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ERYTHROPOIETIN IN OVARIAN CANCER: CLINICAL IMPLICATIONS FOR TUMOR BEHAVIOR AND ANEMIA MANAGEMENT

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ABSTRACT

Erythropoietin (EPO), a glycoprotein hormone traditionally recognized for its role in erythropoiesis, has emerged as a multifaceted player in oncology. In ovarian cancer, a malignancy with high morbidity and mortality among women worldwide, EPO assumes dual relevance: as a therapeutic agent for anemia and as a potential modulator of tumor biology. Evidence suggests that erythropoietin receptors (EPOR) are expressed in ovarian cancer cells, where EPO signaling may influence proliferation, angiogenesis, apoptosis resistance, and metastatic potential. At the same time, anemia remains a frequent and debilitating complication of ovarian cancer, often resulting from chronic inflammation, myelosuppressive chemotherapy, and disease-related factors. The therapeutic use of recombinant human erythropoietin (rhEPO) in this setting has improved quality of life by reducing transfusion dependence, but concerns persist regarding its possible tumor-promoting effects. This review synthesizes current knowledge on the biological interplay between erythropoietin and ovarian cancer, evaluates clinical evidence on its use for anemia management, and discusses future directions for safely balancing symptom relief with oncologic outcomes.

Keywords: *Erythropoietin, Ovarian Cancer, Tumor Progression, Anemia, Therapeutic Strategies*

Introduction

Ovarian cancer remains one of the most lethal gynecological malignancies, with high rates of late-stage presentation and poor long-term survival [1-2]. Despite advances in surgical techniques and systemic therapies, including platinum-based chemotherapy and targeted agents, most patients eventually experience relapse and treatment resistance [3-4]. Beyond its oncologic challenges, ovarian cancer imposes a significant systemic burden, with anemia emerging as one of the most frequent and debilitating complications. Anemia not only worsens fatigue and quality of life but also impairs tolerance to chemotherapy, increases transfusion dependence, and is associated with poorer survival outcomes [5-6]. Erythropoietin (EPO), a glycoprotein hormone primarily synthesized by the kidneys in response to hypoxia, has long been recognized as the central regulator of erythropoiesis. Its clinical use was transformed by the development of recombinant human erythropoietin (rhEPO), which rapidly became a cornerstone in the management of anemia across chronic kidney disease, hematological disorders, and oncology. For patients with ovarian cancer, the use of rhEPO offered an alternative to frequent transfusions, with the promise of sustained improvements in hemoglobin levels and functional status [7].

However, as research into erythropoietin biology expanded, it became evident that EPO exerts effects beyond hematopoiesis. The discovery of erythropoietin receptors (EPOR) on non-hematopoietic tissues, including ovarian cancer cells, raised new questions about its broader role in tumor biology. Activation of EPO–EPOR signaling pathways has been implicated in cellular proliferation, resistance to apoptosis, angiogenesis, and adaptation to hypoxia—all hallmarks of cancer progression. These findings have led to concerns that therapeutic EPO, while beneficial for anemia, might inadvertently fuel tumor growth or undermine chemotherapy efficacy [8-9]. The paradoxical role of erythropoietin in ovarian cancer underscores a fundamental clinical dilemma: how to alleviate anemia, a complication that significantly diminishes patient well-being, without compromising oncologic outcomes. This dilemma is particularly pressing in ovarian cancer, where anemia is not only common but also often multifactorial, arising from chronic disease, nutritional deficiencies, marrow suppression from chemotherapy, and systemic inflammation driven by tumor biology. The complexity of these mechanisms necessitates a nuanced approach to anemia management that balances symptom relief with long-term disease control [10-11].

