The Use of Erythropoietin in Cancer Treatment and Its Correlation with Ovarian Cancer

Fanqi Meng *

Tianjin Medical University, Tianjin, 300203, China

* Corresponding Author Email: FanqiMeng16@tmu.edu.cn

Abstract. Erythropoietin is produced by the kidneys, which can stimulate the production of red blood cells, and has a better therapeutic and prognostic role in cancer anemia. Ovarian cancer, which originates from ovarian tissue, is one of the malignant tumors of the female reproductive system, with high lethality and not easy to detect. It has been proved that EPO in correlates with the growth of tumor cells, and its receptor EPOR and recombinant human EPO (rhEPO) are expressed in cancer cells. EPO can treat EPO tumors by restoring endothelial erythrocytes and promoting angiogenesis, while rhEPO mainly has a better ameliorative effect on cancer anemia induced by radiotherapy. However, it remains controversial and contradictory whether EPO has a concomitant promoting effect on tumor cells while relieving ischemia. In this article, we will introduce the sources of EPO and EPOR in vivo, analyze the pathways that promote erythropoiesis, and analyze their effects on tumor cells. It will also confirm the correlation between the two by analyzing the EPO content in ovarian cells. The intervention effect of rhEPO analogs on cancer is also briefly described. Since aberrant activation of the JAK/STAT signaling pathway may exist in ovarian cancer patients, in-depth study of such targets may become a new research direction for the treatment of ovarian cancer.

Keywords: Erythropoietin, effect of rhEPO, JAK/STAT signaling pathway, ovarian cancer, EPO and tumor cells.

1. Introduction

Erythropoietin (EPO) is a glycoprotein that plays a crucial role in controlling the production of red blood cells in mammals. It has the ability to promote the development of bone marrow stem cells into red blood cells, as well as regulate the production of hemoglobin and the concentration of red blood cells. Erythropoietin (EPO) is primarily released by the kidney and is a low molecular weight cytokine that is found throughout various tissues in the human body, including the kidney, liver, nervous tissues, digestive tract, and reproductive system. Its main mode of action is through binding to the EPO receptor (EPOR) on the surface of target cells. Notably, EPOR is highly expressed in various malignant tumor tissues. The primary function of this substance is to stimulate the growth and specialization of precursor cells involved in the formation of blood cells, and to control the replenishment of red blood cells. As a result, it plays a significant role in the management of anemia caused by cancer. Furthermore, EPO can also serve as a neuroprotective agent, mitigating the occurrence of neurotoxicity induced by anticancer medications. Through extensive investigation, it has been discovered that the combination of EPO and rhEPO has the benefit of enhanced safety and effectiveness in the simultaneous treatment of tumor-associated anemia. RhEPO has the ability to promote cell proliferation and viability in a controlled laboratory setting, and it may also lead to the development of resistance against certain treatments.

Ovarian cancer, the most prevalent tumor in the female reproductive system, develops mainly due to microvascular and stromal damage and activation of apoptotic pathways caused by follicular depletion, ischemia, necrosis or inflammation. Anemia is a common complication in ovarian cancer patients, especially those with advanced disease. Some cisplatin and carboplatin cytotoxic chemotherapeutic agents inhibit the proliferation of myeloid stem cells and erythroid progenitor cells, which can exacerbate this pre-existing anemia and may lead to loss of ovarian function or premature ovarian insufficiency.

It has been demonstrated that the glycoprotein hormone EPO has been shown to exert multiple biological effects in the treatment of ovarian cancer, including cellular antioxidant, anti-apoptotic,

and anti-inflammatory effects. In addition, EPO prevents the oxidative stress process that occurs during treatment with ovarian cortical autografts, thereby reducing ischemic anemia and increasing tissue vascular repermeability. Also, rhEPO can inhibit cell growth and proliferation directly or indirectly by participating in the process of iron metabolism in ovarian cancer HO-8910 cells [1].

