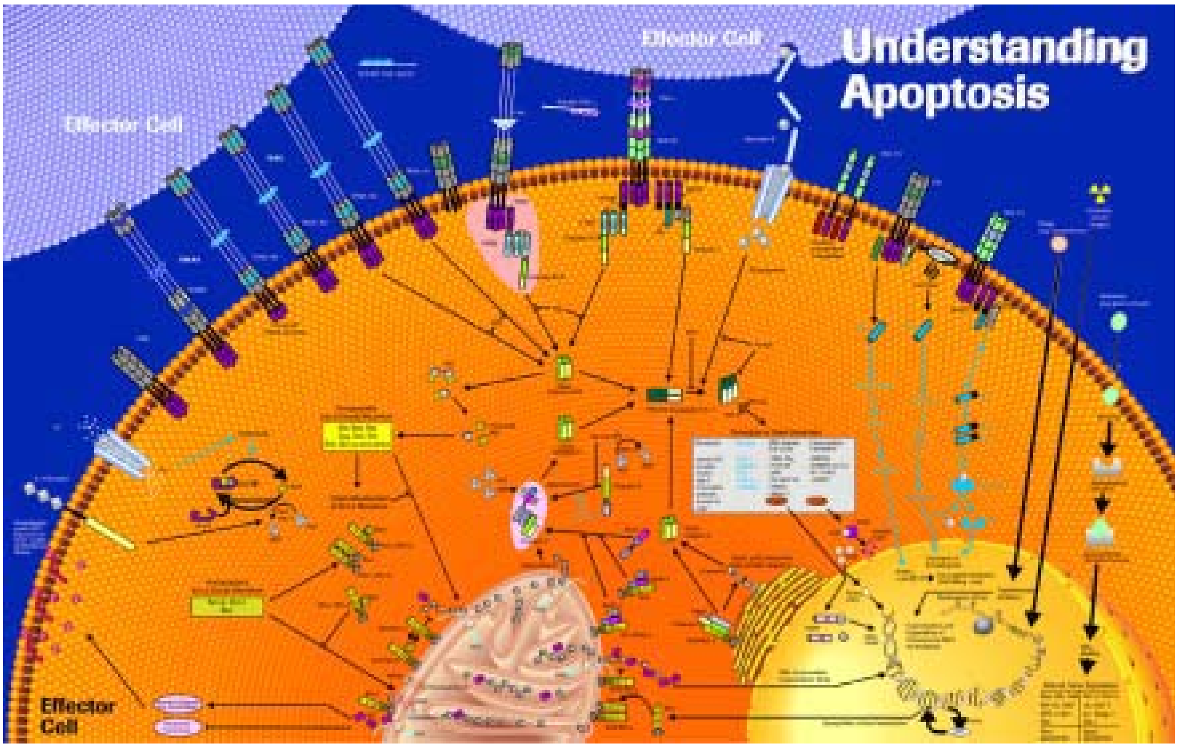
1.3 Apoptotic Pathways

Scientists now recognize that most, if not all, physiological cell death occurs by apoptosis, and that alteration of apoptosis may result in a variety of malignant disorders. Consequently, in the last few years, interest in apoptosis has increased greatly. Great progress has been made in the understanding of the basic mechanisms of apoptosis and the gene products involved (Figure 2 below, Table 20, see Appendix, page 123).



▲ **Figure 2: Apoptotic pathways.** This apoptotic pathways chart represents a compendium of information on different cell lines, from various sources. As the dynamic field of apoptosis changes, the information shown here will likely change. Table 20 in the Appendix, page 123 contains a list of sources that can be consulted for more information about the items on this chart. Have a look on our website **www.roche-applied-science/apoptosis** to find this chart under Scientific Information-Apoptotic Pathways and click on the name of a molecule to get information about its function.

Key elements of the apoptotic pathway include:

Death receptors

Apoptosis has been found to be induced via the stimulation of several different cell surface receptors in association with caspase activation. For example, the CD95 (APO-1, Fas) receptor ligand system is a critical mediator of several physiological and pathophysiological processes, including homeostasis of the peripheral lymphoid compartment and CTL-mediated target cell killing. Upon cross-linking by ligand or agonist antibody, the Fas receptor initiates a signal transduction cascade which leads to caspase-dependent programmed cell death.

Membrane alterations

In the early stages of apoptosis, changes occur at the cell surface and plasma membrane. One of these plasma membrane alterations is the translocation of phosphatidylserine (PS) from the inner side of the plasma membrane to the outer layer, by which PS becomes exposed at the external surface of the cell.

A

Protease cascade

Signals leading to the activation of a family of intracellular cysteine proteases, the caspases, (Cysteinyl-aspartate-specific proteinases) play a pivotal role in the initiation and execution of apoptosis induced by various stimuli. Different members of caspases in mammalian cells have been identified. Among the best-characterized caspases is caspase-1 or ICE (**I**nterleukin-1**β**-**C**onverting **E**nzyme), which was originally identified as a cysteine protease responsible for the processing of interleukin 1**β**.

Mitochondrial changes

Mitochondrial physiology is disrupted in cells undergoing either apoptosis or necrosis. During apoptosis mitochondrial permeability is altered and apoptosis specific protease activators are released from mitochondria. Specifically, the discontinuity of the outer mitochondrial membrane results in the redistribution of cytochrome C to the cytosol followed by subsequent depolarization of the inner mitochondrial membrane. Cytochrome C (Apaf-2) release further promotes caspase activation by binding to Apaf-1 and therefore activating Apaf-3 (caspase 9). AIF (apoptosis inducing factor), released in the cytoplasm, has proteolytic activity and is by itself sufficient to induce apoptosis.

DNA fragmentation

The biochemical hallmark of apoptosis is the fragmentation of the genomic DNA, an irreversible event that commits the cell to die and occurs before changes in plasma membrane permeability (prelytic DNA fragmentation). In many systems, this DNA fragmentation has been shown to result from activation of an endogenous Ca^{2+} and Mg^{2+}-dependent nuclear endonuclease. This enzyme selectively cleaves DNA at sites located between nucleosomal units (linker DNA) generating mono- and oligonucleosomal DNA fragments.

Note: For more information about the elements of the pathways as well as synonyms and abbreviations, please see Table 20 in the Appendix, page 123.