Clinical trials and observational studies have offered mixed insights into the safety and efficacy of erythropoietin in oncology. While many patients experience clear symptomatic benefit and reduced transfusion requirements, concerns persist regarding increased thromboembolic events and possible reductions in overall survival in certain cancer populations. The inconsistent results have prompted regulatory agencies and professional societies to issue cautious guidelines,

advocating for restricted use of EPO in oncology, with careful patient selection and close monitoring. Yet, ovarian cancer remains underrepresented in these discussions, leaving a gap in evidence-based recommendations tailored to this population [12]. At the same time, ongoing research continues to highlight potential therapeutic opportunities. A deeper understanding of EPO–EPOR signaling may not only clarify the risks of EPO therapy but also open new avenues for targeted interventions. For instance, novel erythropoiesis-stimulating agents or modified EPO analogs that retain hematopoietic benefits while minimizing tumor-related risks could offer safer alternatives. Additionally, biomarker-driven approaches that account for EPOR expression in tumors may help identify patients most likely to benefit from, or be harmed by, erythropoietin therapy [13-14]. This review aims to synthesize current evidence on erythropoietin in the context of ovarian cancer, focusing on two interrelated domains: its biological impact on tumor behavior and its clinical utility in anemia management.

Aim

The aim of this narrative review is to evaluate the role of erythropoietin in ovarian cancer, integrating evidence on tumor biology, EPOR signaling, anemia management, and clinical implications.

Methods

This narrative review utilized a structured, non-systematic approach to synthesize evidence on erythropoietin in ovarian cancer. Literature searches were performed in PubMed, Scopus, Web of Science, and Google Scholar using combinations of keywords: *erythropoietin*, *EPOR*, *ovarian cancer*, *anemia*, *tumor proliferation*, *angiogenesis*, and *chemotherapy*. Reference lists of relevant articles were manually screened for additional studies.

Eligible studies included original research, preclinical studies, clinical trials, observational studies, and reviews addressing EPO biology, EPOR expression in ovarian tumors, anemia management, or clinical outcomes related to EPO therapy. Non-English publications and studies unrelated to EPO or ovarian cancer were excluded. Data extraction focused on EPO signaling pathways, EPOR expression, effects on tumor proliferation, angiogenesis, apoptosis, chemotherapy response, anemia correction efficacy, and safety outcomes. Findings were synthesized narratively to summarize mechanisms, clinical implications, and therapeutic considerations.

Mechanisms Linking Erythropoietin to Tumor Behavior

The biological influence of erythropoietin in ovarian cancer extends beyond its classical role in red blood cell production, with growing evidence implicating it as a potential modulator of tumor progression. Central to this expanded role is the discovery that erythropoietin receptors (EPOR) are expressed not only on hematopoietic progenitor cells but also on a range of solid tumors, including ovarian cancer. Activation of the EPO–EPOR axis in malignant tissues initiates intracellular signaling cascades such as JAK2/STAT5, PI3K/AKT, and MAPK/ERK, pathways that are well recognized for their involvement in cell proliferation, survival, and

angiogenesis. This convergence of signaling suggests that erythropoietin may inadvertently promote several hallmarks of cancer [15]. One of the most significant effects of EPO signaling in tumor cells is the enhancement of proliferative capacity. By stimulating STAT5 and ERK-mediated transcriptional activity, erythropoietin promotes DNA synthesis and cell cycle progression, enabling ovarian cancer cells to multiply more aggressively. In parallel, the PI3K/AKT pathway contributes to cellular survival by inhibiting pro-apoptotic mechanisms. This survival advantage is particularly concerning in the context of chemotherapy, as preclinical studies suggest that erythropoietin may shield cancer cells from cytotoxic injury induced by platinum- or taxane-based regimens, which are the mainstay of ovarian cancer treatment [16].

Another mechanism through which erythropoietin may shape tumor behavior is its contribution to angiogenesis. Hypoxic regions within tumors are known to upregulate both EPO and EPOR expression as part of the adaptive response to low oxygen tension. In this setting, erythropoietin not only supports cancer cell survival but also enhances the expression of vascular endothelial growth factor (VEGF), a key driver of neovascularization. By promoting endothelial cell proliferation and protecting the vasculature from apoptosis, EPO fosters the formation of new blood vessels that supply nutrients and oxygen, thereby sustaining tumor growth and facilitating metastatic spread [17]. The role of erythropoietin in hypoxia adaptation further underscores its potential impact on ovarian cancer progression. Hypoxia-inducible factor-1a (HIF-1a), commonly upregulated in ovarian tumors, directly stimulates EPO gene transcription. This creates a feedback loop in which hypoxia promotes EPO expression, which in turn supports tumor cell viability and angiogenesis, thereby enabling malignant cells to thrive in otherwise hostile microenvironments. Such adaptations may contribute to treatment resistance and aggressive disease phenotypes [18].

