The checkpoint of death

Cells that fail to turn on a signaling pathway as instructed go on to commit suicide, according to Olivier Micheau and Jürg Tschopp (University of Lausanne, Switzerland). This checkpoint mechanism may ensure that aberrant signalers do not survive to form tumors or inappropriate cell types.

The mechanism explains how death and differentiation are coordinated from a single receptor, the TNF-receptor I (TNFR1). A host of proteins has been implicated in signaling from TNFR1, but these links have relied on overexpression experiments. On looking more carefully, the Swiss team found that a group of proteins formed complex I with TNFR1, and then later peeled away from TNFR1 and the plasma membrane to form the largely cytoplasmic complex II. Only in complex II were death domains available for the binding of other proteins such as FADD, with their recruitment leading to apoptosis.

But if complex I performed its signaling job correctly, the downstream NF-κB pathway was turned on to produce FLIP. This protein shut down the proapoptotic activity of complex II, and thus cells survived. If the cell has a defect in the NF-κB pathway, says Tschopp, “this cell is probably a dangerous cell, and it needs to be eliminated.” But intact signaling prevents this death, after a delay that allows sufficient time to make sure that the NF-κB pathway is behaving correctly.

References: Micheau, O., and J. Tschopp. 2003. Cell. 114:181–190.

Oscillatory metabolism has been seen in reactions such as glycolysis and proton import into mitochondria. The Stanford group earlier showed that oscillatory metabolism can be more efficient than linear metabolism as the oscillations force large amounts of reactants through a reaction when the reactant to product ratio is at its maximum. (This is comparable to the rush of electrical current at the peak voltage of an alternating current [AC] network.)

But how did the oscillations first arise? After staring at waves in a cove in La Jolla, CA, and seeing a paper stating that wave-exposed organisms can grow faster, Ross had his idea: the waves did it. He modeled glycolysis as an evolving genetic algorithm. As the algorithm ran, systems with a constant influx of glucose took about double the number of generations to reach the more efficient oscillatory state than did systems with an oscillatory influx. Furthermore, the algorithms with an oscillatory input reached a higher final efficiency, as measured by the ATP:ADP ratio.

Most biologists continue to focus on linear metabolism. Ross believes that eventually this will change, and that waves will get due recognition for forming not just cliffs but metabolism.

References: Tsuchiya, M., and J. Ross. 2003. Proc. Natl. Acad. Sci. USA. 100:9691–9695.