Nanotechnology Perceptions
ISSN 1660-6795
www.nano-ntp.com

Pharmacogenetic And Nanomedicine Perspectives For Optimizing Erythropoietin Therapy In Patients With End-Stage Renal Disease

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Erythropoietin (EPO) therapy is essential for managing anemia in patients with end-stage renal disease (ESRD), however, patients' responses can vary due to several clinical and genetic factors. This review explores genetic polymorphisms that may influence EPO responsiveness and highlights the role of nanomedicine in tailoring EPO therapy to provide valuable insights for personalized anemia management strategies in patients with ESRD.

Key genetic variants in proinflammatory cytokines, including Interleukin-1β (*IL-1β*) 511C/T, IL-6 174G/C, and Tumor Necrosis Factor (*TNF*)-α 308G/A and 238A/G, promote inflammation, suppress erythropoiesis, and contribute to EPO resistance. Despite the anti-inflammatory role of IL-10, the *IL-10* gene 1082G/A, 819C/T, and 592C/A polymorphisms can reduce iron availability for erythropoiesis, limiting erythropoietin effectiveness. The DD genotype of the Angiotensin-converting Enzyme Insertion/Deletion polymorphism (*ACE* I/D) is associated with high ACE activity leading to increased Angiotensin II levels and consequently active erythropoiesis and increased EPO requirements. Variants in calcium signaling genes, particularly the *STIM1* rs1561876 AA and AG genotypes, *ORAI1* rs6486795 CC and CT genotypes, and *ORAI1* rs12320939 GG and TG genotypes raise the risk of EPO hyporesponsiveness. The BB variant of the *BsmI* polymorphism in the Vitamin D Receptor (*VDR*) gene is associated with lower EPO requirements and improved responsiveness compared to Bb and bb variants, probably due to higher vitamin D levels that enhance erythropoiesis.

Nanomedicine offers a transformative approach to overcoming the limitations of traditional EPO therapy by enhancing drug delivery, stability, and targeting. This results in improved therapeutic efficacy, reduced dosing frequency, and increased patient adherence. Additionally, the use of nanotechnology in EPO therapy can address drug resistance and allow for more sustained plasma levels, ultimately optimizing treatment outcomes for patients.

Keywords: Erythropoietin responsiveness, Erythropoietin resistance, Genetic polymorphisms, Chronic kidney disease, Pharmacogenetic, Nanomedicine

Introduction

Erythropoietin (EPO) therapy is a cornerstone in managing anemia for patients undergoing hemodialysis, as kidney function in end-stage renal disease (ESRD) is insufficient to produce adequate levels of endogenous EPO (Al-Khalaf *et al*., 2012; Tanveer *et al*., 2019). The primary goal of EPO therapy is to stimulate erythropoiesis, thereby increasing hemoglobin levels and

improving the quality of life for these patients (Ibrahim, 2016). Studies indicate that the administration of recombinant human EPO (rhEPO) significantly raises hemoglobin concentrations, which is essential for alleviating anemia-related symptoms such as fatigue and weakness (Kawano *et al*., 2017, Ghasemi *et al*., 2019). However, various factors can reduce the effectiveness of EPO therapy, leading to EPO resistance or hyporesponsiveness (Al-Ali *et al*., 2014; Dzekova-Vidimliski, 2023).

EPO resistance, also known as erythropoiesis-stimulating agents hyporesponsiveness, is defined as the inability to achieve a hemoglobin increase of at least 1 g/dL after a given treatment period, or the need for significantly higher EPO doses to maintain target hemoglobin levels (Bamgbola, 2011; Suttorp *et al*., 2013). A useful tool used to assess EPO resistance is the Erythropoietin Resistance Index (ERI), which is calculated by dividing the weekly EPO dose by the patient's hemoglobin concentration. It not only measures resistance but also helps identify patients at higher risk for adverse outcomes, such as increased mortality (Chung *et al*., 2011; Lu *et al*., 2020).

Several factors contribute to EPO resistance in hemodialysis patients, nutritional deficiencies, systemic inflammation, and various comorbidities. Inflammatory cytokines can disrupt iron metabolism, leading to functional iron deficiency and consequently EPO hyporesponsiveness, which worsens anemia. Comorbid conditions like cardiovascular disease, diabetes, hyperparathyroidism, and other chronic kidney disease (CKD)-related complications further influence the body's responsiveness to EPO therapy (Perl *et al*., 2012; Luo *et al*., 2016; El-HadyAhmed & El-Maghraby, 2016; Lu *et al*., 2020; Santos *et al*., 2020; Zhang *et al*., 2021; Ahmed *et al*., 2023). In addition to these clinical factors, genetic variations are believed to play a crucial role in modulating EPO therapy. They can alter how patients respond to EPO, influencing the dosage required to reach target hemoglobin levels (Khan *et al*., 2023).

