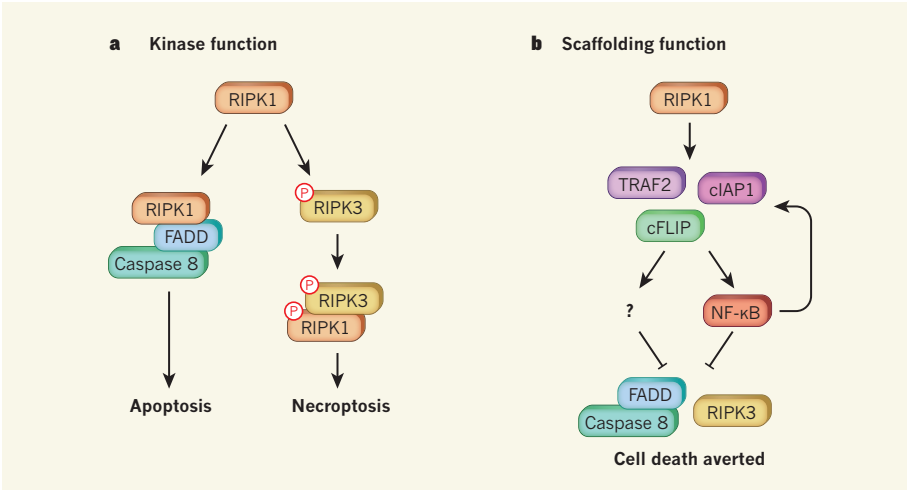

Figure 1 | Regulation of survival and death by RIPK1. **a**, The protein RIPK1 drives cell death through apoptosis, by activating the FADD–caspase-8 protein complex, and through necroptosis, which involves interaction between phosphorylated forms of RIPK1 and its partner protein RIPK3. These death-inducing activities of RIPK1 require the protein's activity as a kinase enzyme. **b**, But RIPK1 can also promote cell survival. Dannappel *et al.*[1] and Takahashi *et al.*[2] show that, in epithelial cells in the gut, this occurs independently of the protein's kinase activity and involves maintaining the activity and levels of the proteins TRAF2, cIAP1 and cFLIP — possibly through a 'scaffolding' process in which RIPK1 shields these proteins from degradation. This function may involve the NF-κB signalling pathway, but also seems able to act by an NF-κB-independent mechanism.

death termed necroptosis[8]. These apparently conflicting functions of RIPK1 have puzzled researchers for years, and we are still struggling to join the dots on how RIPK1 deficiency leads to perinatal lethality.

To try to fill this gap, Dannappel *et al.*[1] and Takahashi *et al.*[2] generated mice lacking RIPK1 specifically in the intestinal epithelium. These mice survived longer after birth than mice with whole-body deficiency of RIPK1, but they developed severe inflammatory bowel disease within the first few weeks of life and died as a result. This colitis was largely due to the heightened sensitivity of the mice to TNF. Histological examination revealed that the intestinal epithelial cells in these animals had undergone extensive apoptosis.

In contrast to previous reports[9,10], the activity of the survival factor NF-κB was not significantly affected in the RIPK1-deficient cells. Hence, the sensitivity of these cells to death was not a result of impaired NF-κB. Previous work had shown[11,12] that the function of RIPK1 as a kinase enzyme is essential for cell death by apoptosis and necroptosis, but not for its stimulation of NF-κB. However, both Dannappel *et al.* and Takahashi *et al.* found that the kinase function of RIPK1 is also not responsible for the severe colitis, because mice engineered to express a kinase-inactive version of RIPK1 developed normally and showed no abnormalities. Nonetheless, the severe colitis was fully reversed when FADD–caspase-8-mediated apoptosis and RIPK3-dependent necroptosis were both inactivated. These results indicate that a yet-to-be defined, kinase-independent function of RIPK1 is responsible for protecting intestinal cells from injury.

Dannappel and colleagues also found that deletion of RIPK1 only in the skin epidermis led to psoriasis-like inflammation. However, unlike in the intestine, blocking necroptosis alone was sufficient to prevent this skin inflammation. Inhibition of FADD–caspase-8-mediated apoptosis and RIPK3-dependent necroptosis has also previously been found to prevent the perinatal lethality of mice with whole-body RIPK1 deficiency[4–6]. Together, these results indicate that RIPK1 promotes cell survival by inhibiting apoptosis and necroptosis and, hence, that the protein has the enigmatic role of both a promoter and an inhibitor of cell death (Fig. 1).

How does RIPK1 orchestrate these diametrically opposing signals? Both groups found that, on TNF stimulation, RIPK1-deficient cells lost expression of the proteins cIAP1, TRAF2 and cFLIP — proteins that switch on the pro-survival factor NF-κB. Moreover, active NF-κB can further increase the levels of these factors. Thus, RIPK1 may protect cells by preserving the integrity of survival proteins such as cIAP1, TRAF2 and cFLIP. In this regard, it is noteworthy that these proteins are regulated by ubiquitination, a process that often tags proteins for degradation by a macromolecular structure called the proteasome. Because the kinase function of RIPK1 is not required for cell survival, it is possible that RIPK1 forms a protective 'scaffold' that shields the survival proteins from ubiquitination and proteasomal degradation. Alternatively, RIPK1 may directly inhibit FADD–caspase-8-mediated apoptosis and RIPK3-dependent necroptosis.

Regardless of the molecular mechanism

50 Years Ago

'Interferometric Raman spectroscopy using infra-red excitation' — Many pure substances and industrial intermediates are strongly coloured and their Raman spectra cannot be recorded using ultra-violet and visible lines, but nearly all compounds have a region of transparency in the near infra-red … Our sample tube used with the laser [has] plain glass windows at each end so that the exciting radiation passes through the sample and directly into the interferometer. The laser is pulsed and the photomultiplier voltage pulses are 'gated' to remove the noise between pulses. The output is recorded digitally … and spectra are obtained by Fourier transformation in a digital computer … Using this apparatus we have observed the Raman spectrum of iodine dissolved in carbon tetrachloride at a molar ratio of 1:1,000 … The possibilities of Raman measurements with near infra-red exciting lines have thus been demonstrated.
From *Nature* 5 September 1964

100 Years Ago

'The type-reading optophone' — Any instrument designed for translating optical into acoustic effects, or light into sound, and thus to some extent substituting the ear for the eye, may be appropriately termed an "optophone" … The latest of these … is designed with the object of enabling blind persons to "read" ordinary letterpress by means of the ear … An optical system throws the image of a glowing Nernst filament upon the printed paper, laid face downwards on a suitably perforated desk. This image is broken up into a series of … luminous dots, flashing with different musical frequencies, by means of a rotating siren disc … It has been found possible to obtain a "readable" sound from type of the ordinary newspaper size.
From *Nature* 3 September 1914