Erythropoiesis in the context of cancer therapy still presents several unresolved aspects and potential adverse consequences. One such example is the possibility that rhEPO, when used in conjunction with other erythroid stimulating agents (ESAs), may facilitate tumor cell invasion and metastasis. This article will analyze and summarize the role of monoclonal antibody drugs related to EPO in the treatment of ovarian cancer. It will examine existing research results and provide ideas for the development of new targeted drugs to treat cancer-associated anemia.

2. EPO's Mechanism of Action and Related Applications

2.1. Structure and Mechanism of Action of EPO

Erythropoietin (EPO) is a significant growth factor that controls the process of erythropoiesis in the bloodstream. It achieves this by promoting the survival, multiplication, and specialization of erythroid precursors in the bone marrow. Erythropoietin (EPO) is first released by the fetal liver and is thereafter synthesized in humans after birth mostly by renal tubular mesangial cells or fibroblasts in superficial rental units. However, it is also generated by the liver, macrophages, and nucleated erythrocytes.

The human EPO gene, located on chromosome 7, region 22 (7q22), is a glycoprotein with a relative molecular weight of approximately 30,000, consisting of 166 amino acids, and is a heat- and acid-stable protein.

EPO is a cytokine produced by the superfamily of hypoxia-inducible factors through induction. Its mechanism of action is that when the partial pressure of oxygen in the peritubular capillaries of the kidney is reduced by hypoxia in humans, the hypoxia-responsive element (HRE) in the 3' non-coding region of the EPO gene promotes the expression of EPO. Studies have confirmed the presence of two hypoxia-inducible enhancer-1 (HIF-1) at the 3' end of EPO, and HIF-1α affects tumor-related biological behaviors during tumor evolution. For example, under tumor hypoxic conditions, HIF-1α is highly expressed and specifically binds to its binding site, which contains transcription factors on the quasi-sequence at the Binding 5' end of the gene. Hypoxia also increases the level of intracellular second messengers and enhances gene transcription of EPO, as well as prolongs the half-life of EPO mRNA, leading to elevated local concentrations of EPO [2].

2.2. EPO and EPOR

EPO acts through autocrine and paracrine channels. The primary signaling pathway is through the erythropoietin receptor (EPOR), which binds to EPO and undergoes a homodimerization reaction that results in activation of the linked janus kinase (JAK2), causing intercellular signaling. As shown in figure1, activated JAK2 causes EPOR to generate phosphorylated sites Y343 and Y401, leading to a change in the spatial conformation of the receptor and exposing the site of action of the shear enzyme. Hydrolysis of specific cytoplasmic proteins containing SH-2 fragments ultimately activates the transcription factor STATS, which promotes value-added differentiation of erythrocytes and maintenance of erythrocyte and hemoglobin concentrations [3].

Furthermore, JAK2 has the ability to directly induce tyrosine phosphorylation in EpoR cells, therefore triggering the activation of PI3 kinase (PI3K) and Ras-MAK. These pathways, namely the EPOR-JAK2-PI3K route and the EPOR-JAK2-Ras-MAPK pathway, are essential for transmitting signals that promote cell proliferation and survival.