Erythropoietin may also interact with immune regulation within the tumor microenvironment. Experimental studies suggest that EPO signaling can dampen anti-tumor immunity by inhibiting apoptosis of immune-suppressive cell subsets or modulating cytokine profiles, although this remains an evolving area of investigation. If confirmed, such effects would position erythropoietin not only as a facilitator of tumor cell survival but also as a contributor to immune evasion in ovarian cancer (Table 1) [19].

Table 1: Mechanisms of Erythropoietin Action in Ovarian Cancer

Mechanism	Pathway/Effect	Clinical Implication
Cell proliferation	JAK2/STAT5, MAPK/ERK	Enhances tumor growth and DNA synthesis, potential resistance to chemotherapy
Cell survival / apoptosis resistance	PI3K/AKT, Bcl-2 upregulation	Protects cancer cells from cytotoxic effects of chemotherapy
Angiogenesis	VEGF upregulation, endothelial cell survival	Promotes neovascularization, supports tumor progression and metastasis
Hypoxia adaptation	HIF-1α → EPO upregulation	Allows tumors to thrive in low-oxygen microenvironments, contributes to therapy resistance
Immune modulation	Altered cytokine profile, immune-suppressive cell survival	Potentially dampens anti-tumor immune response, promoting tumor evasion

Anemia in Ovarian Cancer: Burden and Clinical Implications

Anemia is one of the most prevalent and debilitating complications encountered in patients with ovarian cancer, with studies estimating its occurrence in up to two-thirds of women during the disease trajectory. Its development is multifactorial, reflecting the combined influence of tumor biology, treatment-related toxicities, nutritional deficiencies, and systemic inflammation. As a clinical manifestation, anemia extends beyond a laboratory abnormality; it represents a major determinant of patient well-being, treatment tolerance, and overall prognosis [20]. Tumor-related factors play a central role in the genesis of anemia. Ovarian cancer, like many advanced malignancies, induces a state of chronic inflammation marked by elevated cytokines such as interleukin-6 and tumor necrosis factor-a. These mediators disrupt iron homeostasis, suppress erythropoietin production, and impair the responsiveness of bone marrow progenitors, leading to anemia of chronic disease. In addition, direct effects of the tumor, including gastrointestinal involvement causing occult blood loss or peritoneal spread resulting in nutritional malabsorption, can further exacerbate red cell deficiency [21].

Treatment-induced factors add another layer of complexity. Chemotherapy, particularly platinum- and taxane-based regimens that form the backbone of ovarian cancer therapy, exerts myelosuppressive effects that blunt erythropoiesis. Repeated cycles of treatment compound marrow suppression, progressively deepening anemia over time. Moreover, supportive medications such as antiangiogenic agents may exacerbate anemia by impairing vascular integrity and contributing to microvascular bleeding [22]. The clinical consequences of anemia in ovarian cancer are profound. Fatigue, cognitive impairment, reduced exercise tolerance, and dyspnea are among the most common symptoms, significantly diminishing quality of life. From a therapeutic perspective, anemia limits the ability of patients to tolerate full-dose chemotherapy, leading to treatment delays or dose reductions that may compromise oncologic efficacy.

Additionally, hypoxic tumor microenvironments created by low hemoglobin levels may promote resistance to chemotherapy and radiotherapy, further worsening outcomes [23].

Importantly, anemia has also been identified as a prognostic marker in ovarian cancer. Several studies have linked low baseline hemoglobin levels with poorer progression-free and overall survival, suggesting that anemia is not merely a complication but also a potential indicator of aggressive disease biology. The association between anemia and survival may, in part, reflect the combined effects of hypoxia-driven tumor progression and impaired treatment delivery in anemic patients [24]. The management of anemia in this context therefore assumes dual significance: as a strategy to improve patient-reported outcomes and as an intervention that may indirectly influence oncologic prognosis. Conventional approaches, such as red blood cell transfusion, provide rapid relief of symptoms but are associated with risks including transfusion reactions, iron overload, and infection. Erythropoiesis-stimulating agents (ESAs), including recombinant human erythropoietin, have transformed anemia management by reducing transfusion dependence, but their use has been tempered by safety concerns related to thromboembolic risk and potential tumor-promoting effects. Iron supplementation, particularly intravenous formulations, represents an important adjunct that enhances ESA efficacy while addressing functional iron deficiency commonly seen in cancer patients (Figure 1) [25].

