Erythropoietin: is it more than correcting anaemia?

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The ‘old’ hormone erythropoietin

Erythropoietin (Epo) is a glycoprotein with a molecular weight of 30.4 kDa. The gene for Epo encodes a protein precursor of 193 amino acids, which after cleavage of a 27 amino acid sequence, glycosylation of four amino acids and removal of the C-terminal arginine yields the final circulating Epo molecule with 165 amino acids. The tertiary Epo structure is defined by four antiparallel α-helices and the binding of a single molecule to two adjacent Epo receptors on the membrane of target cells triggers intracellular signalling cascades. In the healthy adult, Epo is mainly produced in the kidney in response to hypoxia. The production of circulating Epo is regulated in order to maintain an optimal red cell mass, which in turn is closely linked to tissue oxygen demand. The basal level of Epo secretion in the picomolar range maintains a plasma concentration between 15 and 25 U/l. Reduced oxygen delivery to the kidney results in increased Epo production and stimulation of erythropoiesis.

Our present understanding of the physiological role of Epo goes back to the work of French scientists: Bert and Jourdanet established the link between tissue hypoxia and the production of erythrocytes and in 1906 Carnot and Deflandre [1] hypothesized that a circulating factor—hemopoietine—regulates red cell production. It was later renamed erythropoietin and the isolation of Epo in 1977 paved the way for cloning the gene and the industrial production of recombinant human Epo (rHuEpo) [2–4]. Currently, the main indication for the use of rHuEpo is the treatment of anaemia due to Epo deficiency in patients with chronic renal failure—a major advantage in clinical nephrology [5]. In addition, rHuEpo is used in patients with anaemia due to cancer, since it relieves symptoms of anaemia and improves quality of life [6].

Emerging new facets of Epo’s ego

In the last decade increasing evidence has accumulated to show that Epo has pleotropic effects on the body well beyond the maintenance of red blood cell mass [7–9]. In the embryo Epo is a major regulator of vascular formation and organ growth and Epo receptors are found in almost every embryonic tissue [10]. Epo receptors have been discovered in numerous adult tissues as well and even the idea of an autocrine or paracrine action of Epo has been raised, e.g. astrocytes are capable of producing both Epo and Epo receptors [7]. Because of its large molecular weight, circulating Epo does not cross the blood–brain barrier, but there is evidence for a separate Epo paracrine system in the brain [11,12]. In neural tissue, interactions between Epo and its receptor have been reported to induce a range of cellular responses, including mitogenesis, angiogenesis and inhibition of apoptosis. Furthermore, experimental work has revealed that Epo may protect neurons from ischaemic insult [13–15] and (high dose) rHuEpo treatment is being tested in patients with stroke in order to limit the sequelae of cerebral ischaemia. The preliminary results are promising [16].

Of even greater clinical significance could be the observation that Epo has direct biological effects on endothelial cells. Epo receptors have been found in umbilical cord endothelial cells and Epo increases endothelial cell proliferation in vitro and protects the cells against apoptosis [17,18]. Furthermore, human endothelial cell lines express Epo receptors and respond to Epo by differentiating into vascular structures [19,20]. Thus, it is tempting to speculate...
that Epo could preserve its role as a regulator of vascular formation and repair also in the adult.

**Epo and endothelial progenitor cells**

Current research in cardiovascular regenerative medicine focuses on bone marrow-derived endothelial progenitor cells (EPCs), which promote vascular reparative processes [21,22]. EPCs are considered to originate from CD34+ stem cells, which differentiate via separate pathways into erythrocytes, thrombocytes, various lineages of leukocytes and also into endothelial cells (Figure 1). EPCs are mainly found in the bone marrow, but may also circulate in the vasculature where they home and incorporate into sites of active neovascularization [22]. In experimental studies, increased neovascularization by these cells improves cardiac function after myocardial ischaemia [23,24]. In patients with myocardial infarction the clinical outcome is strongly correlated with the number of mobilized EPCs from the bone marrow [25]. Moreover, it has been shown that even in subjects without manifest cardiovascular complications the number of EPCs significantly correlates with endothelial function and cardiovascular risk factors [26].

Recently, we were able to demonstrate that administration of rHuEpo or the Epo analogue darbepoetin alpha significantly enhanced mobilization of EPCs in patients with advanced renal failure [27]. Similarly, as has been shown for statins, the effect of Epo on EPCs is mediated via activation of the Akt-1 intracellular pathway [27,28]. Importantly, the effect was observed with a standard therapeutic dose, in contrast to most previous observations of *in vitro* studies on cardiovascular effects of Epo, in which supra-therapeutic doses were used. Our observations, together with the results from animal and cell culture experiments, permit the conclusion that Epo is a potent regulator of EPC proliferation and differentiation [27,29]. Furthermore, in patients with an acute coronary syndrome, Epo blood levels were strongly and independently related to the number of EPCs in peripheral blood [29]. Taken together, Epo seems to be a key molecule in the process of vascular repair in the adult age.

These findings may be of particular relevance for renal patients. Most die of complications related to atherosclerosis, namely myocardial infarction and stroke. Possibly, impaired vascular repair mechanisms may contribute to the problem. Treatment with rHuEpo reduces left ventricular mass, ameliorates exercise-related cardiac ischaemia and improves outcome in patients with advanced renal failure. These salutary actions are thought to be the consequence of improved tissue oxygenation. A reduced number and/or impaired function of EPCs due to Epo deficiency could be another causal factor for the high cardiovascular morbidity and mortality in renal patients. Replacement therapy with rHuEpo may ameliorate this problem via the endothelial cell pathway. Thus, treatment with rHuEpo or Epo analogues could open new therapeutic strategies in cardiovascular medicine [30].

**Conflict of interest statement.** None declared.

**References**

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the serum in blood regeneration.] C R Acad Sci (Paris) 1906; 143: 384–386