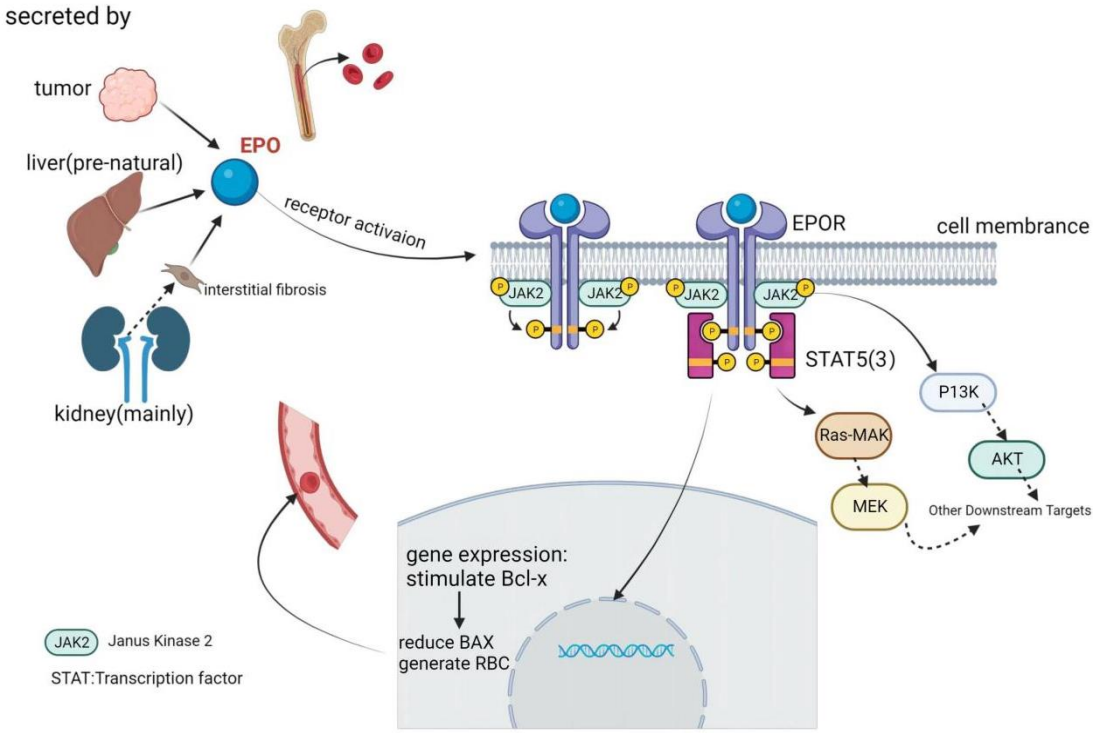


Fig. 1 Inactivation of the EPO-EpoR signaling system is usually achieved by internalization and degradation processes.

2.3. Application Mechanism of rhEPO

Studies have shown that rhEPO can reduce anemia and is a safe and beneficial blood substitute, especially suitable for transfusion treatment of chemotherapy-induced anemia [4]. It is well known that rhEPO promotes angiogenesis by promoting the proliferation of endothelial cells, the transformation of endothelial cells from mixed suspension to tubular structure, and the lengthening of tubular structure. Yang's experiments have demonstrated that rhEPO also suppresses the expression of transferrin cell mRNA (TfRmRNA) on the surface of ovarian cancer. This affects the process of iron metabolism and directly or indirectly hinders the growth and proliferation of tumor cells [5].

In recent years, tumor cells have been found to have the ability to secrete EPO, and these cells are called EPO tumors. Increased tumor inflammatory mediators (e.g., TNF and IL-1) inhibit the expression of EPO, which suppresses bone marrow proliferation, reduces iron utilization, and induces tumor-associated anemia. Patients with malignant tumors have less endogenous EPO in their bodies, are insensitive to EPO, and are prone to tumor anemia. It is well known that apoptosis is regulated by a variety of tumor-related genes, such as ras, p53, BCL-2 and C-myc, etc. EPO, as an antitumor factor, can reduce cell tissue damage and delay apoptosis, while other antitumor drugs, such as platinum compounds, paclitaxel compounds and radiotherapy also produce myelosuppressive effects and hemorrhage or hemolysis [6]. Cisplatin-based anticancer drugs often cause renal tubular dysfunction, and in severe cases, damage to the glomerulus, which ultimately leads to a decrease in the body's EPO level, and anemia caused by these drugs can be prevented or treated by EPO.