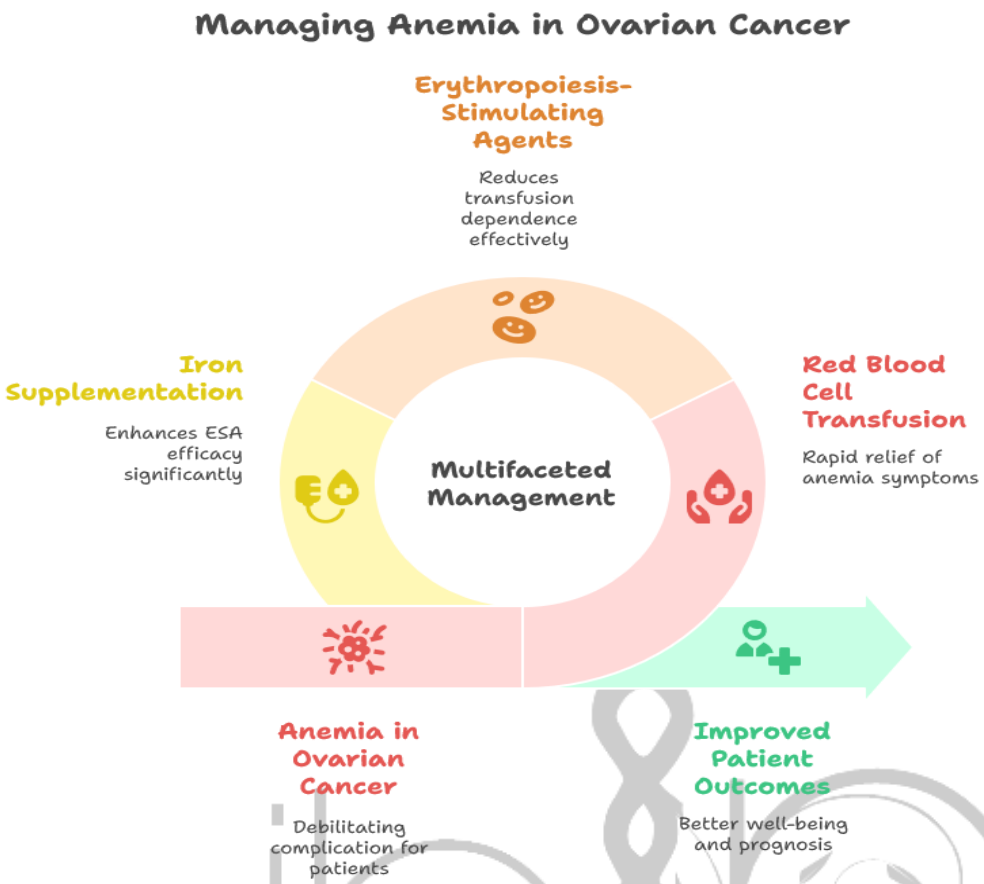

Figure 1: Managing Anemia in Ovarian Cancer

Clinical Use of Erythropoietin in Ovarian Cancer Anemia

The introduction of recombinant human erythropoietin (rhEPO) revolutionized anemia management in oncology by offering a therapeutic alternative to repeated red blood cell transfusions. In ovarian cancer, where anemia is highly prevalent and often exacerbated by platinum- and taxane-based chemotherapy, rhEPO has been employed to alleviate symptoms, reduce transfusion dependence, and improve patient quality of life. Clinical trials and real-world studies have consistently shown that rhEPO increases hemoglobin levels, restores functional capacity, and enhances patient-reported outcomes such as fatigue and physical performance. These benefits are particularly meaningful in a disease where treatment toxicity and systemic complications already compromise quality of life [26-27]. Despite these advantages, the use of erythropoietin in ovarian cancer remains surrounded by caution due to safety concerns. A number of randomized controlled trials across cancer populations have raised the possibility that ESAs may negatively influence overall survival and disease progression. The biological plausibility of these findings lies in the expression of erythropoietin receptors on ovarian tumor cells and the activation of signaling pathways that enhance survival, proliferation, and angiogenesis. While direct clinical evidence in ovarian cancer

remains limited and somewhat inconsistent, the theoretical risk of tumor promotion necessitates careful patient selection and judicious prescribing [28].

