of disease progression.

Keywords: Erythropoietin, HIV, Pathogenesis, Molecular Mechanisms, Immune Response, Anemia, EPO Receptors.

Review Article

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INTRODUCTION

Human immunodeficiency virus (HIV) continues to represent one of the most pressing global health challenges, with an estimated 39 million people living with the infection worldwide. Despite significant progress in antiretroviral therapy (ART) and improved survival outcomes, HIV remains associated with a spectrum of systemic complications beyond immune suppression. Among these, hematological abnormalities—particularly anemia—are highly prevalent and substantially contribute to morbidity, reduced quality of life, and poor prognosis. Anemia in HIV is multifactorial, often resulting from bone marrow suppression, nutritional deficiencies, chronic inflammation, opportunistic infections, and drug-induced cytotoxicity. A critical mediator within this pathophysiological landscape is erythropoietin (EPO), the glycoprotein hormone classically known for regulating erythropoiesis but increasingly recognized for its pleiotropic functions [1-2].

EPO is primarily synthesized by renal peritubular interstitial fibroblasts in response to hypoxia, exerting its effects through binding to the erythropoietin receptor (EPOR). The EPO–EPOR interaction activates downstream signaling pathways, including Janus kinase 2/signal transducer and activator of transcription 5 (JAK2/STAT5), phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt), and mitogen-activated protein kinase (MAPK). While these pathways are crucial for the survival and differentiation of erythroid progenitors, they also mediate broader biological effects, encompassing cytoprotection, antioxidant defense, and modulation of immune and inflammatory responses. Such pleiotropy has spurred growing interest in EPO's role in conditions beyond anemia, including cardiovascular disease, neurodegeneration, and infectious diseases [3-4].

In the context of HIV, the role of EPO extends well beyond the correction of anemia. The chronic immune activation, oxidative stress, and accelerated

apoptosis characteristic of HIV infection provide a unique environment in which EPO's molecular mechanisms become highly relevant. EPO has been shown to suppress excessive pro-inflammatory cytokine production, reduce oxidative damage, stabilize mitochondrial function, and limit apoptotic pathways. At the same time, persistent inflammation and viral proteins such as gp120 and Tat may impair EPO signaling, leading to functional resistance and blunting its protective effects. This paradox highlights a complex interplay between viral pathogenesis and host protective mechanisms mediated by EPO [5-6].

Moreover, EPO may exert indirect effects on HIV replication dynamics. By promoting cell survival and protecting CD4+ T lymphocytes from apoptosis, EPO could contribute to the preservation of immune function. However, these same mechanisms might inadvertently favor viral persistence by maintaining survival of infected cells, reflecting the dual and context-dependent roles of EPO in HIV biology. Clinically, recombinant human EPO (rhEPO) has been employed to treat HIV-associated anemia with substantial benefits in hemoglobin restoration and patient well-being. Nevertheless, the broader implications of EPO therapy—particularly its effects on immune regulation and viral dynamics—remain insufficiently understood.[7] Given these complexities, a comprehensive understanding of the molecular mechanisms of EPO in HIV pathogenesis is both timely and necessary. Such insights not only enrich our knowledge of host–pathogen interactions but may also identify new therapeutic opportunities. This review aims to explore the molecular underpinnings of EPO activity in the context of HIV infection, with a particular focus on its roles in hematopoietic dysfunction, immune modulation, oxidative stress, apoptosis, and potential influence on viral replication. By bridging molecular biology with clinical observations, we seek to underscore EPO's potential as both a therapeutic agent and a biomarker in HIV disease management [8-9].

AIM

The aim of this review is to explore the therapeutic potential of erythropoietin (EPO) beyond the treatment of anemia, exploring its pleiotropic effects across various organ systems and medical conditions.

Rationale

Erythropoietin, primarily recognized for its role in erythropoiesis, has garnered increasing attention for its diverse biological activities extending beyond hematopoiesis. While EPO therapy has been widely used for the treatment of anemia associated with chronic kidney disease, cancer chemotherapy, and other conditions, accumulating evidence suggests that EPO exerts pleiotropic effects on multiple organ systems and cellular processes. Understanding the broader therapeutic potential of EPO is of significant clinical interest and may offer novel treatment strategies for a range of medical conditions.

