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REVIEW ARTICLE

Cell death in drug design

Richard A. Lockshin
Department of Biological Sciences, St. John's University, Jamaica, NY, USA

ABSTRACT

Cell death is a major factor separating healthy physiology from pathology and is rightly the target of considerable attention in the development of new therapies. Most of the effort has been directed at the activation of key effectors of apoptosis and the molecules that regulate this activation. This approach may be valid to address cancer, but otherwise, while efforts are making progress, they miss an important point that addresses cells that die too soon or inappropriately. In these situations, the stress on the cell often derives from an external source, and ultimately this stress must be relieved. If it is not, the cell is still likely to die, though perhaps not by apoptosis. Controlled autophagy, in which specific organelles are removed, begins to give us clues by which we may learn to understand how organelles are targeted.

Keywords: *Cell Death, Apoptosis, Drug Design, Autophagy, Lysosome.*
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INTRODUCTION

Cell death is clinically an important event for many reasons. Beyond early development, where it is a major component of organogenesis, the specificity of the immune and central nervous systems is defined by the massive overproduction of cells and the selective elimination of up to two thirds of them. Excessive or uncontrolled deaths, or failure of cell death at the appropriate time, lead to severe pathologies, and even death. In adult life, failure of cell homeostasis can occur either through failure of cells to divide or by deregulation of their normal death mechanisms. Thus, neurodegenerative diseases, autoimmune diseases, and many forms of cancer can be linked to problems with the control of cell death.

Reprint or Correspondence: Richard A. Lockshin. Department of Biological Sciences, St. John's University, Jamaica NY USA.
E-mail: lockshir@stjohns.edu

By far the greatest number of these deaths occur through the process of apoptosis. Most prominently in the immune system, a receptor-ligand interaction triggers the activation of the initiator caspase, caspases 8, leading to a cascade that ultimately activates the effector caspases 3 and 7. The effector caspases are the most important destroyers of the cell. In other situations, any of several metabolic changes lead to the deep polarization of the mitochondria in the activation of initiator caspase 9, which in turn can activate caspases 3 and 7. However, early attempts to control cell death by interfering with caspase function did not work very well. Presumably, they reason that they did not work well was that, while the destruction of the cell might have been delayed, the targeted cell remained in very poor condition, owing to problems that had brought on the condition in the first place, and cellular function was not restored.

Today's efforts are targeted mostly against cancer and overactive or hyper-proliferative immunocompetent cells. The techniques include: monoclonal antibodies, SI RNAs, small molecule inhibitors, antisense message, proteins capable of interacting with one or more regulators of cell death, targeted assassins, and gene therapy. For most of these approaches, the goal is to activate apoptosis in potentially noxious cells. There is less effort today to prevent cell death in the more chronic situations of neuronal death, such as in Parkinson's disease or Alzheimer's. In the more acute situation of cell loss owing to viral infection, especially AIDS, the effort has been more supportive -- delivery of growth factors, mitogens, or hormones that potentially will tip the balance of the cell from death towards survival. For a sampling of current efforts, see (1-17).

LOGIC OF THIS APPROACH

There is a reason for this approach. When a cell is in trouble, several things happen: first, it will attempt to survive, using autophagy or any other protective mechanism to keep going. This autophagy may ultimately lead to the death of the cell in the same sense that is starving individual will finally burn skeletal and cardiac muscle. That is vital for survival. The second issue is that in most circumstances, the origin of the problem is not from within the cell, but rather derives from an external source. Because of an undefined limitation -- deriving from a circulatory problem, a lack of a critical growth factor, a corrupted or otherwise unsatisfactory substratum, failure of nutrient delivery or removal of waste, or other problem -- the cell is not thriving. If that problem is not corrected, manipulation of the machinery of cell death will not lead to an improved existence.

This then is the problem that faces us: we now know a great deal about the mechanics of apoptosis -- thanks to the magnificent studies of many researchers far more brilliant than I -- and we know a considerable amount about the mechanics of autophagy. We sometimes know how the process of death starts (with the coupling of a ligand such as Fas-ligand or TNF) or what the initiating trigger might be (overloading of the endoplasmic reticulum, oxidation of unknown proteins or lipids, or damage to mitochondria). But what is really missing is the transduction. A case in point is being very directly controlled, manifestly physiological, process of insect metamorphosis. Although insects have caspases, what is seen in the metamorphic death of the large, post-mitotic cells of insect larvae is massive autophagy, which may or may not terminate in a final phase of apoptosis. The cells were previously in excellent health, and the autophagy targets specific organelles in sequence -- glycogen particles mitochondria and ER. Typically, and similar to what is seen in mammalian cells in culture, mitochondria are among the last organelles to be consumed. As is typical of "autophagic cell death," the nuclei do not collapse until the mitochondria are gone (18-27).

AUTOPHAGY AND AUTOPHAGIC CELL DEATH

These metamorphic deaths are typically brought about by the rise of the molting hormone ecdysone. The facts that the hormone creates this situation and that the autophagy targets one organelle after another, make it hard to accept the idea that the autophagic process is aggressive. In other words, one can imagine only with difficulty, a situation in which the autophagic membranes suddenly alter to recognize an otherwise functioning organelle. It is far more likely that the organelle has altered to admit a signal that causes the autophagic vacuole to form. For instance, there is evidence that be polarized mitochondria are subjected to autophagy. We would consider the autophagosome to be more a hyena than a lion, more a vulture than a raptor.

It is much more likely, though still unproven, that the autophagosome is a scavenger rather than a predator. If this is true, then knowledge of all of its genes, while helpful, does not directly address the problem of transduction. We still need to know what initiates the formation of the isolating membranes and what causes them to identify and contact specific organelles. In the same sense that an emergency room physician must identify symptoms and decide which are the most life-threatening, we need to be able to identify this symptoms and molecular causes that define a cell as sick. To do so, we must focus more on the molecular changes in the target organs and in the milieu of the cell. This knowledge will allow us to understand the vulnerabilities and strengths of the cell. We will then be able to target our therapeutics specifically toward these vulnerabilities and strengths. The drugs that we will design will thus become far more delicate and effective.

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