Molecular Medicine

Erythropoietin Receptor (EpoR) Agonism Is Used to Treat a Wide Range of Disease

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The erythropoietin receptor (EpoR) was discovered and described in red blood cells (RBCs), stimulating its proliferation and survival. The target in humans for EpoR agonists drugs appears clear—to treat anemia. However, there is evidence of the pleitropic actions of erythropoietin (Epo). For that reason, rhEpo therapy was suggested as a reliable approach for treating a broad range of pathologies, including heart and cardiovascular diseases, neurodegenerative disorders (Parkinson's and Alzheimer's disease), spinal cord injury, stroke, diabetic retinopathy and rare diseases (Friedreich ataxia). Unfortunately, the side effects of rhEpo are also evident. A new generation of nonhematopoietic EpoR agonists drugs (asialoEpo, Cepo and ARA 290) have been investigated and further developed. These EpoR agonists, without the erythropoietic activity of Epo, while preserving its tissue-protective properties, will provide better outcomes in ongoing clinical trials. Nonhematopoietic EpoR agonists represent safer and more effective surrogates for the treatment of several diseases such as brain and peripheral nerve injury, diabetic complications, renal ischemia, rare diseases, myocardial infarction, chronic heart disease and others.

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In principle, the erythropoietin receptor (EpoR) was discovered and described in red blood cell (RBC) progenitors, stimulating its proliferation and survival. Erythropoietin (Epo) is mainly synthesized in fetal liver and adult kidneys (1–3). Therefore, it was hypothesized that Epo act exclusively on erythroid progenitor cells. Accordingly, the target in humans for EpoR agonists drugs (such as recombinant erythropoietin [rhEpo], in general, called erythropoiesis-simulating agents) appears clear (that is, to treat anemia). However, evidence of a kaleidoscope of pleitropic actions of Epo has been provided (4,5). The Epo/EpoR axis research involved an initial journey from laboratory basic research to clinical therapeutics. However, as a consequence of clinical observations, basic research on Epo/EpoR comes back to expand its clinical therapeutic applicability.

Although kidney and liver have long been considered the major sources of synthesis, Epo mRNA expression has also been detected in the brain (neurons and glial cells), lung, heart, bone marrow, spleen, hair follicles, reproductive tract and osteoblasts (6–17). Accordingly, EpoR was detected in other cells, such as neurons, astrocytes, microglia, immune cells, cancer cell lines, endothelial cells, bone marrow stromal cells and cells of heart, reproductive system, gastrointestinal tract, kidney, pancreas and skeletal muscle (18–27). Conversely, Sinclair *et al.* (28) reported data questioning the presence or function of EpoR on nonhematopoietic cells (endothelial, neuronal and cardiac cells), suggesting that further studies are needed to confirm the diversity of EpoR. Elliott *et al.* (29) also showed that EpoR is virtually undetectable in human renal cells and other tissues with no detectable EpoR on cell surfaces. These results have raised doubts about the preclinical basis for studies exploring pleiotropic actions of rhEpo (30).

For the above-mentioned data, a return to basic research studies has become necessary, and many studies in animal models have been initiated or have already been performed. The effect of rhEpo administration on angiogenesis, myogenesis, shift in muscle fiber types and oxidative enzyme activities in skeletal muscle (4,31), cardiac muscle mitochondrial biogenesis (32), cognitive effects (31), antiapoptotic and antiinflammatory actions (33–37) and plasma glucose concentrations (38) has been extensively studied. Neuro- and cardioprotection properties have been mainly described. Accordingly, rhEpo

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therapy was suggested as a reliable approach for treating a broad range of pathologies, including heart and cardiovascular diseases, neurodegenerative disorders (Parkinson's and Alzheimer's disease), spinal cord injury, stroke, diabetic retinopathy and rare diseases (Friedreich ataxia).

Unfortunately, the side effects of rhEpo are also evident. Epo is involved in regulating tumor angiogenesis (39) and probably in the survival and growth of tumor cells (25,40,41). rhEpo administration also induces serious side effects such as hypertension, polycythemia, myocardial infarction, stroke and seizures, platelet activation and increased thromboembolic risk, and immunogenicity (42–46), with the most common being hypertension (47,48). A new generation of nonhematopoietic EpoR agonists drugs have hence been investigated and further developed in animals models. These compounds, namely asialoerythropoietin (asialoEpo) and carbamylated Epo (Cepo), were developed for preserving tissue-protective properties but reducing the erythropoietic activity of native Epo (49,50). These drugs will provide better outcome in ongoing clinical trials. The advantage of using nonhematopoietic Epo analogs is to avoid the stimulation of hematopoiesis and thereby the prevention of an increased hematocrit with a subsequent procoagulant status or increased blood pressure. In this regard, a new study by van Rijt *et al*. has shed new light on this topic (51). A new nonhematopoietic EpoR agonist analog named ARA 290 has been developed, promising cytoprotective capacities to prevent renal ischemia/reperfusion injury (51). ARA 290 is a short peptide that has shown no safety concerns in preclinical and human studies. In addition, ARA 290 has proven efficacious in cardiac disorders (52,53), neuropathic pain (54) and sarcoidosis-induced chronic neuropathic pain (55). Thus, ARA 290 is a novel nonhematopoietic EpoR agonist with promising therapeutic options in treating a wide range of pathologies and without increased risks of cardiovascular events.

Overall, this new generation of EpoR agonists without the erythropoietic activity of Epo while preserving tissue-protective properties of Epo will provide better outcomes in ongoing clinical trials (49,50). Nonhematopoietic EpoR agonists represent safer and more effective surrogates for the treatment of several diseases, such as brain and peripheral nerve injury, diabetic complications, renal ischemia, rare diseases, myocardial infarction, chronic heart disease and others.

DISCLOSURE

The authors declare that they have no competing interests as defined by *Molecular Medicine*, or other interests that might be perceived to influence the results and discussion reported in this paper.

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