Table 2-4 Selected Examples of Diseases Caused by Misfolding of Proteins

Disease	Affected Protein	Pathogenesis
Cystic fibrosis	Cystic fibrosis transmembrane conductance regulator (CFTR)	Loss of CFTR leads to defects in chloride transport
Familial hypercholesterolemia	LDL receptor	Loss of LDL receptor leading to hypercholesterolemia
Tay-Sachs disease	Hexosaminidase β subunit	Lack of the lysosomal enzyme leads to storage of GM_2 gangliosides in neurons
Alpha-1-antitrypsin deficiency	α_1-antitrypsin	Storage of nonfunctional protein in hepatocytes causes apoptosis; absence of enzymatic activity in lungs causes destruction of elastic tissue giving rise to emphysema
Creutzfeldt-Jacob disease	Prions	Abnormal folding of PrPsc causes neuronal cell death
Alzheimer disease	Aβ peptide	Abnormal folding of Aβ peptides causes aggregation within neurons and apoptosis

misfolding, culminating in cell injury and death. A list of diseases associated with protein misfolding is provided in Table 2-4).

Apoptosis Induced by the TNF Receptor Family. FasL on T cells binds to Fas on the same or neighboring lymphocytes. This interaction plays a role in the elimination of lymphocytes that recognize self antigens, and mutations affecting Fas or FasL result in autoimmune diseases in humans and mice (Chapter 6).

Cytotoxic T Lymphocyte-Mediated Apoptosis. Cytotoxic T lymphocytes (CTLs) recognize foreign antigens presented on the surface of infected host cells (Chapter 6). Upon activation, CTLs secrete *perforin*, a transmembrane pore-forming molecule, which promotes entry of the CTL granule serine proteases called *granzymes*. Granzymes cleave proteins at aspartate residues and thus activate a variety of cellular caspases. In this way the CTL kills target cells by directly inducing the effector phase of apoptosis.

Disorders Associated with Dysregulated Apoptosis

Dysregulated apoptosis ("too little or too much") has been postulated to explain aspects of a wide range of diseases.

- *Disorders associated with defective apoptosis and increased cell survival*. An inappropriately low rate of apoptosis may permit the survival of abnormal cells, which may have a variety of consequences. For instance, as discussed earlier, cells that carry mutations in *TP53* are susceptible to the accumulation of mutations because of defective DNA repair, which in turn can give rise to cancer. The importance of apoptosis in preventing cancer development is emphasized by the fact that mutation of *TP53* is the most common genetic abnormality found in human cancers (Chapter 7). In other situations, defective apoptosis results in failure to eliminate potentially harmful cells, such as lymphocytes that can react against self antigens, and failure to eliminate dead cells, a potential source of self antigens. Thus, defective apoptosis may be the basis of *autoimmune disorders* (Chapter 6).
- *Disorders associated with increased apoptosis and excessive cell death*. These diseases are characterized by a loss of cells and include (1) *neurodegenerative diseases*, manifested by loss of specific sets of neurons, in which apoptosis is caused by mutations and misfolded proteins (Chapter 28); (2) *ischemic injury*, as in myocardial infarction (Chapter 12) and stroke (Chapter 28); and (3) *death of virus-infected cells* in many viral infections (Chapter 8).

KEY CONCEPTS

Apoptosis

- Regulated mechanism of cell death that serves to eliminate unwanted and irreparably damaged cells, with the least possible host reaction
- Characterized by enzymatic degradation of proteins and DNA, initiated by caspases; and by recognition and removal of dead cells by phagocytes
- Initiated by two major pathways:
  - Mitochondrial (intrinsic) pathway is triggered by loss of survival signals, DNA damage, and accumulation of misfolded proteins (ER stress); associated with leakage of pro-apoptotic proteins from mitochondrial membrane into the cytoplasm, where they activate caspases; inhibited by anti-apoptotic members of the BCL2 family, which are induced by survival signals including growth factors
  - Death receptor (extrinsic) pathway is responsible for elimination of self-reactive lymphocytes and damage by cytotoxic T lymphocytes; is initiated by engagement of death receptors (members of the TNF receptor family) by ligands on adjacent cells.

Necroptosis

As the name indicates, this form of cell death is a hybrid that shares aspects of both necrosis and apoptosis. The following features characterize necroptosis:

- Morphologically, and to some extent biochemically, it resembles necrosis, both characterized by loss of ATP, swelling of the cell and organelles, generation of ROS, release of lysosomal enzymes and ultimately rupture of the plasma membrane as discussed earlier.
- Mechanistically, it is triggered by genetically programmed signal transduction events that culminate in cell death. In this respect it resembles programmed cell death, which is considered the hallmark of apoptosis.