Letter and Reply

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The elusive erythropoietin receptor

Elliott et al. [1] have shown that erythropoietin receptor (EpoR) protein is low to undetectable in human renal cells and other tissues with no detectable EpoR on cell surfaces. This result was obtained by western blotting with an EpoR-specific monoclonal rabbit antibody (A82) and measurement of the binding of radiolabelled recombinant human Epo ([125I]rHuEpo). RHuEpo did not induce intracellular signalling or proliferation of renal cell lines. EpoR and Jak2 knockdown had no effect on viability of renal and other non-haematopoietic cell lines. The expected 59-kDa EpoR was apparent with cultured erythroid cells, whereas no 59-kDa EpoR was detected in any other human tissue including kidney, brain, heart, liver, lung and colon among others. These findings are in contrast to previous studies with non-specific anti-EpoR antibodies, and they call into question the hypothesis that cells from renal tissues—and other non-haematopoietic tissues—express functional EpoR and that Epo is a pleiotropic cytoprotective factor.

However, the findings carry weight with respect to an open question regarding the long-term administration of rHuEpo or other erythropoiesis-stimulating agents (ESAs) to patients with chronic kidney disease (CKD), namely whether this therapy could impact on the development of malignancies. The EpoR promoter lacks a TATA box, which is characteristic of a ubiquitously expressed gene. EpoR messenger RNA is present at low basal levels in non-erythroid tissues, but it is questionable whether this is translated into functional EpoR protein integrated in the membrane. Some preclinical studies have suggested that tumour cells are responsive to Epo [2], and in cancer patients, there is concern that the therapy with ESAs may affect tumour growth and/or mortality [3]. Noteworthily, Elliott et al. [1] investigated several different renal and non-renal tumour cell lines, and none of these presented with measurable Epo-R protein or responded to Epo. This finding is further evidence against a direct tumour-promoting effect of ESAs. In regard to the possibility that Epo might promote tumour angiogenesis through mobilizing bone marrow-derived endothelial progenitor cells in CKD patients, it is noteworthy that long-term ESA treatment did not affect endothelial markers in patients on haemodialysis [4]. Taken together, there is little evidence to assume that ESAs directly or indirectly stimulate tumour growth in CKD patients.

Foley et al. [5] argued that if ESAs truly predispose to malignancy in haemodialysis patients, cancer-specific mortality rates should rise in parallel with rising ESA doses (which more than tripled in the USA since ESAs were introduced). The authors performed a retrospective incident cohort study including 873 493 US patients aged ≥20 years who initiated haemodialysis between 1995 and 2005. The study has shown that yearly cancer mortality rates were static throughout the observation period of 10 years, even though ESA doses escalated dramatically. Furthermore, the authors observed modest declines in overall and cardiovascular mortality, which militates against the reasoning that ESAs lead to death exclusively through cardiovascular disease [5].

Conflict of interest statement. The author has received honoraria for consultations and educational lectures from several pharmaceutical companies marketing ESAs.

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Outcome of the living kidney donor

Sir,

In a recent paper, the outcome of the living kidney donor was discussed. Obese donors were discussed separately and the authors stated their worries for the nephrological prognosis of the donor because of the possibility of hypertension and proteinuria [1]. We wish to point out that several centres are therefore sceptical to accept an obese kidney donor, which has led to the policy of mandatory weight loss prior to donation.

We evaluated this practice in the 63 living donors who donated in the University Medical Centre Utrecht in 2009 and 2010. Weight at initial presentation, time of donation and a year after donation was measured. Forty-eight per