

## Introduction

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It is now firmly established that mitochondria play a central role in programmed cell death, i.e. apoptosis. However, the script of this play is far from finalized. It contains many corrections, erasures, insertions and alternate plots. This volume contains a set of cutting-edge reviews that reflect the current state of the field, help guide the reader through the sometimes contradictory literature, and point to promising future directions. Indeed, some delay in generating this volume arose from the need to wait for the publication of key papers.

Most of the reviews address aspects of the key irreversible step in the initiation of the execution phase of apoptosis by mitochondria: the release of critical intermembrane space proteins into the cytosol. It is remarkable to consider that a mere 5 nm barrier keeps two sets of proteins apart, thus, allowing cells to live a little longer. The mingling of these proteins activates the caspase cascade leading to the repackaging of the cell into membrane-enclosed packets of food. The process is efficient, cold, and calculating. The cell is poised to commit suicide much like a manic-depressive protagonist in a tragedy. Without the daily infusion of stabilizing drugs, here growth factors and without favorable communication

from the outside world, the innate selection is in favor of death.

It is most ironic that the same organelle whose capture eons ago allowed the cell to respire, use energy efficiently, perform a myriad of catabolic and anabolic reactions, and hence gain an enormous survival advantage is the same one that contains the keys to cell death. The Creator must have a sense of the dramatic.

It is also interesting to note how the mitochondrial outer membrane, a mere footnote in the mitochondrial physiology of the 1960s, 1970s, and 1980s, has become a critical player. Not only is this membrane the barrier that keeps cells alive, it is the site of regulation of mitochondrial physiology including mitochondrial fission and fusion. The outer membrane also allows communication with the endoplasmic reticulum and the extent of the functional resonance between these compartments is just beginning to be appreciated.

The rapid evolution of this field will no doubt doom these reviews to a relatively short useful half life. However, it is hoped that the insights and guidance provided by these reviews will mean that this short life will be intense and fruitful, guiding research into productive directions.