EPO and HO-1 in cardiovascular and renal protection: just a common signaling pathway or a mechanistic link?

Sir,

The study of Ishii et al. [1], published in the April issue of *Nephrology Dialysis Transplantation*, which I read with great interest, reporting in an animal model that the renoprotective effect of erythropoietin (EPO) against ischemia-reperfusion injury (IR/I) is exerted mainly via inhibition of apoptotic cell death and inflammation induced by IR/I, adds another important piece of evidence regarding renoprotective effects of EPO beyond anemia correction.

Cardiovascular and renoprotective effects of EPO, including protection from IR/I have been recently added to the number of non-haematological actions of the hormone [2]. We have a long-standing interest in the effects of EPO [3] and would like to suggest that EPO-mediated induction of Heme oxygenase-1 (HO-1) might play an important role in the effects of EPO, including its cardiovascular and renoprotective effects. Results from our study of EPO effects in chronic haemodialysis (CH) patients [4] provide additional support for the conclusions by Ishii et al. and add a mechanism for the EPO-mediated renoprotection via induction of HO-1. In CH patients treated with epoetin α (50–100 UI/kg, three times per week aiming toward a target hemoglobin of 11 g/dL and then adjusted to maintain it), in fact, EPO increased mononuclear cell HO-1 gene expression via a possible direct effect of EPO [4]. HO-1 is a Phase II enzyme induced by oxidative stress that possesses potent antioxidant, antiapoptotic and anti-inflammatory activities [3] and HO-1 expression is transcriptionally regulated by the phosphatidylinositol 3 kinase (PI3K)/Akt pathway [3]. EPO antiapoptotic effect is also dependent on JAK2 signaling and PI3K-mediated phosphorylation of Akt [3], which, once triggered, activates multiple antiapoptotic effects. Given that both EPO and HO-1 antiapoptotic and anti-inflammatory effects occur via the PI3K/Akt pathway, HO-1 might play an important role in the antiapoptotic effect of EPO.

It is also noteworthy that CH patients who fail to respond to EPO have an improved response to EPO when treated with carnitine and that carnitine stimulates erythropoiesis [3]. These reports again are consistent with a linkage between EPO and HO-1 as carnitine treated human endothelial cells in culture show increased HO-1 messenger RNA and protein expression [3]. The involvement of HO-1 in cardiovascular and renoprotection is also shown by HO-1 increase, which paralleled the reduced expression of oxidative stress- and inflammation-related proteins, including Transforming growth factorβ, induced by Ramipril and/or Carvedilol we reported in kidney transplant patients with calcineurin inhibitors induced posttransplant hypertension [5,6]. EPO’s role in endothelial progenitor cell (EPC)-mediated vascular repair has also been reported [2] and further strengthens our contention that HO-1 is involved, given that increasing HO-1 levels increases EPCs [7]. Our recent demonstration in a human model with clinical and biochemical characteristics opposite to hypertension and related diseases such as reduced cardiovascular remodeling and atherosclerosis, lack of oxidative stress and reduced inflammatory cytokines, that increased EPC number correlates with the increased HO-1 expression [8], further contributes to a mechanistic link between EPO and HO-1. Finally, there are reports that a statins’ treatment increases the EPC number and differentiation via the PI3K/Akt-signaling pathway [1], the same induced by EPO. Crucially, the statin-induced antiapoptotic and anti-inflammatory effect-related responses have been shown to occur via PI3K/Akt-mediated induction of HO-1 [3].

In conclusion, the occurrence of a common signaling pathway (PI3K/Akt) for the antiapoptotic and anti-inflammatory effects of both EPO and HO-1, the same effects exerted on EPCs by EPO and HO-1, the EPO-mediated protection from oxidative stress via increase of HO-1 as shown in CH patients as well as that exerted by the induction HO-1, which paralleled the reduction of calcineurin inhibitors induced oxidative stress and inflammation in kidney transplant patients, support not only the conclusions of Ishii et al. of an EPO-mediated renoprotection from IR/I [1], but also provide a further mechanistic explanation for the EPO cardiovascular and renoprotective effects via induction of HO-1.

Editorial Note: Dr Ishii et al. had been invited to reply to this letter but we did not receive a response.

Conflict of interest statement. None declared.

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