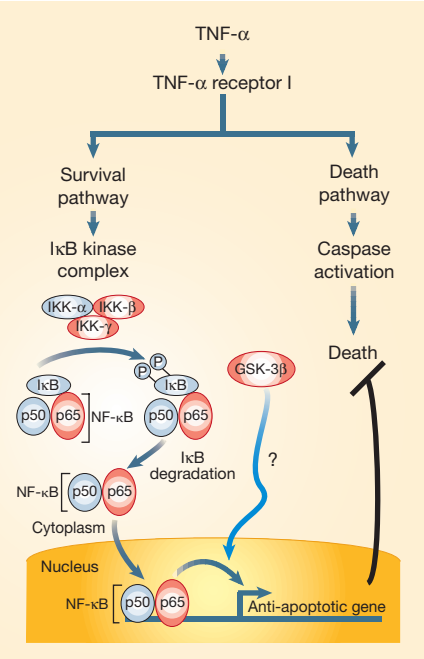

Figure 1 **Life-and-death decisions in cells. Cellular stimulation with tumour-necrosis factor-α (TNF-α, top) simultaneously activates survival (left) and death (right) signalling pathways. The survival pathway leads to the activation of NF-κB, which induces the expression of anti-apoptotic genes in the nucleus. NF-κB (subunits p50 and p65) is normally held captive in the cytoplasm by the IκB protein. Cell stimulation with TNF-α leads to activation of the IκB kinase (IKK) complex, which phosphorylates IκB. The phosphate tag (circled 'P') singles out IκB for destruction. NF-κB is then free to move into the nucleus and activate its target genes. Hoeflich *et al.*[1] have revealed an unexpected requirement for glycogen synthase kinase-3β (GSK-3β) in the NF-κB-mediated activation of genes needed for survival. It is not yet clear how GSK-3β works in this pathway, but it probably involves a critical step following the movement of NF-κB to the nucleus. Targeted disruption in mice of any of the molecules coloured red leads to death of the embryo, accompanied by TNF-α-induced apoptosis of hepatocytes.**

suffer from defects similar to those of mice lacking components of the NF-κB pathway. GSK-3β-deficient mice are morphologically normal at day 12 of embryonic development, but die between days 13.5 and 14.5 with hepatocyte apoptosis, which can be prevented by injection of antibodies that block the function of TNF-α. Embryonic fibroblast cells from these mice are overly sensitive to TNF-α-mediated apoptosis, but not to other apoptotic stimuli. In addition, GSK-3β-deficient fibroblasts show reduced induction of an NF-κB-responsive 'reporter' gene in response to TNF-α or interleukin-1, another cytokine involved in immune responses.

Intriguingly, the GSK-3β-deficient cells still allow the degradation of IκB and the release of its prisoner, NF-κB, to the nucleus. Presumably GSK-3β is required for a later step in the signalling pathway (Fig. 1) — perhaps once NF-κB has already bound to its target genes. One possibility is that GSK-3β is directly or indirectly required for phosphorylation of the NF-κB subunit p65. This modification is important for the activation of transcription by NF-κB[12], and occurs when cells are stimulated with TNF-α or interleukin-1 (refs 13, 14). GSK-3β does not need to enter the nucleus to achieve this task. Instead, it may influence the modification of p65 in the cytoplasm, before or during the translocation of NF-κB into the nucleus. But there are other possibilities, too, and we are sure to learn much about how NF-κB is regulated by finding out how GSK-3β works in this rescue response.

Interestingly, IκB is itself encoded by an NF-κB-responsive gene, and is induced as part of a negative feedback loop to inhibit NF-κB activity. It appears from the results of Hoeflich *et al.* that TNF-α-mediated induction of IκB expression is intact in GSK-3β-deficient cells. So GSK-3β may be required for the expression of only a subset of NF-κB-responsive genes. But further work is needed to discover what determines this specificity of GSK-3β action.

The results of Hoeflich *et al.* are also remarkable for the effects on embryogenesis that do not occur. GSK-3β is involved in the Wnt/Wingless signalling pathway[15], which is required for early embryonic development and cell-fate determination. Here, GSK-3β works together with a tumour-suppressor protein called adenomatous polyposis coli and with a protein called Axin to phosphorylate β-catenin, singling it out for destruction. If GSK-3β activity is inhibited, β-catenin accumulates in the cytoplasm. It can then enter the nucleus, bind to certain protein co-factors, and help to induce the expression of Wnt/Wingless target genes. Proper control of β-catenin levels is therefore critical for axis determination and other events in embryogenesis. So another surprise in the results of Hoeflich *et al.* is that their GSK-3β-deficient mice do not suffer morphological defects before day 12 of embryonic development. Perhaps GSK-3α or other related proteins functionally substitute for GSK-3β during early development.

Given that uncontrolled accumulation of β-catenin is associated with colon cancer[16], it would be interesting to know the incidence of tumours in mice lacking one or both copies of the gene encoding GSK-3β. Mice lacking both copies of the GSK-3β gene die as embryos, but perhaps mice that lack TNF-α or its receptor TNFR1, as well as GSK-3β, might survive for long enough to make such a study possible.

The unexpected participation of GSK-3β in this hepatocyte survival pathway highlights the need to consider the biological

100 YEARS AGO

When the pseudopodium of an *Amoeba* has reached a certain development it suddenly retracts, or rather collapses, for [in this book] Kassowitz regards the phenomenon as a rapid tumbling to pieces of the molecular structure owing to stimulation: certain protoplasm-molecules are shattered, atom-groupings of carbon and hydrogen split the molecular oxygen and are at once burnt to CO_2 and OH_2, the heat-vibrations evolved during the combustion shattering more molecules, and so on, throughout that part of the mass. This process exhausted, a period of restitution sets in, and new molecules are built up from the fragments of proteids, carbohydrates, fats and mineral substances at disposal, and become interpolated between those which had escaped destruction, and a new pseudopodium is put out by assimilative growth. Among other arguments for the view that this is really a process of growth, Kassowitz points out that the rate of protrusion of such a pseudopodium, rapid as it appears under a high power, is really not much more rapid than the growth of a stem of asparagus, a mushroom or a bamboo.

From *Nature* 5 July 1900.

50 YEARS AGO

It is the purpose of this communication to describe a novel chromatographic method of using ion-exchange resins so that only one of two possible adsorption mechanisms associated with their use can function. Weak organic electrolytes and, in particular, aromatic organic ions can be adsorbed on an ion-exchange resin by a combination of salt linkages and Van der Waals' adsorption forces, if the electrical charge of the resin has the opposite sign to that of the organic ions. Partridge and Davies have recently… shown that a major limitation of ion-exchange resins to-day is their inability to fractionate mixtures containing aromatic molecules. It is suggested that these difficulties can be resolved if aromatic molecules are adsorbed on a dissociated ion-exchange resin the electrical charge of which has the same sign as the aromatic ions. Under these conditions only the undissociated aromatic molecules can be adsorbed, since the corresponding ions cannot approach the surface against its repulsive electrostatic forces. Any change in the pH which dissociates the adsorbed aromatic molecules will result in their desorption. **D. E. Weiss**

From *Nature* 8 July 1950.