REVIEW METHODOLOGY

Literature Search Strategy

A systematic literature search was conducted to identify relevant studies published in peer-reviewed journals, clinical trial registries, and scientific databases such as PubMed, Scopus, and Embase. The search strategy employed a combination of keywords and Medical Subject Headings (MeSH) terms related to erythropoietin, therapeutic effects, and specific medical conditions (e.g., neuroprotection, cardioprotection, tissue repair). The search encompassed articles published up to the present date to ensure inclusivity.

Inclusion Criteria

The inclusion criteria for selecting relevant studies were as follows:

- Studies investigating the therapeutic effects of EPO beyond its role in anemia treatment.
- Original research articles, reviews, meta-analyses, and clinical trials published in English.
- Studies reporting data on the pleiotropic effects of EPO across various organ systems and medical conditions.
- Studies with clear methodologies and data analysis procedures.

Exclusion Criteria

Studies were excluded based on the following criteria:

- Articles not directly related to the therapeutic potential of EPO beyond anemia treatment.
- Studies lacking sufficient detail on methodology, data analysis, or results.
- Non-English publications.
- Duplicate publications or articles lacking original data.

Screening and Selection Process

The initial screening of articles was conducted based on title and abstract relevance to the topic. Subsequently, full-text assessment was performed to determine eligibility based on the inclusion and exclusion criteria outlined above. Any discrepancies in study selection were resolved through consensus among the reviewers.

Quality Assessment

Quality assessment of included studies was performed to evaluate the methodological rigor, validity, and reliability of the findings. Various tools and criteria were utilized, depending on the study design (e.g., Newcastle-Ottawa Scale for observational studies, Cochrane risk of bias tool for clinical trials).

Ethical Approval

Not applicable

EPO and EPO Receptors in HIV

The traditional understanding of EPO's role primarily revolves around its function in erythropoiesis, regulating the production of red blood cells to maintain oxygen homeostasis [10]. However, recent investigations have revealed a more intricate relationship between EPO and Human Immunodeficiency Virus (HIV), extending beyond its classical hematopoietic role [11]. Studies have documented the presence of EPO and its receptor (EPOR) not only in hematopoietic cells but also in various non-erythroid tissues and immune cells [12-13]. In the context of HIV, the expression patterns of EPO and EPOR become crucial determinants of their potential impact on disease progression. Dysregulation of EPO expression in HIV-infected individuals has been observed, raising questions about its implications for both hematopoietic and non-erythroid cellular functions [14]. Beyond its canonical role in erythropoiesis, the expression of EPOR on immune cells suggests a potential immunomodulatory function for EPO in the context of HIV [15]. Emerging evidence points to the involvement of EPO in the regulation of immune cell proliferation, differentiation, and cytokine production [12]. This dual role of EPO as both an erythropoietic and immunomodulatory agent prompts a closer examination of its contribution to the delicate balance between host defenses and viral persistence in HIV infection [16].

1. EPO–EPOR Signaling Pathways

EPO binding to EPOR induces receptor dimerization and subsequent activation of Janus kinase 2 (JAK2). Activated JAK2 phosphorylates tyrosine residues on EPOR, initiating multiple downstream signaling cascades:

- **JAK2/STAT5 pathway:** promotes erythroid progenitor proliferation and survival, and in immune cells, enhances lymphocyte viability and cytokine regulation.
- **PI3K/Akt pathway:** mediates anti-apoptotic effects by stabilizing mitochondrial membranes, reducing cytochrome c release, and inhibiting caspase activation.
- **MAPK pathway:** contributes to cell proliferation, stress adaptation, and the modulation of inflammatory responses [19].

2. Regulation of Apoptosis

HIV pathogenesis is characterized by accelerated apoptosis of CD4+ T cells. EPO mitigates this through PI3K/Akt and STAT5 signaling, which upregulate anti-apoptotic proteins (e.g., Bcl-2, Bcl-xL) and suppress pro-apoptotic mediators. This protective role may slow immune cell depletion but could also preserve HIV-infected cells, complicating the balance between host defense and viral persistence [20].

The dysregulation of EPO and EPOR expression in HIV may contribute to anemia, a common complication in HIV-infected individuals [17]. Additionally, altered EPO signaling may impact immune cell responses, potentially influencing the dynamics of viral replication and the progression of HIV to more advanced stages. Understanding the intricacies of EPO dysregulation in the context of HIV is pivotal for unraveling the complexities of disease pathogenesis. Given the dual nature of EPO as a hematopoietic growth factor and an immune modulator, exploring its therapeutic potential in HIV management becomes paramount [18]. Strategies targeting the EPO pathway may not only address anemia but also modulate immune responses, presenting a novel avenue for adjunctive therapeutic interventions. However, challenges such as the potential risk of viral reactivation and optimal dosing regimens need careful consideration in the pursuit of effective therapeutic strategies.