3. Association between EPO and Tumor Cells

3.1. Tumor cells induce the production of EPO.

As illustrated in Figure 2, PDGF-BB can be generated by tumors and is capable of selectively targeting stromal cells (including perivascular and stromal fibroblasts) via PDGFR-b activation. The PDGF-BB/PDGFR-b system activates the Atf3-cJun-Sp1 transcriptome, which in turn leads to the

transcriptional activation of the EPO promoter. The generation of EPO produced by the PDGF-BB/PDGFR-b system leads to increased tumor growth and invasion, as well as a considerable stimulation of tumor angiogenesis, by promoting the proliferation of tumor cells, blood vessel formation, and the creation of red blood cells [7].

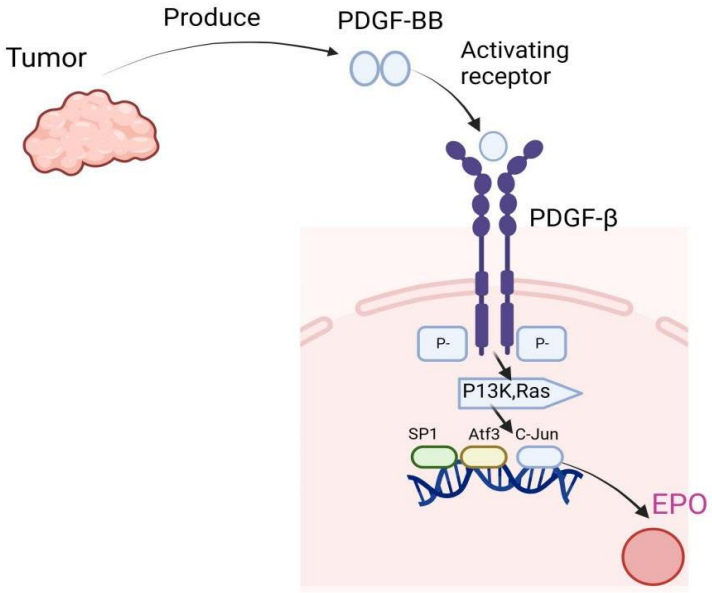


Fig. 2 Tumor cells promote EPO production.

Ovarian malignant tumors, as one of the three major malignant tumors of the female reproductive system, occur most frequently in middle-aged women, and their metastatic and spreading nature is not easily detected. The tumor marker of ovarian cancer is the cell surface glycoprotein CA125, and it has been shown that the concentration of blood erythropoietin affects the expression of CA125 [8]. In addition, EPOR mRNA is also expressed in ovarian cancer cells.

3.2. EPO and tumor-related factors

Exogenous EPO can stimulate the synthesis and release of vascular growth factor, vascular endothelial cell growth factor, and placental growth factor in tumor cell lines, hence facilitating the proliferation of vascular endothelial cells and promoting tumor vascular expansion. Several experiments have proved that EPO participates in the process of anti-apoptosis of tumor cells and promotes tumor angiogenesis, and the high permeability of newborn capillaries may allow cancer cells to metastasize through the blood. Ascites is one of the clinical features of ovarian cancer beginning to metastasize, the reason is that EPO can synergize with VEGF to cause ascites in ovarian cancer.

Studies have demonstrated that the levels of HIF-1α and EPO expression are much greater in malignant tumors compared to benign tumors. Furthermore, there is an inverse relationship between the degree of leukocyte differentiation in cancer cells and the expression rates of both HIF-1α and EPO. In the early stages of ovarian cancer, increased expression of EPO usually indicates a tendency for the tumor to transform from benign to malignant; therefore, both HIF-1α and EPO are often used as indicators of ovarian carcinogenesis and metastasis [9].

The tumor control and prognosis of EPO remain controversial. Therefore, other pathways that EPO may exist and its prognosis for ovarian cancer still have a lot of room for research.

