Erythropoietin (EPO), as the name suggests, was first discovered as a cytokine for red blood cells, but as is so often the case, turns out to have other highly interesting physiological effects. It is produced primarily in the kidneys, and its synthesis increases in response to a decrease in blood oxygen levels. In 1989, the use of recombinant EPO was approved for the treatment of anemia resulting from chronic renal failure. Anemia also occurs quite frequently in patients with chronic heart failure, and may be an independent risk factor for adverse outcomes [1]. Preliminary data suggests that treatment with EPO may improve symptoms in these patients [1]. However, exciting developments in recent years indicate that erythroid progenitors are not the only cells that express the EPO receptor (EpoR), and EPO may have direct effects on other cell types. Functional EpoR pathways have been observed in cardiomyocytes, neurons, and other cell types.

In a report in this issue of *Cardiovascular Research*, Tada and colleagues have used a powerful genetic approach to evaluate the importance of the endogenous EpoR signalling pathway in myocardial ischemia and reperfusion [2]. They made use of EpoR knockout mice that had been transgenically re-engineered to re-express EpoR under the control of the GATA-1 promoter, and therefore solely in the hematopoietic cell lineage. These mice, which they denote as “RES” for “rescued”, survive by virtue of having a normal hematopoietic compartment, but express no EpoR in the heart [3]. After being subjected to 30 min regional myocardial ischemia followed by 24 h reperfusion, infarct size was significantly greater in RES mice compared to WT, indicating that endogenous circulating levels of EPO may activate pathways downstream of the EpoR that are potentially available to protect the heart and aid in its functional recovery.

Three weeks post myocardial infarction (MI), RES mice appeared to have defective left ventricular (LV) remodelling compared to wild type (WT), despite the extent of fibrosis being similar in both lines. Importantly, hematocrit remained the same in both RES and WT mice, indicating that the remodelling defect was a direct consequence of the absence of EpoR in tissue. It is also interesting to note that MI caused a much greater increase in serum EPO levels in WT mice compared to the RES mice, which indicates that the increase in serum EPO, post-MI, is stimulated via signalling through EpoR in tissue.

In humans, an association has been found between high serum EPO levels and smaller infarct size in patients with acute myocardial infarction (MI) undergoing primary angioplasty [4]. However, other studies have found that in chronic heart failure patients, higher levels of EPO were associated with a worse prognosis [5]. Somewhat surprisingly, in the current study, larger infarcts and deficient ventricular remodelling did not translate into a significant reduction in long-term survival. Nevertheless, slightly higher death rates were recorded in RES mice, so greater numbers may have demonstrated a difference.

The debate over the importance of apoptosis to cardiac injury after MI tends to be rather polarised [6,7]. In this study, Tada et al. [2] present data in support of the argument that apoptosis is important, since they measured 24±2% TUNEL-positive cells in the hearts of WT mice 6 h
after MI, increasing to 26±2% after 24 h. Even higher values were recorded in RES mice (31±2% and 42±4%). However, on its own, we don’t find this data entirely convincing, since electron microscopy has previously been used to examine TUNEL-positive myocytes in the hearts of rabbits subjected to ischemia and reperfusion and found that the majority of them were actually oncotic (neecrotic) [8]. Tada et al. concede that, since they did not examine cellular ultrastructure, this possibility cannot be excluded; however, they did show that caspase 3 activity reflected changes in TUNEL staining, which certainly seems to indicate that cardiac EpoR confers protection against apoptosis to some degree, at least.

We have suggested that the activation of the PI3-kinase/Akt pathway is involved in the cardioprotection of many different agents applied after ischemia and at the point of reperfusion [9]. Consistent with this proposal for a common protective pathway, a number of previous studies have demonstrated that activation of the PI3K/Akt pathway is involved in the protection of EPO against cardiac MI, in both in vitro and in vivo settings [10–13]. Here, Tada et al. detected much less phosphorylation of p38 and JNK in response to MI in RES compared to WT hearts and suggest that activation of these kinases is required for protection by EPO. This is not inconsistent with the possibility that Akt activation is required in addition for this protection, since they also found that Akt was phosphorylated post-MI in both WT and RES hearts — but it does appear to indicate that Akt is not sufficient for protection mediated by endogenous EPO.

In considering the possibility of treating patients with EPO as a means of protecting the cardiovascular system, an important consideration is the fact that EPO is usually administered chronically in order to cause a stable rise in hematocrit. In this regard, hearts isolated from rats after chronic administration of EPO have been shown to be protected against ischemia and reperfusion, independent of hematocrit [14]. Interestingly, chronic protection by EPO appears to depend upon the production of nitric oxide [14], and hypoxia fails to activate endothelial nitric oxide synthase (eNOS) in the lungs in RES mice compared to WT mice [15].

A higher rate in myocardial infarction has been found in dialysis patients undergoing treatment with rhEPO [16], suggesting a risk of thrombotic events upon increase of hematocrit. A very promising approach that has been taken to avoid this serious problem is to carbamylate recombinant EPO. The RES mice may be a useful model to investigate this possibility.

In recently published work, the same group has shown that mobilization of endothelial progenitor cells (EPCs) and their recruitment to the pulmonary endothelium is significantly impaired in RES mice in response to chronic hypoxia [15]. These and other studies [19] raise the intriguing idea that endogenous EPO can protect the heart by facilitating the recruitment of EPCs to the heart to promote neovascularization [20] or even transdifferentiate into cardiomyocytes [21] — a possibility that will no doubt set many hearts beating.

References


