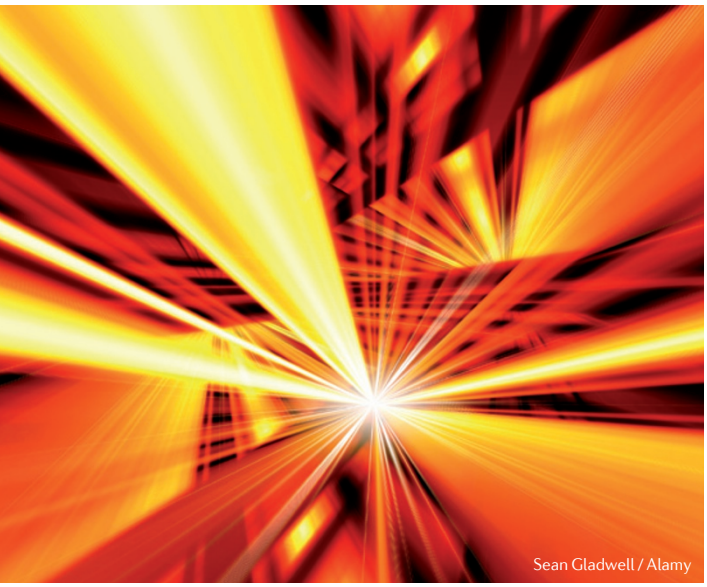
RADIATION INJURY

EGF aids recovery after blast of radiation

Exposure to high levels of radiation can have a profound deleterious effect on the haematopoietic system; however, the mechanisms of haematopoietic stem cell (HSC) recovery after radiation injury are poorly understood. Reporting in *Nature Medicine*, Doan and colleagues now show that epidermal growth factor (EGF), secreted by bone marrow endothelial cells, has a central role in HSC recovery.

Bone marrow endothelial cells are known to regulate HSC homeostasis and regeneration and to have a crucial role in HSC recovery after radiation injury. To investigate the molecular mechanisms of HSC recovery following radiation injury, the authors used *Tie2*^{Cre};*Bak1*$^{-/-}$;*Bax*$^{flox/-}$ mice, which have a radioprotective phenotype owing to the selective deletion of the pro-apoptotic proteins BAK and BAX in angiopoietin 1 receptor (TIE2)-expressing endothelial cells. After high-dose total-body irradiation (TBI), these mice had previously been shown to have improved survival rates and better bone marrow cellularity compared to control mice.


Sean Gladwell / Alamy

In vitro experiments with BAK- and BAX-deficient endothelial cell lines generated from these mice, which were placed in non-contact culture with irradiated HSCs, indicated that the endothelial cells secrete survival factors that aid HSC recovery.

Subsequent cytokine analysis of the bone marrow serum of the radioprotected mice revealed that EGF was substantially enriched compared to control mice. Moreover, it was shown that irradiation induces the expression of EGF receptor (EGFR) on HSCs.

The role of EGF was further investigated in *in vitro* experiments, where EGF supplementation of irradiated HSCs had a similar radioprotective effect as co-culture with BAK- and BAX-deficient endothelial cells, whereas the addition of an EGF-specific antibody abrogated the radioprotective effect of BAK- and BAX-deficient endothelial cells.

Several *in vivo* experiments further underscored the role of EGF in radioprotection. Treatment of wild-type mice with intraperitoneal EGF 2 hours after TBI led to increased bone marrow cellularity compared to saline-treated mice, and transplant experiments showed that bone marrow from EGF-treated irradiated mice contained more than 10-fold higher HSC repopulating capacity compared to bone marrow from saline-treated irradiated donors. Importantly, it was shown that systemic treatment of mice subjected to lethal doses of radiation with EGF boosts survival: at radiation doses that cause ~50% lethality after 30 days in saline-treated mice, EGF treatment led to a 100% survival rate. Conversely, experiments with the small-molecule EGFR inhibitor erlotinib showed that blocking EGF signalling reverses the radioprotective phenotype of *Tie2*^{Cre};*Bak1*$^{-/-}$;*Bax*$^{flox/-}$ mice, that it lowers the capacity of HSC engraftment in transplant experiments, and that it leads to dismal survival (less than 10%) in lethal irradiation experiments as described above.

Examining the molecular pathways of EGF function in radiation recovery, it was found that EGFR activation induces early HSC cycling after radiation exposure by activating the phosphoinositide 3-kinase (PI3K)–AKT signalling pathway. Moreover, EGFR stimulation was shown to repress the transcription factor PUMA (p53 upregulated modulator of apoptosis) — a known inducer of radiation-induced toxicity.

These results reveal a previously unknown role for EGF and indicate that the systemic administration of EGF could be useful in patients who receive TBI-based conditioning before HSC transplants, as well as in victims of radiation sickness.

Alexandra Flemming

ORIGINAL RESEARCH PAPER Doan, P. L. *et al.* Epidermal growth factor regulates hematopoietic regeneration after radiation injury. *Nature Med.* **19**, 295–304 (2013)