Programmed cell death and the protozoan parasite

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Preface

Although programmed cell death in metazoan, particularly mammalian, cells was observed early in the development of cell biology, it was only after many decades – some 15 to 20 years ago – that the process claimed its rightful place as a key process at the core of the subject. The importance – even the very existence – of programmed cell death in protozoan parasites is still controversial, with some old arguments getting a fresh airing in this new arena.

It is useful to remember that, in the 1980s and even the early 1990s, there was considerable resistance to the concept of a widespread programme of cellular self-destruction, such as apoptosis, even in metazoan cells. The unequivocal demonstration of such a programme in the nematode *Caenorhabditis elegans* by Nobel laureates Horvitz, Sulston and colleagues provided the crucial breakthrough, and the subsequent identification of homologous genes playing critical roles in mammalian apoptosis was extremely important. The genetic programme of cell death in *C. elegans* not only provided a broad framework on which to develop the analysis of mammalian apoptosis, but also gave a convincing demonstration that genetically programmed, active, cellular self-destruction was a real phenomenon that had to be taken seriously. Since then it has become generally accepted that programmed cell death, in the form of caspase-dependent apoptosis or other mechanisms, plays an essential role in mammalian physiology, from developmental embryology to immunology. No analysis of mammalian cell populations can now be complete without some consideration of the potential role of programmed cell death.

Since programmed cell death plays such a widespread role in metazoan physiology, dysfunction of programmed cell death – either deficiency or overactivation – is clearly implicated in the pathology of many different diseases, from cancer to degenerative diseases. It is no exaggeration to state that the acceptance of programmed cell death into the mainstream has revolutionised mammalian cell biology and medicine. One of the areas of mammalian biology most profoundly affected has been the analysis of the interactions between viruses and their host cells and it has become clear that many viruses manipulate host cell apoptosis to maximise infection. The host cell often responds to intracellular viral infection by self-destruction through apoptosis, which benefits the host organism as a whole by limiting the spread of virus. The phenomenon is now a central part of our understanding of virus biology. The chapters in this supplement dealing with protozoan regulation of host cell apoptosis (Schaumberg *et al.* and Heussler *et al.*) are on reasonably safe ground since they deal with the active death of mammalian cells which has already received a lot of attention. The signals regulating apoptosis, i.e. those coming from the parasitic protozoa, are different from those previously studied, but the broad concept of manipulation of mammalian host cell apoptosis is familiar from the numerous previous studies on the control of apoptosis by viruses. The regulation of protozoan infection of mammalian cells by phagocytosis of neutrophils (Ribeiro-Gomes *et al.*) is an even more complex phenomenon which may have important implications for the progress of diseases like leishmaniasis.

The potential role of programmed cell death in the biology of the parasitic protozoa themselves has only received serious attention in the past 10–15 years. The chapters in this volume which deal specifically with this area (Welburn *et al.*, Holzmuller *et al.* and Hurd *et al.*) are therefore necessarily concerned with recent studies of the protozoa, which build on the precedents set by the large body of previous work on programmed cell death in metazoan cells. This seems reasonable as long as we bear in mind that the evolutionary distance between higher

Parasitology (2006), **132**, S1–S2.
doi:10.1017/S0031182006000801 Printed in the United Kingdom

mammals and protozoa makes it extremely unlikely that exactly the same pathways will be followed in these different organisms. Acceptance of the existence of programmed cell death in any unicellular organism has had to overcome the conceptual difficulty involved in understanding how a cell can possibly benefit from its own death. The answer to this question, as is actually also the case for metazoan cells, is that the genes of the cell opting for self-destruction are maintained by other genetically similar cells. Indeed, the further propagation of these genes is favoured by the death of the cell – for example, through the restriction on the release of viruses or other infectious agents when an infected cell undergoes self-destruction. This criterion can be met by single-celled organisms existing as populations of genetically similar cells, as demonstrated in bacteria and in several free-living single-celled eukaryotes. While the principle is a clear one, the molecular mechanisms involved may vary. We should therefore be prepared for examples of convergence during evolution, with the same end, the controlled self-destruction of the cell, being achieved by different molecular mechanisms. Where similarities exist between the molecular mechanisms of active cell death in parasitic protozoa and mammals, it is unsurprising, and nearly inevitable, that these show significant divergence (Welburn *et al.*, Holzmuller *et al.* and Hurd *et al.*). As the parasitic protozoan programmed cell death field continues to develop and mature, we should anticipate further striking similarities with the process in other organisms, as well as many unique features.

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June 2006

https://doi.org/10.1017/S0031182006000801 Published online by Cambridge University Press