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Circle of life

The well-being of a large ecosystem such as the African savannah relies on an intimate link of life with death. Similarly, the maintenance and renewal of life within the microcosm of our body makes cell death a necessity for organismal survival. This month *Nature Immunology* and *Nature Reviews Immunology* together present a special Focus on Cell Death and Immunity. The Focus contains a collection of eight review articles, four in each journal, on the latest advances in this area. Our Focus website (http://www.nature.com/focus/celldeathimm/) provides access to the full set of specially commissioned material, an annotated list of classic landmark papers that shaped the field, and a Round-up and Highlights section of summaries of recent papers from the cell death literature as it pertains to immunity. The entire site will be free until the end of June to anyone who registers or who is already a registrant or subscriber to any Nature journal.

The study of cell death dates back to the turn of the century, when scientists marveled at the morphology of dying cells. Subsequent advances describing developmentally planned cell deaths in the worm *Caenorhabditis elegans*, were celebrated by the award of the 2002 Nobel Prize in Medicine and Physiology to Sydney Brenner, H. Robert Horvitz and John E. Sulston. This knowledge provided the underpinnings for deciphering the role of cell death in human physiology. Because immunologists were already grappling with questions of cell death during immune system maturation, and the lack of cell death in leukemias, much of the work on cell death in mammals came to be centered on immunological issues.

The need for precise control of cell death in the immune system was never a contentious issue. However, until the elucidation of the death pathways and the advent of mammalian genetic manipulations, the role of cell death in specific immune processes could not be appreciated. Early work that characterized mice with mutations in death receptors foreshadowed a similar defect in humans with autoimmune lymphoproliferative syndrome (ALPS). The underlying molecular mechanism of ALPS was traced to molecules in cell death pathways that contain the death effector domain (DED). Recent studies of DED-containing proteins, as discussed by Lenardo and colleagues in a review in this issue, highlight their apoptotic, anti-apoptotic and proliferation-inducing properties.

Although each immune cell has an intrinsic control over its own life and death, which is necessary to avoid autoimmunity, cells such as cytotoxic T cells are well equipped to determine the fate of other cells. The review by Trambas and Griffiths discusses the delivery of toxic granules from professional killer cells to their targets. Natural mutations in this delivery pathway are manifested as immunodeficiency disorders, some associated with pigmentation defects, as delivery of pigment granules sometimes relies on the same systems. The contents of these granules, and the different flavors of granzymes, are discussed in the review by Lieberman in the May issue of *Nature Reviews Immunology* (accessible through the Focus website).

Granzymes may trigger cell death by activating the caspases, an enzyme family that is synonymous with the execution of death pathways. However, as emphasized by Jäätelä and Tschopp in this issue, the less well examined caspase-independent pathway provides another way for cells to die. Notwithstanding, caspases remain a critical regulator and executioner of cell death. A key group of intracellular proteins that bridge death signals to caspases belong to the Bcl-2 family. As discussed by Opferman and Korsmeyer, both pro- and anti-apoptotic members of this family are critical in determining cell fate. The expression of these molecules is triggered by many stimuli and is tightly controlled. Members of the Bcl-2 family regulate thymocyte development (reviewed by Palmer in the May issue of *Nature Reviews Immunology*), a process that confers on the immune system the ability to kill foreign pathogens and damaged cells while simultaneously ignoring self.

The recognition and elimination of pathogens draws the immune system into a necessary game of cat and mouse with the pathogens, as discussed by Gugeon in a review of the mechanisms by which HIV-infected cells escape death, appearing in the May *Nature Reviews Immunology*. Thus, our body has evolved to use pattern recognition receptors that bind critical elements of the pathogen. This is an area of intense research and intersects the cell death pathway by means of the NOD proteins (reviewed by Inohara and Nunez, also in May's *Nature Reviews Immunology*), some of which are intracellular sensors of pathogens, whereas others are integral members of the death machinery.

The revelation that several diseases are linked to defective cell death mechanisms emphasizes the physiological importance of specific pathways and enables the design of more effective immunotherapies. Examining these canonical cell death pathways in the context of diseases has also alerted researchers to both redundancies and alternate pathways, the details of which are not yet worked out. The holy grail of immunology remains the understanding of how the body's micro-ecosystem discriminates healthy self-tissues from pathogenic foreign antigens. Attaining this lofty goal will require the mapping of all roads that lead to death.