

## Editorial

### Erythropoietin: friend and foe!

Our knowledge of the erythropoietin (Epo) molecule has come a long way since Carnot and Deflandre's landmark observations, over a century ago, attributing the increase in red blood cells to a factor called 'hemopoietin'. For decades, the scientific community thought that the role of Epo was limited to red blood cell production. However, since the mid 1990s, Epo has been shown to exert numerous extrahematopoietic effects (see Fig. 1 – 'Traditional'). Just as one could have thought that we knew everything about this molecule, Bailey *et al.* (2014) have demonstrated that recombinant Epo (rHuEpo) can equally serve as a very potent antioxidant (see Fig. 1 – 'Evolving'). Indeed, in the current issue of *Acta Physiologica*, we learn how the authors utilized in the first instance an *in vitro* approach to demonstrate the antioxidant characteristics of the rHuEpo molecule, which was then followed up by an *in vivo* experiment that involved exposing healthy volunteers to 12 h of hypoxia ( $\approx 13\%$  oxygen) (Bailey *et al.* 2014). In the *in vitro* arm, the authors demonstrated that rHuEpo is a potent scavenger of the hydroxyl radical (HO $\cdot$ ), both directly and indirectly, subsequent to catalytic iron chelation. The hydroxyl radical is able to react with any biological molecule inducing cellular damage and as such has been linked with vascular ageing (Bailey *et al.* 2010). For the human study, the authors decided to take advantage of inspiratory hypoxia, a model they previously used to induce both erythropoiesis and oxidative-nitrosative stress (Bailey *et al.* 2014). Exposure to hypoxia revealed that the increase in endogenous Epo can help maintain redox homeostasis by limiting the increase in oxidative-nitrosative stress through its antioxidant function. From a functional point of view, it therefore appears that the hypoxia-induced stimulation of Epo serves different purposes. Chronologically, the antioxidant effect would most likely come first during the acute phase of hypoxia, while the red blood cell production requires a sustained hypoxic stimulus which stretches beyond the peak of Epo which usually occur within 48 h (Brugniaux & Pichon 2007).

### The Janus Face of Epo; adaptive aspects

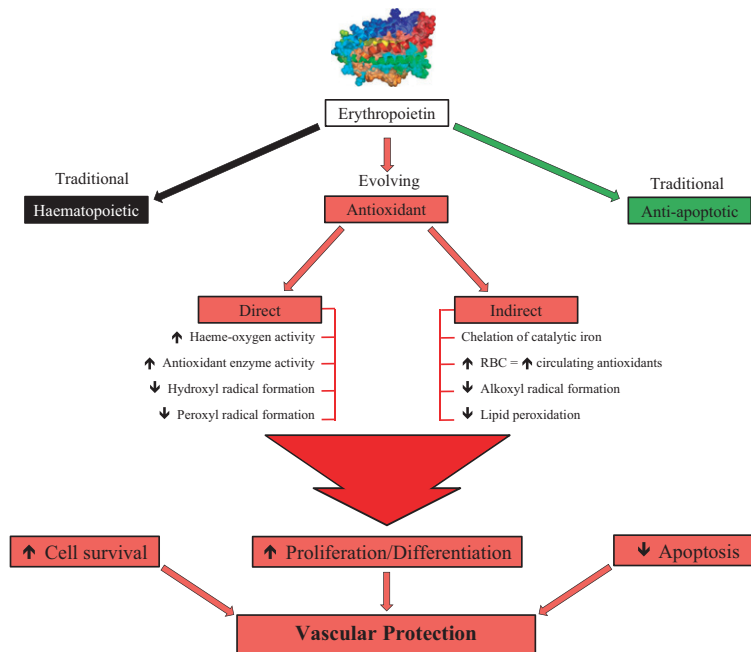
Erythropoietin, be it endo- or exo-genous, is best known for its stimulating effect on erythropoiesis and its use in blood doping (Jelkmann & Lundby 2011).

Indeed, Epo secretion increases upon exposure to hypoxia which in turns improves the oxygen carrying capacity of blood and aerobic performance (Brugniaux *et al.* 2006). While this is a normal physiological response, athletes can be tempted to use rHuEpo doping as an illegal means of improving performance. On another hand, rHuEpo injections can also have clinical benefit such as in renal failure.

