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Erythropoietin-mediated tissue protection: reducing collateral damage from the primary injury response.

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Abstract

In its classic hormonal role, erythropoietin (EPO) is produced by the kidney and regulates the number of erythrocytes within the circulation to provide adequate tissue oxygenation. EPO also mediates other effects directed towards optimizing oxygen delivery to tissues, e.g. modulating regional blood flow and reducing blood loss by promoting thrombosis within damaged vessels. Over the past 15 years, many unexpected nonhaematopoietic functions of EPO have been identified. In these more recently appreciated nonhormonal roles, locally-produced EPO signals through a different receptor isoform and is a major molecular component of the injury response, in which it counteracts the effects of pro-inflammatory cytokines. Acutely, EPO prevents programmed cell death and reduces the development of secondary, pro-inflammatory cytokine-induced injury. Within a longer time frame, EPO provides trophic support to enable regeneration and healing. As the region immediately surrounding damage is typically relatively deficient in endogenous EPO, administration of recombinant EPO can provide increased tissue protection. However, effective use of EPO as therapy for tissue injury requires higher doses than for haematopoiesis, potentially triggering serious adverse effects. The identification of a tissue-protective receptor isoform has facilitated the engineering of nonhaematopoietic, tissue-protective EPO derivatives, e.g. carbamyl EPO, that avoid these complications. Recently, regions within the EPO molecule mediating tissue protection have been identified and this has enabled the development of potent tissue-protective peptides, including some mimicking EPO's tertiary structure but unrelated in primary sequence.