Molecular Mechanisms of Erythropoietin in HIV Pathogenesis

The biological actions of erythropoietin (EPO) in HIV infection are mediated primarily through its interaction with the erythropoietin receptor (EPOR) and the activation of downstream signaling pathways. These mechanisms extend well beyond erythropoiesis, intersecting with key processes in HIV pathogenesis, including immune regulation, oxidative stress, apoptosis, hematopoietic dysfunction, and viral replication.

3. Modulation of Oxidative Stress

Oxidative stress, driven by HIV proteins such as gp120 and Tat, contributes to immune dysfunction and tissue damage. EPO reduces reactive oxygen species (ROS) accumulation by inducing antioxidant enzymes like superoxide dismutase and glutathione peroxidase. Additionally, EPO enhances mitochondrial integrity, limiting oxidative injury and promoting cellular resilience in the face of chronic infection [21].

4. Immune Modulation

EPO exerts immunomodulatory effects relevant to HIV-induced chronic inflammation. It reduces the expression of pro-inflammatory cytokines (TNF-α, IL-1β, IFN-γ) via inhibition of NF-κB signaling, while enhancing regulatory T-cell activity. These effects may counterbalance immune hyperactivation, a hallmark of HIV progression, and support immune homeostasis [22].

5. Hematopoietic Dysfunction

Anemia in HIV is frequently linked to impaired EPO signaling. Inflammatory cytokines inhibit EPOR expression and disrupt erythroid progenitor responsiveness, creating a state of functional EPO resistance. This mechanism underlies the anemia of chronic disease observed in HIV, which persists despite elevated EPO levels, thereby contributing to poor clinical outcomes [23].

6. Influence on Viral Replication

EPO's effects on HIV replication remain incompletely defined. By protecting host cells from apoptosis, EPO may indirectly prolong the survival of HIV-infected cells, creating reservoirs that sustain viral persistence. Conversely, its anti-inflammatory and antioxidant effects may reduce the cellular environment favorable to viral replication. This duality underscores the complex, context-dependent role of EPO in viral dynamics [24].

Immunomodulatory Effects of EPO in HIV

Beyond its classical role as a key regulator of erythropoiesis, EPO has emerged as a multifaceted cytokine with immunomodulatory properties [19]. In the context of HIV infection, the intricate interplay between EPO and the immune system has garnered increasing attention, shedding light on its potential impact on immune responses and viral dynamics. Recent studies have uncovered the expression of EPO receptors (EPORs) on various immune cells, including T lymphocytes and monocytes [20]. This distribution implies a direct role for EPO in modulating immune cell function. EPO has been shown to influence the differentiation, proliferation, and survival of immune cells, suggesting a regulatory role in shaping the immune response during HIV infection. EPO has been implicated in the regulation of cytokine production, influencing the intricate network of signaling molecules that govern immune responses [21]. The cytokine milieu plays a crucial role in determining the balance between pro-inflammatory and anti-inflammatory signals in HIV-infected individuals. Understanding how EPO influences this balance may provide insights into the dynamics of chronic immune activation and inflammation characteristic of advanced HIV disease. The immunomodulatory effects of EPO extend to its potential impact on viral replication. Studies have suggested that EPO may influence the permissiveness of target cells to HIV, affecting the efficiency of viral entry, integration, and replication [22-23]. By modulating host cell factors, EPO may indirectly shape the course of HIV infection, impacting both the initial stages of viral establishment and the ongoing viral dynamics during chronic infection.

