Thrombopoietin emerges as a new haematopoietic cytokine that confers cardioprotection against acute myocardial infarction

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Editorial commentary on 'Human thrombopoietin reduces myocardial infarct size, apoptosis, and stunning following ischaemia/reperfusion in rats.' (Baker et al. ⁴)

Colony stimulating factors (CSFs), also called haematopoietic growth factors, are circulating cytokines that regulate the bone marrow production of red cells, white cells, and platelets. CSFs have also been reported to act on stem cells to regulate lineage-specific differentiation. ¹ Erythropoietin (EPO) controls red cell production and has been utilized in recombinant form for the treatment of anaemia in patients with end-stage renal disease since 1988. Granulocyte CSF (G-CSF) acts on haematopoietic stem cells to regulate neutrophil progenitor proliferation and differentiation. G-CSF is routinely used to mobilize stem cells in normal patients for transplantation of cells into patients with haematological malignancies, or in the patients themselves. Several recent reports have suggested that these cytokines possess properties that extend beyond their haematopoietic properties, such as the ability to protect the heart against injury caused by ischaemia and reperfusion (I/R).²,³ Baker et al. ⁴ now demonstrate for the first time in this issue of Cardiovascular Research that a third haematopoietic growth factor, thrombopoietin (TPO), is able to provide cardioprotection against myocardial I/R injury in a rat model by mechanisms independent of its haematopoietic properties.

TPO affects nearly all aspects of platelet production, from self-renewal and expansion of haematopoietic stem cells, through stimulation of the proliferation of megakaryocyte progenitor cells, to support the maturation of these cells into platelet-producing cells.⁵ Since its purification in 1994, TPO has been used to treat thrombocytopenia caused by many conventional chemotherapy regimens.⁶ Recently, TPO was reported to protect against doxorubicin-induced cardiotoxicity.⁷ The current study expands on the reported cardioprotective actions of TPO and provides the first evidence that TPO protects against acute myocardial infarction. The authors first demonstrated that the receptor for TPO, c-Mpl, is present in the heart and localized to the myocytes. Using both in vitro and in vivo models of global and regional myocardial I/R, they found that a single treatment with recombinant human TPO prior to ischaemia exerts an immediate protective effect, as manifested by a reduction in myocardial cell death and an improved recovery of ventricular function following ischaemia. This immediate cardioprotective effect of TPO was found to be concentration- and dose-dependent with an optimal protection occurring at 1.0 ng/mL in vitro and 0.05 μg/kg (i.v.) in vivo. In the clinic, patients generally receive medical treatment for acute myocardial infarction after the onset of symptoms. Therefore, in subsequent experiments, the authors investigated if a single injection of TPO (0.05 μg/kg, i.v.) administered either 15 min after the onset of ischaemia or 10 s after the onset of reperfusion would protect the myocardium. In both instances, TPO reduced infarct size to the same degree as the administration prior to ischaemia. The authors then demonstrated that TPO-induced cardioprotection was mediated by Janus family of tyrosine kinase 2 (JAK-2), signal transducers and activators of transcription 3 (STAT-3), mitogen-activated protein kinases (MAPK, p42/44), sarcolemmal ATP-sensitive potassium (K<sub>ATP</sub>) channels and mitochondrial K<sub>ATP</sub> channels. The increased resistance to injury was observed immediately after treatment with TPO, indicating that the induction of new genes is not necessary for its cardioprotective effect to be manifested. Importantly, TPO confers its protective effect against injury from myocardial I/R without increasing platelet levels or haematocrit, which further suggests that it has direct cardioprotective properties, independent of its ability to promote platelet production.

Potentially, the most important finding of the current study by Baker et al. ⁴ is that like EPO, TPO appears to provide cardioprotection by activating the JAK/STAT signalling cascade and K<sub>ATP</sub> channels.⁸ The cardioprotective signalling pathway is conceivably initiated by the binding of TPO to its receptor, c-Mpl, which then, like other haematopoietic cytokine receptors, transmits numerous biochemical
signals through the activation of the JAK.5 JAK promotes cell survival and proliferation by STATs and MAPks. MAPks are a family of serine-threonine protein kinases that are activated in response to a variety of stimuli, such as myocardial I/R.9 The STAT pathway has recently been shown to be an integral part of the response of the myocardium to various cardiac insults. In particular, the overexpression of STAT-3 has been shown to provide protection,10 whereas cardiotoxic specific deficiency of STAT-3 exacerbates cardiac injury,11 suggesting a protective role of STAT-3 in I/R injury. Mechanistically, STAT-3 can inhibit cell death by upregulating the expression of several anti-apoptogens, including Bcl-2.12 This signalling pathway could, therefore, account for the reduction in apoptotic cell death observed in the current study by Baker et al.4 Furthermore, the activation of KATP channels by TPO could also account for the reduction in cell death. KATP channels play an important role in the cardioprotective signalling of ischaemic preconditioning (IPC). In addition, pharmacological agents that selectively open the KATP channel have been shown to have infarct-limiting effects as potent as IPC.13 There is still some debate, however, as to whether the sarcolemmal KATP channel or mitochondrial KATP channel plays a more prominent role in this cardioprotection.14 However, it appears that both play a role in TPO-induced cardioprotection. Baker et al.4 found that the sarcolemmal KATP channel acts as a trigger and the mitochondrial KATP channel acts as an effector of TPO-induced cardioprotection, as evidenced by the inhibition of the signalling cascade when the sarcolemmal KATP channel was inhibited and by the abolishment of the infarct size reduction when the mitochondrial KATP channel was inhibited.

The most striking finding of the study by Baker et al.4 is that TPO afforded cardioprotection independent of its ability to promote platelet production, suggesting that TPO possess pleiotropic actions. The concept that pharmacological agents may possess actions beyond their intended uses is becoming a common finding, with the best example to date being the use of statins. Statins were once thought to provide cardioprotection by reducing serum cholesterol levels. However, it has now become increasingly clear through both clinical and experimental studies that the beneficial effects of statins are not solely related to the lipid lowering effects of these drugs, but rather to a number of diverse signalling mechanisms.15 The same is true for EPO, as it has been shown to provide cytoprotection against ischaemic injury through signalling mechanisms that did not result in an increase in hematocrit.8 The authors of the current study suggest that their results may cause a paradigm shift in how we view the mechanisms and biological effects of TPO. This may be the case, but more broadly the results of the current study and other recent studies, at the very least, suggest that it is necessary to have an open mind in the consideration of potential pharmacological interventions for the treatment of myocardial infarction.

There are many prospective pharmacological agents that are currently being used for the treatment of other diseases that, if used at different doses or if administered differently, could open a window of therapeutic opportunity where a single treatment may offer immediate and substantial protection against myocardial infarction.

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