Erythropoietin Is More than Just a Promoter of Erythropoiesis

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The red cell production is continuously adjusted to cope with the loss of aged blood cells and to guarantee optimal oxygen supply to tissues and cells. Erythropoietin (EPO) is the critical growth factor that is produced either in the fetal liver or the adult kidney and acts on erythroid progenitor cells in the bone marrow to prevent them from undergoing programmed cell death. In turn, EPO production is controlled by the systemic availability of oxygen in the sense of a tightly regulated feedback circle (1). Under physiologic conditions the levels of the hormone remain constant and approximately 2 pmol of EPO per liter of plasma evoke the production of enough erythrocytes to maintain a sufficient oxygenation of organs and tissues. In anemias and other conditions of reduced oxygen supply to the kidney the rate of EPO secretion increases, which enhances the production of new erythrocytes. Probably the most important factor in the cellular response to hypoxia is hypoxia-inducible factor (HIF), which acts as a transcription factor and promotes the expression of EPO and other hypoxia-induced genes. HIF is a heterodimer consisting of an α-subunit (HIF-1α, HIF-2α, HIF-3α) and a β-subunit (HIF-1β), also denoted as aryl hydrocarbon receptor nuclear translocator (ARNT). HIF target genes contain one or more so-called hypoxia response elements (HREs), 5'-ACGTG-3', in their respective promoters and upon binding of the HIF heterodimer, the expression of genes coding for glucose uptake, glycolytic enzymes, and growth factors like EPO or vascular endothelial growth factor (VEGF) is up-regulated (2,3).

The kidney is an organ highly vulnerable to renal hypoxic or toxic insults that impose changes in the redox potential and oxidative stress. The expression of antioxidant enzymes in response to hypoxia plays important protective roles and serves to accommodate metabolic requirements and to coordinate endogenous defense mechanisms in the kidney, as well as in other organs. An interesting facet in redox regulation of gene expression is the fact that hypoxia targets a wide variety of genes that partially overlap with genes regulated by nitric oxide and reactive oxygen species (4). The increased expression of these gene products is in large part responsible for the phenomenon of delayed hypoxic preconditioning that makes cells and tissues more resistant to subsequent periods of oxygen deprivation. Oxygen sensing is a widespread phenomenon and is found not only in the kidney but in other organs as well. Indeed, Ratcliffe and colleagues (5) were the first to report that also EPO is produced in organs other than the kidney and the liver. Moreover, not only erythroid precursor cells but most renal cell types were found to express receptors for EPO (6), thus making it tempting to speculate that EPO might exert paracrine functions other than merely promoting erythropoiesis. EPO is up-regulated in the brain and spinal cord under conditions of hypoxia. Two functions have been appointed to this locally produced EPO: a direct protective effect on neuronal cells during cerebral ischemia and an indirect protection provided by increased angiogenesis triggered by VEGF and other hypoxia-induced growth factors, and subsequently augmented blood supply (7). The neuroprotective action of EPO depends on EPO receptor-triggered Janus-tyrosine kinase 2 (JAK2) activation, and nuclear factor κB (NFκB)-mediated expression of anti-apoptotic genes comprising, besides others, the inhibitors of apoptosis proteins clAP-2 and XIAP (8). In the rat retina, systemic administration of EPO also reduces the degree of programmed cell death induced by high-intensity light exposure (9). In addition, EPO treatment leads to a significant improved cardiac function following myocardial infarction. This protective action of EPO was associated with attenuated cell apoptosis and necrosis and involved protein kinase B (Akt) activation. Importantly, the hematocrit was not increased in this experimental setting, thus demonstrating that EPO directly protects ischemic heart tissue (10). Renoprotective and anti-apoptotic effects of EPO have also been reported in animal models of acute renal failure. In rats subjected to ischemia-reperfusion injury (6,11) or to cis-platinum-induced acute renal failure (12) EPO treatment promoted functional and morphologic tubular regeneration. Recently, Fishbane et al. (13) demonstrated anti-apoptotic effects of a long-acting EPO analog (Darbepoetin alpha) in pig tubular (LLC/PK1) and mouse mesangial cells exposed to toxic or hypoxic stimuli.

In this issue of the Journal of the American Society of Nephrology, Sharples et al. (14) take the story a crucial step further to approach the therapeutic application of erythropoietin to the prevention of ischemia-reperfusion injury in the kidney. These authors report that EPO protects the rat kidney in a model of severe ischemia-reperfusion injury, with inhibition of caspase-3, -8, and -9 activation in vivo and reduced apoptotic cell death. Most importantly for clinical relevance, EPO administration 30 min after the onset of reperfusion still caused a significant reduction in serum creatinine and histologic features of tubular injury. The mechanism by which EPO protects renal cells and the kidney against ischemia-reperfusion-triggered injury is increasingly becoming clearer. Sharp-
les et al. (14) were unable to detect any significant hemodynamic effect of an acute application of EPO and, consequently, propose that EPO acts directly on proximal tubular epithelial cells to protect them from undergoing programmed cell death. In proximal tubular epithelial cells EPO evokes JAK2 signaling with downstream activation of the phosphatidylinositol 3-kinase (PI3K) and protein kinase B cascade. This in turn causes phosphorylation and inactivation of the pro-apoptotic factors Bad, Bax, and caspase-9 and up-regulation of the anti-apoptotic players Bcl-XL and XIAP, as well as a reduction of caspase-3 activation. Taken together, these changes in protein expression and activity may constitute the potent protective capacity of EPO in renal ischemia-reperfusion injury.

Cytokine action and cytokine receptor signaling pathways are typically characterized by their pleiotropic nature (15). In this sense EPO has a typical cytokine nature. Another facet of the pleiotropic actions of EPO has been recently highlighted by Bahlmann et al. (16) and comprises a significant mobilization of CD34+/CD45+ circulating progenitor cells in peripheral blood and an increased number of functionally active endothelial progenitor cells. With these new findings we begin to appreciate that administration of EPO may open new therapeutic strategies in regenerative medicine. Due to its capacity to directly protect the kidney and to preserve renal function, EPO treatment may represent a novel approach for the treatment of ischemia-reperfusion injury associated with renal diseases. Moreover, the success story of EPO provides a case in point that targeting the central hypoxia signaling devices, such as HIF-1 may provide an attractive target for future drug development (17).

References

See related article, “Erythropoietin Protects the Kidney against the Injury and Dysfunction Caused by Ischemia-Reperfusion,” on pages 2115–2124.