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Editorial

Apoptosis in viral pathogenesis

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It is difficult if not impossible for a virus to infect a cell and not trigger the cell's 'burglar' alarm, activating the cellular programmed cell death pathway. Early discoveries with viruses taught us a great deal about both viral and cellular death pathways. Eileen White and colleagues identified viral apoptosis-inhibitory genes by studying adenovirus mutants with an unusual *deg* (degradation) phenotype,[1,2] leading to an understanding of how E1b 55K and E1b 19K inhibit apoptotic cell death by distinct mechanisms. Lois Miller's laboratory made a link to virus-induced disease when they demonstrated that the baculovirus-encoded caspase inhibitor P35 was required for pathogenesis.[3,4] Jeurissen *et al*. first associated virus-induced apoptosis with disease in chickens when they showed that chicken anemia virus infection of hatchlings resulted in thymocyte apoptosis.[5] Cellular anti-apoptotic genes were then found to convert a lytic virus infection to a persistent infection, perhaps explaining the long-term persistence of alphaviruses in the brain.[6] Early in the apoptosis field, a number of laboratories gathered evidence for HIV-triggered apoptosis in AIDS.[7] Several years and many genes later, it is surprising how little we understand about the role of apoptotic cell death in viral disease mechanisms. For example, the role of viral Bcl-2 and other virus-encoded apoptosis regulatory proteins encoded by herpes viruses have been studied in some detail but the mechanisms by which these genes might alter herpesvirus-associated disease and tumorigenesis is unknown. It turns out that the issues are complex and these are difficult questions to answer.

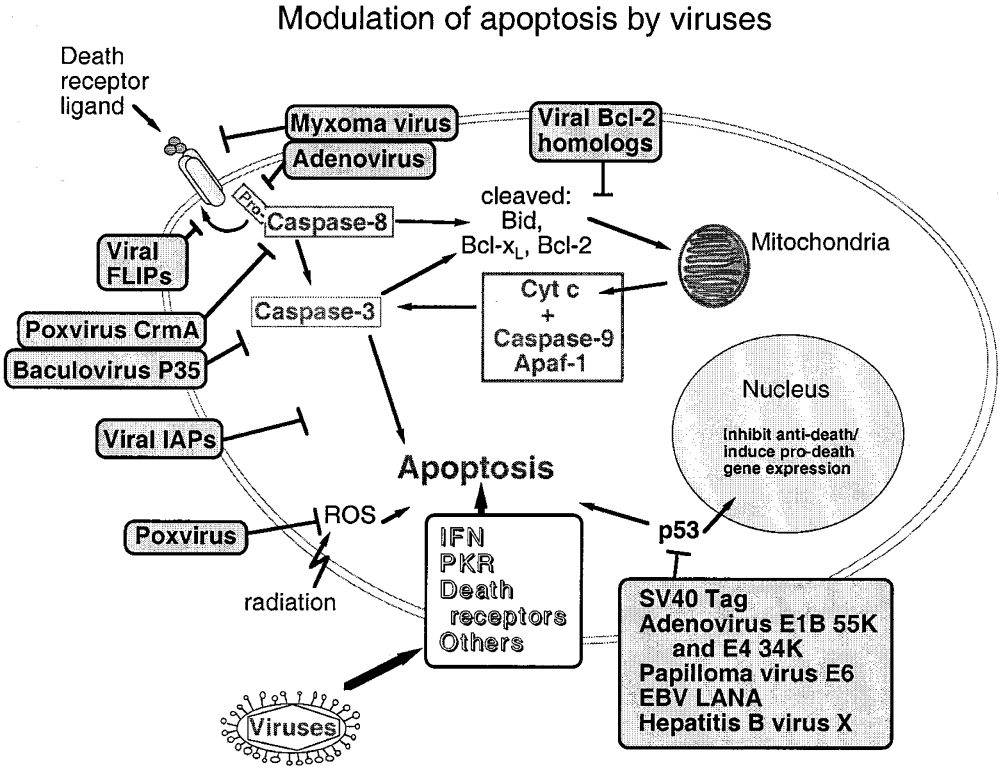

Figure 1 Modulation of apoptosis by viruses

Adenovirus takes the prize for having the greatest number of identified gene products that induce or inhibit programmed cell death.[8–10] Many other viruses have now been shown to trigger apoptotic cell death and/or encode inhibitors of apoptosis.[11,12] Viruses interfere with programmed cell death from the beginning of the cell death pathway to the end (shaded boxes in Figure 1). One of the mechanisms by which myxoma virus (a poxvirus) modulates the cellular response to infection is encoding viroceptors or virokines that mimic cellular receptors and cytokines.[13] M-T2 of myxoma virus is a secreted tumor necrosis factor receptor homologue.[14] At the distal end of the pathway, the baculovirus AcMNPV and cowpox virus encode protease inhibitors that prevent cellular caspases from terminating the cell.[15,16] Although many of these viral factors have been studied in great molecular detail, it is less clear how these factors alter a disease state.

The following three review articles deal with various aspects of apoptosis in virus infections with special emphasis on disease pathogenesis. Glen Barber considers cellular defense mechanisms against viruses including cytotoxic lymphocytes and cytokines. Interferon, interferon-induced genes and interferon regulatory factors (IRFs) modulate apoptosis of virus-infected cells. But viruses also manipulate these host cell defense mechanisms. The use of knockout and transgenic animals has helped determine the roles of these host factors in viral infections.

Terry Finkel (HIV) and Rollie Clem (baculoviruses) discuss individual viruses and their effects on host cells and host organisms. Baculoviruses trigger apoptosis of insect cells by several possible mechanisms, and inhibit apoptosis by encoding either an IAP protein or P35. These inhibitors are required to kill caterpillars, but there is an exception when the host (*T. ni*) provides a compensating function. AIDS patients die from the consequences of lymphocyte cell death. But the mechanisms by which HIV triggers the death of uninfected cells in AIDS patients is still a mystery that is beginning to unfold.

We wish to dedicate this set of reviews to the memory of Lois Miller as a small tribute to her pioneering work in this area.

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