Another important concern is the risk of thromboembolic events, which are already elevated in ovarian cancer patients due to disease biology and treatment factors. Erythropoietin therapy, by increasing hemoglobin levels and blood viscosity, may compound this risk. Large meta-analyses have confirmed that ESA use is associated with higher rates of venous thromboembolism in oncology patients. For this reason, treatment guidelines recommend conservative hemoglobin targets (10–12 g/dL) and discourage normalization of hemoglobin levels, as overcorrection has been linked to higher complication rates [29]. Guideline recommendations therefore emphasize a cautious and individualized approach. The use of erythropoietin should be reserved for patients with chemotherapy-induced anemia, rather than anemia driven by iron deficiency, bleeding, or nutritional deficiencies. Therapy is most appropriate in symptomatic patients who experience functional impairment due to anemia, particularly those undergoing palliative treatment where quality-of-life benefits may outweigh long-term risks. Conversely, in patients receiving therapy with curative intent, erythropoietin use should be minimized or avoided unless no suitable alternatives exist [30].

To optimize efficacy, iron status should be assessed prior to initiation, and intravenous iron supplementation should be considered in cases of functional iron deficiency. Hemoglobin levels should be closely monitored during therapy, with discontinuation advised if no meaningful response is observed after six to eight weeks. For patients requiring rapid correction of anemia or in whom erythropoietin is contraindicated, red blood cell transfusion remains a viable option (Table 2) [31].

Table 2: Clinical Use of Erythropoietin in Ovarian Cancer Anemia

Aspect	Key Points	Recommendations / Notes
Indication	Chemotherapy-induced anemia (Hb <10 g/dL)	Symptomatic patients with impaired functional status benefit most
Contraindications / Caution	EPOR-positive tumors (theoretical risk), high thrombotic risk, uncontrolled hypertension	Use judiciously in curative-intent therapy; avoid overcorrection of Hb
Target Hemoglobin	10–12 g/dL	Avoid normalization above 12 g/dL to minimize thromboembolic risk
Adjunctive Therapy	Iron supplementation (oral or IV)	Correct functional iron deficiency to optimize EPO response
Monitoring	Hb every 1–2 weeks during initiation, then monthly	Discontinue if no meaningful response after 6–8 weeks
Alternative / Rescue	RBC transfusion	Reserved for rapid correction, severe anemia, or EPO contraindications
Quality-of-Life Benefits	Improved fatigue, exercise tolerance, reduced transfusion dependence	Particularly relevant in palliative care settings

Future Perspectives and Research Directions

The evolving understanding of erythropoietin's role in ovarian cancer underscores the need for continued research that bridges molecular biology with clinical practice. Future studies must clarify the extent to which erythropoietin influences tumor progression in vivo, particularly in ovarian cancer, where data remain sparse compared to other malignancies. A priority lies in distinguishing between its hematopoietic benefits and potential tumor-promoting risks, an endeavor that requires translational research integrating molecular profiling, preclinical modeling, and clinical observation [32]. One promising avenue is the identification of predictive biomarkers that can guide the safe use of erythropoietin. Assessing erythropoietin receptor (EPOR) expression in ovarian tumors may help stratify patients according to their risk of tumor stimulation. Similarly, genomic and proteomic profiling could provide insights into which patients are most likely to derive benefit from erythropoietin therapy without compromising oncologic outcomes. Such precision-medicine approaches could move anemia management away from a one-size-fits-all model toward individualized care [33].

The development of novel erythropoiesis-stimulating agents (ESAs) and EPO derivatives also represents an important frontier. Engineering EPO analogs that selectively activate erythropoietic pathways while avoiding tumor-related signaling could preserve the therapeutic benefits of anemia correction while minimizing oncologic risks. Biosimilars, already in clinical use, offer opportunities for broader accessibility, but further comparative effectiveness research is needed to ensure their safety and efficacy in ovarian cancer populations [34]. Combination strategies may also refine the role of erythropoietin in supportive care. For example, integrating EPO with intravenous iron supplementation or emerging hepcidin antagonists may enhance treatment response, reduce the required dose of ESAs, and lower associated risks. Exploring how erythropoietin interacts with newer ovarian cancer treatments, such as PARP inhibitors and anti-angiogenic therapies, will be equally important, given the potential for synergistic or antagonistic effects [35].