EPO has garnered significant attention in the context of HIV infection due to its multifaceted effects beyond its classical role in erythropoiesis. While traditionally recognized for its ability to stimulate red blood cell production, EPO's actions extend to modulation of immune function, inflammation, and tissue repair [24] HIV infection often leads to anemia due to multiple factors, including impaired erythropoiesis, chronic inflammation, and opportunistic infections. EPO administration can mitigate anemia by stimulating erythroid progenitor cells and promoting red blood cell production, thereby improving hemoglobin levels and alleviating symptoms of anemia in HIV-infected individuals. EPO and its receptor (EPOR) are expressed on various immune cells, including T lymphocytes, macrophages, and dendritic cells [25]. EPO signaling has been implicated in the regulation of immune cell proliferation, differentiation, and function. In the context of HIV infection, EPO may influence the balance between pro-inflammatory and anti-inflammatory cytokines, modulating immune activation and potentially impacting disease progression [26]. HIV-associated neurocognitive disorders (HAND) represent a significant complication of HIV infection, characterized by cognitive impairment and neurological dysfunction. EPO has neuroprotective properties and has been shown to attenuate neuronal damage, enhance neurogenesis, and improve cognitive function in various disease models. In HIV-infected individuals, EPO administration may hold promise for mitigating neurocognitive impairment and enhancing quality of life [27]. Emerging evidence suggests that EPO may influence HIV replication and disease progression through direct and indirect mechanisms. EPO signaling pathways intersect with those utilized by HIV viral proteins, potentially affecting viral transcription, replication, and latency. Additionally, EPO-induced modulation of immune responses and inflammation may impact the host-virus interaction and influence HIV disease outcomes. Given its pleiotropic effects, EPO has garnered interest as a potential therapeutic agent for managing HIV-related complications, including anemia, immune dysfunction, and neurocognitive impairment. Clinical trials investigating the use of EPO in HIV-infected individuals have shown promising results in improving hematological parameters and quality of life, although further research is warranted to delineate its long-term safety and efficacy [28-29].

EPO's cytoprotective effects, traditionally associated with its role in preventing apoptosis in erythroid progenitor cells, may also extend to immune cells.20 This anti-apoptotic property could contribute to the maintenance of immune cell populations and potentially influence the overall immune competence of individuals living with HIV. The immunomodulatory effects of EPO in the context of HIV have direct implications for disease progression.30 A delicate balance exists between enhancing host immune responses and preventing excessive inflammation, as chronic immune activation is a hallmark of advanced HIV disease. Understanding how EPO influences this balance is essential for elucidating its potential as a therapeutic target in mitigating immune dysregulation associated with HIV infection.

The Role of EPO in HIV Pathogenesis

The role of EPO in HIV pathogenesis is multifaceted and extends beyond its classical function in erythropoiesis. While traditionally recognized for its role in red blood cell production, EPO has emerged as a potential modulator of various aspects of HIV infection and disease progression. EPO and its receptor, EPOR, are expressed not only in hematopoietic cells but also in various immune cell types, including T lymphocytes,

macrophages, and dendritic cells. EPO signaling has been implicated in the regulation of immune cell proliferation, differentiation, and function. In the context of HIV infection, EPO may influence the balance between pro-inflammatory and anti-inflammatory cytokines, thereby modulating immune activation and potentially impacting disease progression [31]. Chronic inflammation is a hallmark of HIV infection and plays a central role in driving disease progression. EPO has been shown to possess anti-inflammatory properties, including the ability to suppress the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6). By attenuating inflammation, EPO may mitigate immune activation and reduce the systemic inflammatory burden associated with HIV infection. Anemia is a common complication of HIV infection, arising from multiple factors including impaired erythropoiesis, chronic inflammation, and opportunistic infections. EPO administration can stimulate erythroid progenitor cells and promote red blood cell production, thereby improving hemoglobin levels and alleviating symptoms of anemia in HIV-infected individuals. HIV-associated neurocognitive disorders (HAND) represent a significant complication of HIV infection, characterized by cognitive impairment and neurological dysfunction [32]. EPO has been shown to possess neuroprotective properties, including the ability to attenuate neuronal damage, enhance neurogenesis, and improve cognitive function in various disease models. In HIV-infected individuals, EPO administration may hold promise for mitigating neurocognitive impairment and enhancing quality of life. Emerging evidence suggests that EPO may influence HIV replication and disease progression through direct and indirect mechanisms. EPO signaling pathways intersect with those utilized by HIV viral proteins, potentially affecting viral transcription, replication, and latency. Additionally, EPO-induced modulation of immune responses and inflammation may impact the host-virus interaction and influence HIV disease outcomes [33].