4. Effect of rhEPO on Preventing Anemia and Hypoxia on the Results of Radiotherapy and Chemotherapy

rhEPO, a recombinant of human erythropoietin, is an important growth factor in the body, and likewise plays a role in promoting the survival and proliferation of red progenitor cells. Most of the

chemotherapeutic drugs used in the clinic have different degrees of myelosuppressive effects, often manifested in the reduction of patients' neutrophils and platelets, which can cause the inhibition of erythropoiesis and lead to anemia in patients, and in severe cases, they will be forced to terminate cancer treatment, and some patients even need blood transfusion to alleviate the anemia caused by the reduction of endogenous EPO due to the platinum-based anticancer drugs. However, rhEPO can effectively promote the abnormal hematopoietic function of bone marrow system damaged by chemotherapy. It has been proved that rhEPO can significantly increase the hemoglobin (Hb) content and hematocrit (HCT) level of patients after chemotherapy, improve the fatigue feeling of patients, and improve the tolerance of patients to chemotherapy; and it has fewer adverse reactions, and is safer to use [10]. Additionally, it exhibits a reduced number of negative consequences and is deemed to be more secure for use. Hence, the prompt administration of rhEPO following the initiation of chemotherapy can sustain the patient's hemoglobin at an elevated level and substantially enhance the patient's quality of life. Nevertheless, the administration of rhEPO may lead to undesirable consequences such as increased blood thickness, blockage of blood vessels, and elevated levels of potassium in the blood.

5. Other Possible Research Directions

The aforementioned JAK/STAT signaling pathway, as an important pathway for extracellular signaling to the nucleus, is also a hot spot in the research of tumor-targeted therapy. Among them, the activation of STAT3, STAT5 have oncogenic effects, which can inhibit tumor cell apoptosis and promote tumor invasion and metastasis [11]. Therefore, inhibiting the activation of STAT3 and STAT5 can induce tumor cell death. In recent years, some monoclonal antibodies against this pathway have gained great research progress, and STAT inhibitors have been widely used in cancer treatment.

Bevacizumab has recently been employed in the management of both initial and recurring ovarian cancer, demonstrating a positive effectiveness and safety profile in patients with first ovarian cancer. Since now some ovarian cancer patients have been discovered to have abnormal activation of JAK/STAT signaling pathway, so perhaps STAT3 and STAT5 could be novel targets for anti-ovarian cancer drugs.

6. Conclusion

In conclusion, EPO is a small molecule glycoprotein secreted by the kidneys that stimulates bone marrow hematopoietic stem cells and induces erythrocyte maturation for the prevention of anemia caused by medication during cancer treatment. The expression of EPO increases significantly in tumor cells under hypoxia. EPO homodimerizes with its receptor EPOR and promotes erythrocyte proliferation and differentiation through the EPOR-JAK2-PI3K and EPOR-JAK2-Ras-MAPK pathways. EPO promotes angiogenesis, and blocking this process slows the proliferation of tumor cells. However, some studies believe that EPO promotes angiogenesis, increases the secretion of vascular endothelial growth factor and promotes the value-added of endothelial cells, which further induces tumor neovascularization and triggers tumor blood metastasis, leading to the emergence of ascites and other symptoms.

For ovarian cancer, EPO can affect the expression of CA125, which has been used as an indicator of ovarian carcinogenesis and metastasis and combined with HIF-1α for diagnosis and treatment of ovarian cancer. Recombinant human erythropoietin rhEPO is indicated for transfusion treatment of chemotherapy-induced anemia and can significantly increase hemoglobin levels in post-chemotherapy patients with fewer and safer adverse effects. Due to the lack of experimental data, whether the benefits of using EPO to treat tumor-associated anemia outweigh the disadvantages cannot be confirmed, and it needs to be considered comprehensively in terms of improving patients' anemia symptoms and stimulating the extent of tumors.

Currently, novel STAT3 and STAT5 inhibitors can induce tumor cell death and inhibit only this target without affecting the erythropoietic properties of EPO itself, which may be a research direction in this field for future use in the treatment of ovarian cancer. Compared with traditional radiotherapy techniques and anticancer drugs with central nervous system inhibition, EPO not only has fewer toxic side effects, but also improves the prognosis and significantly enhances the quality of life of the patients and has a very promising development prospect.

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