Nevertheless, it is now evident that the effects of Epo stretch far beyond the regulation of red cell production, with the central nervous system, the heart, and vasculature having received most of the attention. Within the brain, administration of rHuEpo is known to induce neuroprotection following focal brain ischaemia or concussive brain injury in rats (Brines *et al.* 2000). In humans, preliminary work showed that Epo can reduce the infarct size following an acute stroke by penetrating the blood-brain barrier, but the authors failed to replicate their results during a more extensive trial (Ehrenreich *et al.* 2009). The work from Bailey *et al.* (2014) published here sheds a new light on the aforementioned studies. Indeed, while these studies assumed that the effects of (rHu)Epo are secondary to activation of gene expression, it now appears that Epo could also mitigate the acute inflammatory response thanks to its antioxidant properties.

Bunn (2013) recently published a comprehensive review on the effects of Epo in which he highlighted that it confers protection against cardiac hypoxia/ischaemia and myocardium infarct, and help preserving kidney or liver integrity. During ischaemia and inflammation, Epo seems to exert its protective effects by stimulating the proliferation, mobilization and differentiation of endothelial cells, by enhancing endothelial cell viability and by reducing apoptosis. Bearing in mind that pro-/antioxidant imbalance negatively impacts vascular function, one could expect the mechanisms of action of Epo to rely, at least during the acute phase of secretion/injection on its antioxidant characteristics.

Another intriguing extrahematopoietic effect of Epo relates to the control of breathing. Strong evidence in transgenic mice overexpressing Epo suggested that the hypoxic ventilatory response (HVR) could indeed be modulated by Epo and its specific Epo receptors (EpoR), and that female rodents show greater improvement than males (Gassmann *et al.* 2009). In humans, similar observations have been made in



**Figure 1** Schematic summarizing the mechanisms underlying the vascular protective benefits associated with endogenous erythropoietin formation with a specific focus on its evolving antioxidant properties. RBC, red blood cell; ↑, increase; ↓, decrease.

healthy males exposed to intermittent hypoxia (Brugniaux *et al.* 2011). The latter study also stressed that the decrease in soluble EpoR participates in maintaining the plasma Epo concentration above normoxic level for the 4 days of exposure. Using two different models of intermittent hypoxia, our group also observed a positive relationship between indirect markers of oxidative stress and HVR (Pialoux *et al.* 2009a,b).

### Maladaptive aspects

Although beyond the scope of this already very comprehensive study, Bailey *et al.* (2014) did not address the effects of sustained or repeated increases in Epo. Chronic mountain sickness (CMS) is characterised by excessive erythrocytosis associated with chronic hypoxaemia. As a consequence, it is not unusual to observe haematocrit levels >60% and arterial oxygen saturation <85%. Intriguingly, these patients do not exhibit an elevated level of circulating Epo when compared to healthy participants living at the same altitude (Leon-Velarde *et al.* 1991). However, Bailey *et al.* (2013) also observed that CMS patients are in a permanent state of elevated oxidative–nitrosative stress contributing to systemic vascular dysfunction. As the authors rightfully highlighted, using targeted antioxidants could help improving the patients' condition. With this in mind, one could argue that, providing that non-hematopoietic Epo derivatives keep similar antioxidant characteristics to rHuEpo, they could constitute an interesting prophylactic avenue.

### Food for thoughts

In summary, Bailey's work (Bailey *et al.* 2014) is particularly noteworthy because of the comprehensive approach the authors used combining both *in vitro* and *in vivo* work. Their approach is further strengthened by the techniques used in particular electron paramagnetic resonance (EPR) spectroscopy, which is the only available technique allowing direct detection of radical species whereas most of the other studies such as Pialoux *et al.* (2009a,b) used indirect markers to estimate the extent of oxidative stress. Nonetheless, some questions remain unanswered. Even if it can be quite complex to decipher the actual effects of Epo as it is situated upstream of the signalling pathway, studying the effect of sustained elevation in Epo appears crucial. According to Bailey *et al.* (2014), acutely, rHuEpo helps maintaining homeostasis by limiting the magnitude of increase in oxidative stress. However, albeit at an unknown concentration, free radicals are required for the adaptive response to hypoxia. In the longer term, by not switching off, Epo could actually disturb homeostasis. Secondly, as previously mentioned there is some evidence that Epo, EpoR and oxidative stress are all involved in regulating chemosensitivity. However, the exact intricacy of these interactions remains unknown.

### Conflict of interest

The author declares no conflicts of interest.

J. V. Brugniaux

Neurovascular Research Laboratory, Faculty of  
Life Sciences and Education, University of South  
Wales,  
Glamorgan, UK  
E-mail: julien.brugniaux@southwales.ac.uk

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