Pharmacogenetics is a branch of medicine that focuses on understanding how genetic variations influence individual responses to drugs. This field has gained significant attention as it offers the potential to tailor drug therapies to the genetic profiles of patients, thereby optimizing treatment efficacy and minimizing adverse effects (Daly, 2010; Skavinska, 2023). In this context, this review provides a comprehensive analysis of the genetic polymorphisms that influence erythropoietin responsiveness to identify how genetic insights can inform personalized therapeutic strategies to optimize anemia management in end-stage chronic kidney disease. Furthermore, it highlights the role of nanomedicine in addressing EPO therapy, as it has emerged as a promising approach to enhance erythropoietin (EPO) responsiveness in several conditions (Kim *et al*., 2017; Rahimmanesh *et al*., 2022).

Genetic variants influencing EPO responsiveness

Genetic polymorphisms of pro-inflammatory cytokines

Interleukin-1 (IL-1), Interleukin-6 (IL-6), and Tumor Necrosis Factor-Alpha (TNF-α) are key pro-inflammatory cytokines that play significant roles in the inflammatory processes associated with CKD and its complications, particularly in patients undergoing hemodialysis. Polymorphisms in the genes encoding these cytokines have been associated with variations in their production, contributing to the inflammatory environment that affects erythropoiesis and influences resistance to EPO therapy (Barartabar, 2018; Nazemian et al., 2021; Dzekova-Vidimliski, 2023; Gao et al., 2023).

Several previous studies have indicated that the *IL-1β* -511C/T polymorphism may influence the expression, secretion, and cellular transport of the IL-1β protein and mRNA translation. Some researchers have proposed that this SNP could disrupt the regulatory mechanism of IL-1β production or lower IL-1a levels, consequently increasing the production or activity of IL-1β in vivo. (Chua et al., 2009). Inflammation is a key predictor of resistance to EPO therapy, with pro-inflammatory cytokines known to inhibit erythropoiesis. IL-1β, in particular, suppresses the formation of bone marrow erythroid progenitors and reduces EPO production, contributing to diminished red blood cell synthesis. Additionally, pro-inflammatory cytokines like IL-1β can impair iron utilization, interfering with hemoglobin synthesis. Given that IL-1β production is influenced by genetic factors, such as polymorphisms, its role in promoting inflammation suggests a potential association with EPO resistance in patients undergoing treatment for anemia. (Jeong et al., 2008).

IL-6 is a pleiotropic pro-inflammatory cytokine involved in various biological processes, including hematopoiesis, inflammation, and the acute-phase response. Its synthesis and degradation are influenced by single nucleotide polymorphisms (Al-Radeef et al., 2018). Polymorphisms in the promoter region of the *IL-6* gene, particularly the 174G/C variant, have been linked to differences in IL-6 production. The G allele in this polymorphism is associated with higher IL-6 levels, contributing to chronic inflammation. This inflammatory state stimulates the release of hepcidin from the liver, which suppresses both intestinal iron absorption and the release of iron from internal stores (Barartabar, 2018; Gao et al., 2023, Ali et al., 2020). Studies have shown that individuals with the G allele of the *IL-6* 174G/C polymorphism require higher doses of erythropoiesis-stimulating agents to achieve target hemoglobin levels (Girndt et al., 2007), suggesting an association with hyporesponsiveness to these treatments.

TNF-α is a key cytokine in the inflammatory response and is produced by various cell types (Louis et al., 1998). Most evidence suggests that endogenous TNF-α production is influenced by promoter polymorphisms, particularly the -308 G/A variant, which affects mRNA and protein expression levels (Khan et al., 2016). Another polymorphism, 238AG, has also been linked to elevated transcriptional activity (Abraham et al., 1999; Hagag et al., 2021). Studies have demonstrated that elevated concentrations of TNF-α increase the need for higher doses of EPO to restore erythrocyte colony formation, highlighting its negative impact on red blood cell production (Louis et al., 1998). Furthermore, a strong correlation has been observed between TNF-α production levels and the EPO doses required in hemodialysis patients, indicating that increased TNF-α may contribute to EPO resistance (Goicoechea et al., 1998).