Another crucial direction is the long-term assessment of patient-centered outcomes. While quality-of-life improvements with erythropoietin are well recognized, there is a need for robust prospective trials that assess not only transfusion reduction but also survival, disease progression, and functional well-being over time. This is particularly relevant in the palliative care setting, where optimizing comfort and independence often takes precedence over survival alone [36]. Global health considerations should not be overlooked. In low-resource settings, where access to blood transfusion is limited and anemia prevalence is high, erythropoietin could play a pivotal role in supportive oncology care. Research into cost-effectiveness, accessibility of biosimilars, and simplified treatment algorithms will be vital to ensuring that advances in anemia

management are equitably applied across diverse health systems [37].

Clinical Recommendations

The clinical application of erythropoietin in ovarian cancer requires a careful balance between improving anemia-related quality of life and minimizing potential oncologic risks. Current evidence supports its use primarily in patients with chemotherapy-induced anemia, particularly when hemoglobin levels fall below 10 g/dL and symptoms such as fatigue or dyspnea significantly impair functional status. Before initiating erythropoietin therapy, clinicians should ensure that correctable causes of anemia—including iron deficiency, vitamin B12 deficiency, and folate deficiency—have been addressed, as these may blunt the therapeutic response. Given the heightened thromboembolic risk associated with both ovarian cancer and erythropoietin use, patient selection is critical. A thorough evaluation of thrombotic risk factors, including prior history of venous thromboembolism, obesity, immobility, and concurrent pro-thrombotic medications, should guide decision-making. In patients with high baseline thrombotic risk, alternatives such as red blood cell transfusion or iron supplementation may be more appropriate.

When erythropoietin is prescribed, therapy should be administered with strict monitoring. Hemoglobin levels should be measured regularly, and the target hemoglobin should remain within the range of 10–12 g/dL to reduce the risk of complications. Treatment should be discontinued if no meaningful hematologic response is observed within six to eight weeks, even with adequate iron supplementation. Importantly, erythropoietin should not be used to normalize hemoglobin to non-anemic levels, as this practice has been linked to adverse outcomes. The integration of erythropoietin into ovarian cancer management should also be contextualized within treatment intent. In patients undergoing chemotherapy with palliative goals, erythropoietin may offer significant improvements in quality of life by reducing transfusion dependence and alleviating anemia-related symptoms. In contrast, in patients receiving therapy with curative intent, caution is warranted due to ongoing concerns about potential tumor-promoting effects of exogenous erythropoietin, particularly in tumors expressing erythropoietin receptors. Erythropoietin should not be viewed as a universal intervention for anemia in ovarian cancer but rather as part of a tailored, patient-centered approach. Its use is most appropriate when the benefits of reducing transfusion burden and improving well-being clearly outweigh the risks of tumor progression and thromboembolic complications. The decision to initiate therapy should be individualized, guided by clinical context, disease stage, treatment goals, and patient preferences.

Conclusion

Erythropoietin occupies a paradoxical role in the management of ovarian cancer, serving as both a therapeutic ally in alleviating anemia and a potential contributor to tumor progression. Its use has significantly reduced transfusion requirements and improved quality of life

for many patients, particularly those with chemotherapy-induced anemia. Yet, concerns regarding erythropoietin receptor expression in ovarian tumors, activation of survival and angiogenic pathways, and increased thromboembolic risk highlight the need for caution. Clinical practice must therefore embrace a balanced and individualized approach. Patient selection, careful monitoring of hemoglobin targets, and integration of supportive measures such as iron supplementation is critical to ensuring that the benefits of therapy outweigh its risks. In palliative care, erythropoietin may play an important role in improving comfort and reducing treatment burden, while its use in curative settings should remain judicious until more definitive evidence emerges.

Conflicts of Interest

The author declares no conflict of interest

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Abbreviations

AKT – Protein kinase B
EPO – Erythropoietin
EPOR – Erythropoietin receptor
MAPK – Mitogen-activated protein kinase
rEPO – Recombinant erythropoietin
STAT5 – Signal transducer and activator of transcription 5
VEGF – Vascular endothelial growth factor

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