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PERSPECTIVES

Is the renoprotective effect of erythropoietin in chronic kidney disease a myth?

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Renal fibrosis is the final common pathway in chronic kidney disease (CKD) whatever the initial etiology is. Sustained inflammatory cell infiltration, epithelial decomposition, microvascular rarefaction, and pericyte–myofibroblast transition lead to renal fibrosis and failure.[1,2] Erythropoietin (EPO), mainly produced in the kidney after birth, can regulate the production of red blood cells to maintain tissue oxygenation. However, the production of EPO is decreased in patients with CKD. Thus far, therapeutic efforts by administering EPO in patients with CKD have been made only to correct anemia and putative hypoxic tissue damage. With increasing number of patients with CKD receiving EPO treatment, emerging evidence suggests that EPO not only has erythropoietic function, but also has renoprotective potentials.[3]

Existing evidence suggests that the pleiotropic effects of EPO are mediated by distinct receptors: erythropoiesis through the EPO receptor (EPOR) homodimer and tissue protection through a heterocomplex composed of EPOR and β-common receptor (βcR also known as CD131).[4] Although the EPOR–βcR heterodimer has been shown in the brain and cultured cells by immunoprecipitation, recent studies demonstrate no functional EPOR in renal, endothelial, cardiac, and neuronal cells.[5] Furthermore, Brines et al[4] demonstrated that carbamylated EPO (CEPO), an EPO derivative without EPOR affinity, has the same tissue-protective effect, but not erythropoietic effect, as EPO, whereas both CEPO and EPO lose the protective effect in the βcR knockout mice. Accordingly, βcR, not EPOR, is indispensible for the tissue-protective effect of EPO. Therefore, further studies are required to define the other critical receptor subunit that constitutes a heteroreceptor with βcR, thereby transducing the tissue-protective signaling of EPO. In addition, the renal cells responding to EPO in the injured kidney is a subject of considerable debate. In contrast to the absence of intracellular signaling in renal epithelial cells, EPO can induce nitric oxide (NO) production through βcR-mediated activation of endothelial NO synthase (eNOS) in endothelial cells.[5,6] Noteworthily, activation of eNOS–NO signaling by EPO needs an interaction between βcR and vascular endothelial cell growth factor receptor 2. NO production by endothelial cells can protect microvasculature from rarefaction.[6] In addition to endothelial cells, EPO can inhibit the stimulation of pro-inflammatory genes including tumor necrosis factor-α and inducible NOS by blocking the activation of nuclear factor-κB (NF-κB).[7] The immunemodulatory effects of EPO may be of therapeutic relevance in its renoprotective effect.

Macrophages and myofibroblasts are at the heart of renal fibrosis.[1,2] Macrophages could be polarized to

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phenotype M1 (classically activated) or M2 (wound healing) according to the distinctive cytokine production and behavior after different activation.[2] In addition, exposure to apoptotic cells or immune complexes can generate macrophages that produce high levels of interleukin-(IL-10) and are actively involved in the suppression of immune responses. This macrophage subpopulation might be better identified as a regulatory macrophage (Mreg).[2] Our own studies have shown macrophage subpopulations that are derived from a single monocyte subset in mice with CKD and that the wound-healing (M2) macrophages can secrete cytokines to drive the pericyte—myofibroblast transition and consequent renal fibrosis.[1,2,8] Using a genetic model for macrophage ablation in mice with CKD, we have discovered the general role of macrophages in renal fibrosis.[2,8] Administration of human serum amyloid P can inhibit renal fibrosis through macrophage regulation and local generation of IL-10.[2] Because EPO can deactivate macrophages by inhibiting the activity of NF-κB, we propose that one of the mechanisms underlying the antifibrotic effects of EPO in CKD is macrophage regulation *in vivo*.

In summary, clinical evidence shows the renoprotective potential of EPO in patients with CKD, but further clinical studies are necessary to define when to start EPO treatment and what is the optimal EPO dosage for slowing disease progression in patients with CKD. The application of EPO treatment for renoprotection may need to be earlier than that for erythropoiesis. Although current evidence shows no expression and function of EPOR in kidney, it is still possible for EPO to attenuate renal fibrosis through macrophage regulation and endothelial cell protection through the other unidentified βcR heterocomplexes. Further bench work needs to be carried out in order to clarify the cellular target of EPO in kidney and develop novel EPO derivative or mimetic for renoprotection.

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