The Sirens' song

Gerry Melino

Individual cells face three choices: to divide (mitosis), to specialize (differentiate) or to commit suicide (apoptosis). The balance between these ensures tight regulation of cell numbers within organisms. If mitosis proceeded without cell death, an 80-year-old person would have 2 tons of bone marrow and lymph nodes, and a gut 16 km long.

Nevertheless, it took a long time for apoptosis to emerge into the limelight. Apoptosis is over 20 times faster than mitosis, and sightings of dying cells are rare. In contrast to passive cell death (necrosis) — which features leakage and inflammation — apoptotic cells are engulfed and degraded by neighbouring cells without a trace. Various morphologies that we would regard as apoptotic have been observed since the middle of the nineteenth century. But it wasn't until the 1980s that apoptosis was generally credited, when Robert Horvitz and collaborators mapped the fate of every cell in the nematode *Caenorhabditis elegans*, including those that were committed to die. It emerged that cell death is determined by a handful of genes. These 'master switches' have been conserved in evolution so that they, or rather their equivalent families, still orchestrate apoptosis in mammals. However, like life, death is not that simple; the wealth of pro- and anti-apoptotic proteins in cells suggests that suicide is as carefully considered by the cell as it was by Camus.

In stating that it is not possible to enter the same river twice, Heraclitus expressed the irreversibility of time. We, too, undergo continuous changes. What controls the changes in the molecules that form our bodies? What provides our sense of permanence? How do our cells constitute a unified whole?

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Death wish: Odysseus is tempted by the Sirens.

Gradually, the idea emerged that the stability of the body is maintained by signals that control the life and death of single cells. This is a powerful concept, implying that there are specific survival and death signals, and corresponding receptors on cells. Such social control of life and death are vital in complex multicellular networks such as the immune system and the nervous system, where communication between cells is crucial.

To survive, we must resist many death signals: here the Greek myths provide striking metaphors. To resist the persuasive songs of the Sirens, Odysseus plugged his sailors' ears (blocking the receptors) and tied himself to a mast (blocking signalling). Orpheus, however, resisted the songs by loudly singing and playing his lyre. Thus, he superimposed his life song (anti-apoptotic) over the Sirens' death song (pro-apoptotic). Does social control inevitably imply navigation between conflicting signals?

Social control (altruism, cheating and selfishness) is a powerful evolutionary force, and its signals can be translated to the molecular level. Jacob, Monod and Wyman demonstrated the existence of 'repressors', through which signals interact to modulate gene expression, fine-tuning the activity of enzymes or the binding of ligands and receptors. It is no surprise, therefore, that social control extends to unicellular organisms. Regulated forms of cell suicide also occur in bacteria, in the protozoa *Trypanosoma* and *Tetrahymena* and in the amoeba *Dictyostelium*. In bacteria, several genes, organized as toxin-antidote modules, control the balance between life and death. Most are encoded by plasmids, but some by the bacterial chromosome itself. This is the case for the toxin MazF (which fragments the genome), which is neutralized by the antidote MazE, which in turn is continuously degraded by a protease, ClpP. It seems that, like Sisyphus and the rock he pushes up the mountain — which always rolls down before he reaches the summit — unicellular organisms must continuously inhibit self-destruction.

We can now revisit the idea that social control of cell death in eukaryotes also involves intracellular signals (as Ameisen believes) rather than just signals between cells (as Raff believes). Two billion years ago, the atmosphere changed from being reducing to oxidizing. The reactivity of oxygen and its products allowed the development of complex reactive structures, such as haem centres. This led to more flexible protein structures, more reactivity and more regulation (allostery). Symbioses developed to maximize biological performance — eukaryotic cells seem to be the result of such symbiosis. Some bacteria captured mitochondria, giving rise to proto-animal cells; others captured chloroplasts, forming proto-vegetal cells. Thus, a dialectic was established between different elements of the symbiotic partnership. However, the toxic potential of components of the consuming partner, such as the electron-transport chain, necessitate their sequestration within mitochondria; for this reason, mitochondrial damage gives rise to signals that can kill the cell. The cell, in turn, protects itself by producing antidotes such as caspase inhibitors and anti-apoptotic proteins.

Understanding apoptosis may require an appreciation of these ancient symbioses. Any change in equilibrium from the inside (DNA damage, metabolic or cell-cycle aberrations) or the outside (signals and receptors) irreversibly activates suicide. The result is a mitochondrion-centred picture of life and death. But if dialogues exist between other intracellular organelles, this view needs rethinking. What's more, apoptosis seems not to be the sole phenotype of cell suicide. Various pathways of self-destruction coexist in our cells that may have been selected during evolution. And several gene products involved in these death pathways also seem to regulate mitosis and differentiation, blurring the frontiers between 'programmes' of life and death.

With the increased understanding of cell suicide has come a shift in our attitude to many diseases. No longer is it fashionable to think of cancers solely as disorders of mitosis, but rather as a failure of apoptosis. Similarly, diseases such as AIDS, neurodegenerative conditions and auto-immunity may result from too much, rather than too little, apoptosis. The complexity and subtlety of cell death not only allows cells to control their fates, but also offers us new therapeutic ways to control them. The effectiveness and selectivity of these interventions will depend on our capacity to dissect the diverse interplay between molecular mechanisms that regulate mitosis, differentiation and death. ■

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Apoptosis

"There is only one serious philosophical problem. It is suicide. To judge whether life is or is not worth living." Albert Camus

FURTHER READING

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