Apoptosis can be used by the host as a defense mechanism against harmful agents. During apoptosis, cellular and viral proteins and nucleic acids are destroyed. It is beneficial for the organism to eliminate infected cells rather than to try to preserve them and risk that the virus may spread. Conversely, it is advantageous for the virus to prolong the life of the infected cells in order to increase viral replication. Apoptosis of an infected cell can either be caused by virus-specific cytotoxic T lymphocytes (CTLs) or may be cell-autonomous, without external signals, and occur as a direct result of viral infection. For example, replication of some viruses, like Herpesviruses, Poxviruses, and insect Baculoviruses, is associated with apoptosis of the infected cell even in the absence of an antiviral immune response. Replication of other viruses, however, like human T-cell leukaemia virus type 1 (HTLV-1) and hepatitis B virus does not necessarily lead to apoptosis of the infected cells.

Viruses have evolved a variety of strategies to oppose cell-autonomous apoptosis and also CTL activity. Viral interference with host cell apoptosis leads to enhanced viral replication and to evasion of cytotoxic T cell effects. Some viruses, in particular those with a large genome like Herpesviruses, Poxviruses and insect Baculoviruses encode immunomodulatory molecules and regulators of apoptosis. In addition, some viruses modify the expression of cellular genes that regulate apoptosis in order to meet their requirement for prolonged survival of infected cells.

Viral inhibitors of caspases: CrmA, P35, IAPs
The effector phase of apoptosis is executed by a common set of cytoplasmic endoproteinases, named caspases. In view of the central role of caspases in apoptosis, it is not surprising that viruses have developed several strategies to block their activity.

Viral inhibition of apoptosis induced by death receptors
An understanding of the adaptor molecules involved in death signalling provided the basis for identifying a novel class of viral anti-apoptotic effectors. Searches for homology to DEDs yielded viral proteins with two DEDs. These viral anti-apoptotic molecules block the activity of FLICE (caspase-8) and were therefore named FLIPs (FLICE inhibitory proteins).

Viral Bcl2 family members
Cellular Bcl2 was discovered originally as an oncogenic protein in follicular B cell lymphoma. The number of cellular Bcl2 family members is still growing and more than 10 cellular Bcl2 family members are currently known. A viral homologue to the cellular anti-apoptotic protein Bcl2 is encoded by several lymphotropic herpesviruses. The adenovirus encoded E1B19K protein has similar functional properties as Bcl2, but shows only limited structural homology. Viral Bcl2 interferes with those apoptotic stimuli that are signalled through mitochondria. Viral FLIPs block the apoptotic signalling of death receptors by inhibiting the activation of FLICE. Therefore these
two viral anti-apoptotic principles are complementary.

**Viral inhibition of CTL-mediated target cell apoptosis**

CTLs combine different strategies for killing. They simultaneously release the content of lytic granules (perforin, granzymes) and trigger the Fas apoptotic pathway. Both pathways lead to the activation of caspases. Viral FLIPs and in some cell types also viral Bcl2 block Fas-mediated cell death. This can reduce the killing efficiency of CTLs. While herpesvirus and poxvirus encoded FLIPs interfere with apoptotic signaling of Fas, the adenoviruses encoded E3-10.4/14.5K mediates loss of cell surface Fas and thereby causes resistance to Fas-mediated apoptosis. CrmA blocks Fas-mediated cell death and the activity of granzyme B and both effects might contribute to the ability of CrmA to inhibit cell mediated cytotoxicity. Another mechanism used by viruses to evade CTL activity is the induction of Fas ligand (FasL) by HIV or the related simian immunodeficiency virus (SIV) enabling the infected cells to evade attacking CTLs.

**Viral inhibitors of cellular stress response**

DNA tumour viruses, such as Papillomaviruses, Polyomaviruses (e.g. SV40), and some Adenoviruses, code for genes which inactivate the tumour suppressor protein P53 and thereby block progression of apoptosis. The MCV encoded selenoprotein MC066L is homologous to human glutathione peroxidase and functions as a scavenger of reactive oxygen metabolites. MC066L protects cells from ultraviolet- or peroxide-, but not from Fas-induced cell death (Shisler 1998).

**Concluding remarks**

Different viruses have evolved distinct strategies to prolong the life of the infected cell. Viruses with a large genome like Herpesviruses, Poxviruses, African swine fever virus, and Baculoviruses carry anti-apoptotic genes with homology to cellular regulators, such as Bcl2, FLIP, IAP, serpins, and TNFR. During evolution, these viruses may have picked up and modified these anti-apoptotic genes from their host. While the anti-apoptotic activity of viral FLIPs might be restricted to apoptosis mediated via death receptors, viral Bcl2 homologs block different apoptotic stimuli that are signalled through mitochondria. CrmA, IAP, and p35 interfere at later stages with the activity of caspases and protect from apoptosis induced by different stimuli. Some viruses like EBV can also enhance the expression of cellular anti-apoptotic genes like Bcl2 and A20. HIV and HTLV-I do not code for anti-apoptotic proteins, but modulate the expression of cellular apoptosis ergulating genes. Induction of the FasL by HIV may lead to evasion of CTL responses. Viral interference with cell-autonomous apoptosis and evasion of CTL activity prolongs the life of the infected cells. This results in enhanced viral replication and may contribute to viral persistence.