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VIEWPOINT

This series focuses on the programmed cell death process referred to as apoptosis. Apoptosis is being increasingly recognized as a fundamental biological process that impacts on the early development, maturation, and acquisition of disease states of multicellular organisms. Although the occurrence of programmed cell death has been identified for many decades, the relatively recent acceptance of this principle is evidenced by the remarkable increase in special conferences and presentations on this topic as well as its rapidly expanding scientific literature.

What are the aspects of apoptosis that make it so interesting to the contemporary scientific community? One is the manner by which apoptosis can be initiated by a change in the extracellular milieu of a specific hormone or polypeptide growth factor. In many cases, such a change involves the local loss or depletion of a substance required for cellular survival. Certainly the requirement for nerve growth factor to maintain the viability of adult sympathetic neurons, the androgenic steroid-dependent survival of prostatic epithelial cells, and the dependence of differentiating hematopoietic cells on cytokine substances provide model systems to study this relationship. At other times, the presence of certain hormones or polypeptides can initiate apoptotic cell death. Transforming growth factor-β, tumor necrosis factor, and glucosteroids are examples of hormonal apogens that act in a cell-specific manner to initiate apoptosis. Given the endocrine aspect of apoptotic control, it is obviously a process that can be regulated by the action of cells at a site far distant from the affected cell.

Secondly, we now understand that signal transduction pathways governing cellular actions require sequential and complex interactions between a diversity of intracellular biomolecules. Recently, there have been important inroads made in defining some components of the signal transduction mechanisms involved in apoptosis. Clearly, the receptors for the growth factors and cytokines that initiate apoptosis have a role in activating the signal transduction pathway leading to programmed cell death. The activity of members of the protein kinase C family as well as GTP binding proteins of the ras family have been shown to contribute to apoptotic signaling. Likewise, the cellular generation of ceramide can be a potent non-polypeptide molecular effector of apoptosis. In summary, we are getting a view of apoptotic signaling that very much resembles the signaling pathways involved in a cellular proliferative response. That is, depending on the cell type and its receptor profile, apoptosis can be elicited by any of a multitude of diverse interacting signaling pathways that converge in the end to the final mechanistic action of cell death.

Finally, given the stringent requirement of programmed cell deaths for the normal early development of multicellular organisms, there is a great interest in the genetic components of apoptosis. This area has most rapidly advanced in the easily studied organism Caenorhabditis elegans. Identification of mutational defects that eliminate developmentally-regulated somatic cell death in these simple organisms have led to the description of numerous distinct genetic loci that regulate apoptosis. In fact, these loci can be sorted into hierarchical groupings of genes (CED genes) that control each of the various stages of the apoptotic process (initiation, killing, engulfment, and removal). Since some of the apoptotic regulatory genes that have been described in C. elegans are conserved in higher organisms, it has already been possible to assign cell death functions to the gene products of the higher organism as well. For example, the cysteine protease activity of the C. elegans CED-3 gene product (involved in cell killing) is shared by the interleukin converting enzyme (ICE) of humans. Indeed, the human ICE gene product has readily shown the potential to initiate apoptosis of human cells when it is inappropriately expressed. Since ICE is a member of a gene family in higher organisms, we may find that other members of this family are linked to apoptosis. More interesting will be the definition of the substrate upon which ICE proteins act to elicit apoptosis.

Genetic studies of Drosophila, begun much more recently, have also identified unique genetic loci associated with developmental or in-

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duced apoptosis (for example, the rpr gene) and the continued study of this organism is also expected to advance our understanding of apoptosis in higher organisms.

For mammalian cells, a number of different gene products have now been characterized as having a role in the cell death pathway. These gene products can be sorted into two important groups: 1) regulators of the process and; 2) effectors of the process. The most prominent regulatory molecules include bcl-2 and its (expanding family of) homologues, most auspiciously the bax protein. By their opposing actions (bcl-2 protein suppresses the cellular response to apoptotic stimuli whereas bax protein sensitizes cells to apoptotic stimuli) the intracellular ratio of these heterodimeric binding partners seem to control the signal transduction pathway by which cells sense and process apoptotic signals in much the same way that a rheostat controls the strength of an electrical signal. Identification of the mechanism(s) by which these molecules control entry into apoptosis remains one of the more intriguing questions to be answered in this field. The number of putative effector molecules of apoptosis is also rapidly increasing. This category includes several gene products that were previously known to have important roles in cell cycle movement. Gene products such as c-myc, p53 and RB, when inordinately expressed, can cause cells to undergo apoptosis. Given the hypothetical importance of cell death for eliminating abnormal (proliferating) cells from an organism, the relationship between cell cycle movement and apoptosis is another extremely interesting area that remains to be elucidated.

Novel and apparently unique gene products involved in mammalian cell apoptosis are being increasingly described (most recently, apt-2 and apt-4). Complete characterization of the structure and function of the polypeptides encoded by these novel genes might help us better understand the cellular mechanisms leading to cell death. Also for the future, there are certain paradoxes of apoptosis that need to be resolved. For example, why do some cellular systems for apoptosis seem to require gene activity (RNA and protein synthesis) prior to cell death whereas others are independent of such activity? How is it that an enucleated cell can seemingly undergo apoptosis? The scientific challenge of all of these questions as well as the importance of this phenomenon to human disease states ensures that there will be continuous discussion and lively debate on apoptosis during future years.

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