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Derivatives of erythropoietin that are tissue protective but not erythropoietic.

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Abstract

Erythropoietin (EPO) is both hematopoietic and tissue protective, putatively through interaction with different receptors. We generated receptor subtype-selective ligands allowing the separation of EPO's bioactivities at the cellular level and in animals. Carbamylated EPO (CEPO) or certain EPO mutants did not bind to the classical EPO receptor (EPOR) and did not show any hematopoietic activity in human cell signaling assays or upon chronic dosing in different animal species. Nevertheless, CEPO and various nonhematopoietic mutants were cytoprotective in vitro and conferred neuroprotection against stroke, spinal cord compression, diabetic neuropathy, and experimental autoimmune encephalomyelitis at a potency and efficacy comparable to EPO.