Executioners of Cell Death

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By 2000 a crucial role for mitochondria in the regulation of cell death had been clearly proven. Cytochrome c is released from the mitochondrial intermembrane space into the cytosol where it activates pro-apoptotic effector cascades. However, the mechanism by which cytochrome c was released from mitochondria was a matter of debate, with different researchers favoring the hypothesis that either the permeability transition pore (PTP) model controls release or the BCL-2 family of proteins directly mediates cytochrome c release. In 2000, Solange Desagher and Jean-Claude Martinou provided the field with a critical analysis of the controversial mechanisms by which mitochondria mediate cell death [1]. Drs. Desagher and Martinou share their thoughts on the ever-expanding mechanisms of apoptosis regulation as well as their advice on writing an impactful review.

What was known about mitochondria's role in apoptosis at the time of writing this review?

When we wrote this review in 2000, a series of papers pointing to the importance of mitochondria as essential centers in the regulation of apoptosis had recently been published. Most notably, it had become clear that the Bcl-2 family proteins were able to either trigger or prevent apoptosis mainly through their interactions with mitochondria, by controlling the release into the cytosol of the cytochrome c, a protein normally confined to the mitochondrial intermembrane space. Cytosolic cytochrome c had been clearly demonstrated to be the crucial factor in apoptosome formation and caspase 9 activation, and thus the role of mitochondria in the control of apoptosis was widely accepted. One of the primary objectives of this review was to assemble the evidence for this consensus view and we chose the title accordingly.

However, the mechanism through which cytochrome c was released from mitochondria was still the subject of much debate. The first hypothesis to be proposed was based on the opening of the permeability transition pore (PTP) leading to swelling of the mitochondrial matrix and the rupture of the outer mitochondrial membrane. This model was supported by data from different groups and it was suggested that Bcl-2 family proteins could control cytochrome c release by modulating the PTP. However, some observations were not compatible with this view and an alternative hypothesis proposed that the Bcl-2 family proteins themselves could form channels or pores in membranes and

that cytochrome c could escape from mitochondria either through a megachannel consisting of Bax oligomers, or through a lipidic pore formed upon Bax activation. The second goal of the review was thus to summarize the arguments in favour of each hypothesis and to attempt to reconcile the apparently contradictory data. Since we were writing this review at a time when the controversy between these two schools of thought was at its height, we deliberately chose not to favour one hypothesis over the other, and this may have been the reason why some considered our review to be necessary and timely.

How has the field evolved since this review?

Since our review, the controversy surrounding the mechanism of cytochrome c release was largely resolved and a consensus view has now emerged based on the formation of Bax-driven membrane pores. Since then, much emphasis has focussed on understanding how the apoptotic components, including the Bcl-2 family members and the mitochondrial membrane lipids, interact to control cell death. An emerging aspect of the research, which we touched on in our 2000 TCB review, concerns the morphological changes of mitochondria which accompany apoptosis, and this has opened new avenues of research on mitochondrial dynamics whose implications go far beyond the control of apoptosis. Regarding the Bcl-2 family members, it was reported that BH3 only proteins could be classified into two categories: the sensitizers, which bind and preferentially inhibit the antiapoptotic proteins; and the activators, which bind and activate the proapoptotic proteins. These protein-protein, and importantly the protein-membrane interactions, have been referred to collectively as the "embedded together model". This research, together with the characterization of the 3D structures of different members of the family, have allowed pharmaceutical companies to design and test small molecule inhibitors of the proapoptotic proteins, so-called BH3 mimetics, which have shown efficacy in several models of cancer. One of these, ABT-199/Venclexta, a Bcl-2 inhibitor, has been recently approved by the FDA for elapsed/refractory 17p-deleted CLL (Chronic Lymphocytic Leukemia). This can be considered as one of the most spectacular achievements in the field of apoptosis thus far, and one which stems directly from the strong fundamental research programmes developed worldwide over the past 30 years. The importance of this research had been anticipated by the Nobel committee who in 2002 awarded the prize for research on the genetics of programmed cell death.

What is the future of the field and what outstanding questions remain?

Much remains to be done to understand how the apoptotic components work together and what controls their activation. This is true in particular for Bcl-2 family members. For

example it remains unclear how the proapoptotic members of the family can affect membrane curvature to alter the permeability of the outer mitochondrial membrane. Success in approaches aimed at solving the structure of membranes and/or proteins will be paramount in resolving this core question. The development of additional BH3 mimetics, in particular those inhibiting MCL1, will also remain a key challenge and current data indicate that such compounds may have huge benefit in treating diverse types of cancer. Finally, much work remains to be done concerning the mechanisms of activation and the function(s) of all the other Bcl-2 family members, including the yet poorly characterized BH3-only proteins. This deeper understanding should allow the development of novel drugs not only that promote cell death, for example for the treatment of different types of cancer, but also drugs that protect cells from the apoptotic events which accompany acute injuries such as stroke or myocardial infarct.

What characteristics do you feel make a review valuable?

A good review should provide the reader with a clear, unbiased and meaningful assessment of the state of the art in a defined field. It should not simply consist of a sterile catalog of results, but should rather extract meaning from the data obtained by different laboratories in order to delineate emerging trends. The most valuable reviews identify key current questions based on converging experimental results from various sources and propose different ways forward. Importantly the review should provide a complete and unbiased view of the field without minimizing data which could question the author's favourite theory. While of course it can be extremely useful for the author to use his or her insight to propose a framework on which to assemble diverse observations, the reader should nevertheless find in the text all the information and references necessary to forge his own appreciation of the field. This is particularly important where the subject matter is controversial. Finally, a review is most useful when it defines the exciting questions that remain unanswered, which hopefully will inspire young scientists and investigators from other fields to provide novel contributions.

What advice would you offer researchers that are writing a review?

Each researcher has his own way of writing. However, a good approach is first to define the question to be addressed in a short introduction, which provides the reader with all the elements necessary to understand the scope of the review. The author should then read extensively the relevant original articles and attempt to identify convergent and conflicting data, try to explain the discrepancies, and finally to provide a meaningful overview of the topic. The temptation to focus on one's own results and pet theories should be resisted

and reference to all articles published on the subject should be a good way to avoid any personal bias in selecting the information presented. Re-reading earlier articles with an open mind may also help, with hindsight, in reviving original ideas that may have slipped the attention of the field at the time of publication. The text of the review should then be organized around a few strong ideas, each accompanied by a succinct description of the arguments for and against. An approach that should avoid the 'catalogue' format is to link the ideas, and where possible, to develop a unifying thread throughout the review. The temptation to simply repeat ideas expressed in previously published reviews is not helpful and should be avoided. The final section should then return to the original question posed by the review, summarizing the major conclusions and underlining the issues which remain unresolved. The author may then finish by indicating possible ways forward, hopefully encouraging the scientific community at large to pursue the adventure.

References

- [1] Desagher, S. et al. (2000) Mitochondria as the central control point of apoptosis.
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