EPO as a Therapeutic Target in HIV

The multifaceted nature of EPO, extending beyond its classical role in erythropoiesis, has prompted investigations into its potential as a therapeutic target in the context of HIV infection [34]. Anemia is a common complication in HIV-infected individuals, contributing to morbidity and negatively impacting quality of life [33]. EPO, known for its erythropoietic function, presents a promising avenue for addressing HIV-associated anemia. Clinical studies have explored the use of exogenous EPO or EPO analogs to stimulate red blood cell production, offering a potential therapeutic strategy to alleviate anemia and improve overall well-being in HIV patients. Beyond its hematopoietic effects, EPO's immunomodulatory properties raise the prospect of using EPO as a therapeutic tool to modulate immune responses in HIV [34]. By influencing immune cell function, EPO may enhance antiviral responses, potentially contributing to the control of viral replication. This dual functionality positions EPO as a unique therapeutic candidate capable of addressing both hematologic and immunologic aspects of HIV-associated complications. Chronic immune activation and inflammation are hallmarks of advanced HIV disease, contributing to disease progression and associated comorbidities [35]. EPO's ability to regulate cytokine production and immune cell survival suggests its potential role in combating inflammation and immune dysregulation. Targeting the EPO pathway may offer a novel approach to modulate the delicate balance between immune activation and tolerance in HIV-infected individuals. Despite the therapeutic promise, challenges exist in harnessing the potential of EPO in HIV management [26]. Concerns about the risk of viral reactivation and the optimal dosing regimens need careful consideration. Additionally, the potential impact of EPO on the dynamics of viral reservoirs and long-term outcomes requires further investigation.

Therapeutic promise of EPO beyond the treatment of anemia

Beyond its well-established role in the treatment of anemia, EPO holds therapeutic promise across a range of medical conditions due to its pleiotropic effects on various organ systems and cellular processes. EPO has demonstrated neuroprotective properties in preclinical and clinical studies, making it a promising therapeutic agent for neurological disorders such as ischemic stroke, traumatic brain injury, and neurodegenerative diseases like Alzheimer's and Parkinson's disease [30]. EPO promotes neuronal survival, reduces inflammation, enhances neurogenesis, and improves functional recovery following neural injury or disease. EPO has been shown to exert cardioprotective effects in experimental models of myocardial infarction and heart failure. It promotes angiogenesis, inhibits apoptosis, reduces infarct size, and improves cardiac function following ischemic injury. Clinical trials have explored the potential of EPO therapy for improving outcomes in patients with acute coronary syndromes, heart failure, and undergoing cardiac surgery. EPO plays a role in tissue repair and regeneration beyond its effects on erythropoiesis [31]. It promotes wound healing, enhances tissue perfusion, and stimulates the proliferation and differentiation of stem and progenitor cells involved in tissue regeneration. EPO-based therapies hold promise for accelerating wound healing, promoting tissue repair following injury or surgery, and improving outcomes in conditions such as diabetic foot ulcers and chronic wounds.36 EPO exhibits immunomodulatory properties that extend beyond its hematopoietic effects. It regulates immune cell function, modulates cytokine production, and suppresses inflammatory responses [37]. EPO-based therapies have been investigated for their potential in modulating immune dysregulation and attenuating inflammation in autoimmune diseases, inflammatory bowel disease, and sepsis. EPO has renoprotective effects in addition to its

role in erythropoiesis [38]. It promotes renal tissue repair, inhibits apoptosis of renal cells, and attenuates kidney injury in various experimental models of acute kidney injury and chronic kidney disease [39]. Clinical trials have explored the use of EPO therapy for preserving renal function and delaying the progression of kidney disease in patients with chronic kidney disease and undergoing renal transplantation. EPO holds therapeutic promise beyond its established role in the treatment of anemia, with potential applications in neuroprotection, cardioprotection, tissue repair, immune modulation, and renoprotection across a spectrum of medical conditions. Further research is needed to elucidate the mechanisms underlying these diverse effects and to optimize EPO-based therapies for clinical use in various disease settings [40].

CONCLUSION

EPO, long recognized for its essential role in red blood cell production, emerges as a multifaceted regulator at the intersection of hematopoiesis, immunity, and cellular stress responses in the context of HIV infection. Its molecular mechanisms-spanning JAK2/STAT5, PI3K/Akt, and MAPK signaling pathways-confer anti-apoptotic, antioxidant, and immunomodulatory effects that may counterbalance key pathological features of HIV, including chronic inflammation, oxidative stress, and accelerated T-cell loss. However, HIV-related factors such as persistent cytokine dysregulation, viral proteins, and bone marrow suppression often impair EPO responsiveness, leading to anemia of chronic disease and limiting EPO's protective potential. The duality of EPO's role in HIV pathogenesis-protective in mitigating immune and hematopoietic damage, yet potentially permissive to viral persistence-highlights the complexity of its biological functions. While recombinant human EPO has demonstrated clinical benefits in managing HIV-associated anemia, its broader therapeutic implications remain underexplored. Future research should focus on delineating context-specific effects of EPO, investigating non-erythropoietic EPO derivatives, and evaluating its potential as a biomarker of disease progression or treatment response.

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