WOUND HEALING

# Phoenix rising

> caspases have a yin and yang role, promoting both cell death and tissue regeneration

The ability to repair damaged tissues is essential for metazoans, but the cellular and molecular events that initiate this process are unclear. Li *et al.* now report a role for cell death in wound healing and tissue regeneration in a 'phoenix rising' pathway, in which tissue damage initiates tissue repair.

The authors postulated that dying cells in wounded tissues might signal to stem and progenitor cells to stimulate their proliferation and initiate tissue repair. As the molecular machinery controlling apoptosis is common to many dying cells, they reasoned that this might have a role in wound repair. To investigate this, they used lethally irradiated wild-type mouse embryonic fibroblasts (MEFs) and MEFs deficient in caspase 3 and caspase 7, which are essential apoptotic proteases, as models of dying cells.

Irradiated MEFs promoted the proliferation of various stem or progenitor cells labelled with firefly luciferase (FLuc) in culture and *in vivo*. By contrast, irradiated caspase 3- and caspase 7-null MEFs were less effective at stimulating the proliferation of these cells. Irradiated caspase 3-null MEFs showed a markedly reduced ability to promote the proliferation of co-injected epidermal keratinocyte progenitor (EKP)–FLuc cells. Furthermore, EKP–FLuc cells injected into the limbs of irradiated caspase 3- or caspase 7-null mice showed decreased proliferation. Caspase 3- and caspase 7-null mice also showed a reduced rate of skin wound repair and decreased cell proliferation in wounded tissues. A reduction in liver regeneration rates following surgery was also seen in these caspase-knockout mice compared with wild-type mice.

So, what factors downstream of the caspases are involved? Arachidonic acid is a precursor of prostaglandin $E_2$ ($PGE_2$), a stimulator of stem cell proliferation and tissue regeneration. Calcium-independent phospholipase $A_2$ ($iPLA_2$) mediates the synthesis and secretion of arachidonic acid, and its activity is enhanced by caspase 3 and caspase 7. Irradiation was shown to induce arachidonic acid release in wild-type MEFs, and this effect was reduced in caspase 3-null MEFs. Furthermore, levels of $PGE_2$ in the supernatant, which increase on irradiation, were lower in the supernatant from caspase 3-null MEF cultures. In addition, decreasing $iPLA_2$ levels by RNA interference in irradiated wild-type MEFs reduced their ability to support the proliferation of EKP–FLuc cells, and the presence of constitutively active $iPLA_2$ in irradiated caspase 3-null MEFs promoted EKP–FLuc proliferation. By implanting MEF-embedded silicone cylinders into mice, the ability to induce host vascular growth was shown to be attenuated by $iPLA_2$ knockdown in irradiated wild-type MEFs and enhanced by constitutively active $iPLA_2$ in caspase 3-null MEFs.

Together, these results provide evidence for a caspase 3–$iPLA_2$ pathway in stem and progenitor cell proliferation and tissue regeneration. It seems, therefore, that caspases have a yin and yang role, promoting both cell death and tissue regeneration; a pathway to cell death leads to cellular life.

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**ORIGINAL RESEARCH PAPER** Li, F. *et al.* Apoptotic cells activate the "phoenix rising" pathway to promote wound healing and tissue regeneration. *Sci. Signal.* **3**, ra13 (2010)
**FURTHER READING** Taylor, R. C. *et al.* Apoptosis: controlled demolition at the cellular level. *Nature Rev. Mol. Cell Biol.* **9**, 231–241 (2008)