Genetic polymorphisms of anti-inflammatory cytokines

IL-10 is a crucial anti-inflammatory cytokine produced by various blood and organ cells. It plays a vital role in controlling excessive inflammatory responses, balancing innate immunity, and promoting tissue repair to maintain homeostasis during inflammation and infection (Mu et al., 2021). The most studied polymorphisms in the *IL-10* gene, 1082G/A, 819C/T, and 592C/A, are located in the promoter region and influence *IL-10* expression. These single nucleotide polymorphisms create three major haplotypes: GCC, linked to higher cytokine production and increased EPO dosage for anemia treatment in chronic disease; ACC, associated with intermediate production; and ATA, with low production (de Oliveira Júnior et al., 2015; Moudi et al., 2018). However, a conflicting finding has been reported regarding the *IL-10* 1082G/A polymorphism's effect on responsiveness to ESPs by Girndt et al. (2007). They

suggested that the absence of a clear association might stem from IL-10's direct inhibitory effects on hematopoiesis, despite its anti-inflammatory benefits. This conflicting evidence indicates a need for further research to clarify the role of *IL-10* polymorphisms in EPO responsiveness.

Angiotensin-converting enzyme insertion/deletion (ACE I/D) polymorphism

The *ACE* I/D polymorphism is a well-known genetic variation associated with various physiological and pathological conditions. This polymorphism results from the presence or absence of a 287-base pair Alu repeat sequence in intron 16 of the *ACE* gene, resulting in three genotypes: insertion homozygous (II), deletion homozygous (DD), and heterozygous (ID). Individuals with the DD genotype have significantly higher serum ACE levels compared to those with the II genotype, with ID individuals showing intermediate ACE levels (Yousef et al., 2014).

Studies have demonstrated that the *ACE* I/D polymorphism can significantly affect EPO resistance in dialysis patients. Those with the DD genotype typically require higher doses of EPO to reach hemoglobin levels similar to those of individuals with the II genotype (Dzekova-Vidimliski, 2023). As ACE plays a crucial role in the production of Angiotensin II (Ang II), DD carriers exhibit the highest levels of both ACE and Ang II. In vitro studies have shown that Ang II stimulates the proliferation of early erythroid progenitors, suggesting that *ACE* DD individuals may have increased erythropoietic activity, leading to a greater need for EPO (Jeong et al., 2008).

Genetic polymorphisms of calcium release-activated proteins

Evidence suggests that intracellular Ca^{2+} levels play crucial roles in the overall physiological processes of erythroid progenitor cell differentiation and proliferation, terminal enucleation, as well as the aging and clearance of mature red blood cells (Zhang et al., 2022).

The STIM1 protein plays a crucial role in regulating store-operated calcium entry (SOCE) by interacting with Orai1, a Ca^{2+} channel located in the plasma membrane. STIM1 undergoes a conformational change that allows it to translocate to areas near the plasma membrane, where it interacts with Orai1 to facilitate calcium influx into the cell (Muik et al., 2011; Derler et al., 2013).

Genetic variations in the *STIM1* gene can affect its expression and function, potentially leading to altered calcium signaling pathways that may influence EPO responsiveness. A study by Kao et al (2021) reported that patients with the AA genotype of rs1561876 in the *STIM1* gene, and the CC or CT genotypes of rs6486795 in *ORAI1* gene, were associated with increased risk of erythropoietin resistance. Another study in Egypt supported the finding that polymorphisms in *STIM1* and *ORAI1* genes confer EPO resistance in patients with end-stage renal disease; they found that AG genotype of rs1561876 in *STIM1* gene, the TC genotype of rs6486795 and TG or GG genotypes of rs12320939 in *ORAI1* gene are associated with an increased risk of erythropoietin resistance (Gomaa et al., 2025).

Vitamin D receptor (VDR) polymorphisms

The active form of vitamin D [1,25(OH)2D3] primarily regulates calcium homeostasis and bone development but also plays non-skeletal roles, as vitamin D receptors (VDRs) are found in various tissues. The vitamin D endocrine system is involved in several biological processes,

including musculoskeletal development, blood pressure regulation, and erythropoiesis (Kim et al., 2016).
Vitamin D deficiency is prevalent among patients with chronic kidney disease (CKD) and has been linked to increased resistance to EPO therapy, complicating anemia management in these patients (Kim et al., 2016; Joksimovic Jovic et al., 2022).
The *BsmI* polymorphism in the *VDR* gene occurs in intron 8, where the substitution of the G allele with an A allele results in the loss of the restriction site (Sah et al., 2024). There are three possible genotypes at the *BsmI* locus: wild-type (bb), heterozygous mutation (Bb), and homozygous mutation (BB). Studies have shown that variations in the BsmI genotypes influence gene transcription and protein expression, affect VDR functionality, and impact vitamin D metabolism and activity. The AA genotype was reported to be associated with higher vitamin D levels than the AG and GG genotypes (Huang et al., 2007; Sezer et al., 2007). The BB variant of *BsmI* has been related to lower recombinant human EPO requirements for achieving higher hemoglobin levels in maintenance hemodialysis patients without chronic inflammation, indicating better EPO responsiveness (Sezer et al., 2007). This can be attributed to the association of the homozygous mutant genotype (AA) with high vitamin D levels which can enhance the response to EPO therapy.

Nanomedicine for optimizing EPO therapy

Nanomedicine represents a revolutionary approach in the field of healthcare, leveraging nanotechnology to enhance the diagnosis, treatment, and prevention of diseases. By utilizing nanoparticles, which are typically between 1 and 100 nanometers in size, nanomedicine enables the creation of drug-delivery systems that improve the pharmacokinetics and bioavailability of therapeutic agents (Meel et al., 2019; Paus et al.; 2021). These nanoparticles can be engineered to achieve targeted delivery, allowing for the accumulation of drugs at specific sites through mechanisms such as the enhanced permeability and retention (EPR) effect (Moacă et al., 2022).
EPO therapy often faces challenges such as a short half-life, rapid clearance from the bloodstream, and the need for frequent dosing, which can lead to patient non-compliance and fluctuations in hemoglobin levels. Nanomedicine has emerged as a promising solution to these issues, particularly through its application in EPO delivery systems to improve the hormone's pharmacokinetics and bioavailability (Dhapake & Avari, 2019; Dygai et al., 2013). A significant application of nanomedicine in EPO therapy is the use of nanoparticles to enhance drug delivery. Polymeric nanoparticles can encapsulate EPO, enabling controlled and sustained hormone release, thus reducing the frequency of administration and potentially enhancing therapeutic effects (Dhapake & Avari, 2019). This sustained release not only minimizes the risk of side effects associated with high doses of EPO but also helps maintain stable plasma levels, addressing resistance in some patients. The Food and Drug Administration (FDA) has approved the PEGylation process which involves attaching polyethylene glycol (PEG) chains to therapeutic proteins including erythropoietin. PEGylation has been shown to increase protein stability and circulation time in the bloodstream, reducing the frequency of injections. This modification not only can improve patient adherence but also enhance the overall therapeutic efficacy of EPO by maintaining more consistent plasma levels (Meng et al., 2012).
Nanotechnology-based modifications to EPO can further enhance its pharmacokinetic properties. The immobilization of EPO via electron-beam synthesis has been demonstrated to

effectively stimulate erythropoiesis while retaining its biological activity and improving stability, an approach that could benefit patients not responding adequately to standard EPO formulations (Dygai et al., 2011). Moreover, nanomedicine can facilitate the co-delivery of EPO with other hematopoietic growth factors, potentially creating synergistic effects that boost erythropoiesis more effectively than EPO alone (Kim et al., 2017).

Targeted nanomedicine strategies can further optimize EPO therapy by engineering nanoparticles to target erythroid progenitor cells in the bone marrow. This precision ensures that EPO is delivered to the most relevant sites, helping to mitigate resistance and enhance therapeutic outcomes (Lu et al., 2023).

Conclusion

Genetic polymorphisms in pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α), anti-inflammatory cytokines (IL-10), Angiotensin-Converting Enzyme (ACE), calcium signaling proteins (STIM1 and ORAI1), and the Vitamin D receptor (VDR) have been shown to influence EPO responsiveness and dosage requirements in patients with ESRD. These findings highlight the need for personalized therapeutic approaches to improve anemia management in these patients. Nanomedicine holds significant potential for improving EPO therapy in patients experiencing resistance. Through innovative drug delivery systems, modifications to enhance pharmacokinetics, and the integration of gene editing technologies, nanomedicine can optimize EPO treatment, ultimately leading to better management of anemia and improved patient outcomes. However, continued research and development in this field are necessary to fully realize the potential of nanomedicine in optimizing EPO therapy and addressing the challenges associated with conventional treatment methods.

Funding Details

No external fund was received

Acknowledgment

The authors are thankful to the University of Bisha, Saudi Arabia, for the financial support through the Research Support Program for the Publication in the Ranked Journals.

Disclosure Statement

The author declares that there is no conflict of interest

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