In the 1920s, Walter Cannon proposed that “homeostasis” is the result of organized self-government. This presumed state of homeostasis can only be maintained by many systems operating together.

Autophagy (self-eating) and apoptosis (self-killing) are the yin and yang of homeostasis. Autophagy is a process of breaking down certain cellular elements so the components may be reused, which is especially important for cell survival when faced with starvation or stress. Apoptosis is the process of programmed cell death. The survival mechanisms of autophagy counteract apoptosis. When autophagic processes are impaired, the cell reaches a tipping point in which apoptotic pathways take over.

Disturbed homeostasis between these two processes has been linked to many diseases, and an understanding of these molecular mechanisms is essential to interfere at the appropriate time to combat entry into the pathologic process.

An example is Philippe Petit’s historic 1974 walk on a tightrope between the twin towers of the World Trade Center. His endeavors illustrate homeostasis. Imagine that Mr. Petit represents the body in a state of homeostasis—in balance. If he goes too far to one side, he falls (apoptosis). If he goes too far to the other side (autophagy, up to a point), disaster again. What keeps these forces in check is the rod (homeostasis) that helps him keep his balance.

Autophagy delivers cytoplasmic contents to lysosomes for degradation (Figure 1). The initial step of autophagy is the formation of double membrane-bound vesicles called “autophagosomes,” initiated by autophagy-related proteins. Autophagosomes form at the phagophore site and envelop the cellular components to be degraded. Autophagosomes then fuse with lysosomes, forming autolysosomes. The autophagic cargo is then degraded by lysosomal hydrolases. The resulting products are amino acids and sugars. These by-products are transported back to the cytosol by lysosomal efflux transporters. The autolysosomes then disintegrate, and the autophagy is terminated. The remaining amino acids and other building blocks are recycled. As a result, the autophagy process promotes cell survival by reusing cellular components to provide new building blocks that replace depleted cellular components. The Nobel Prize in 2016 was awarded for “discoveries of mechanisms of autophagy.”

Apoptosis (programmed cell death) first requires commitment of the cell to a death pathway. The second phase is the execution of death. In apoptosis, the cell kills itself as opposed to the many other ways cells
may be killed. Activation of this specialized cellular machinery is vital at various embryologic and cell development stages. It also activates in pathological conditions, following trauma or ischemia, and in some neurological disorders. The execution stage requires participation of interleukin-converting enzymes. The extent of the initial insult determines the pathway of cell death. Initial phases of cell death include cell shrinkage, membrane ruffling packaging, nuclear fragmentation, and DNA degradation. The term “apoptosis” was first used by Hippocrates of Cos in the fourth century BC to refer to gangrenous necrosis. Programmed cell death was first noted by Vogt in 1842 while studying metamorphic toads, and in 1972 Kerr first used the term to refer to programmed cell death. The Nobel Prize in 2002 was awarded for “discoveries concerning genetic regulation of organ development and programmed cell death.”

Apoptosis can be activated by intrinsic or extrinsic pathways. The intrinsic pathway is triggered when there is an injury within the cell (eg, growth factor withdrawal and/or survival factor deprivation). Stresses to the cell trigger the production of proteins located on the mitochondria that are either death suppressors (eg, Bcl-2 and BclXe) or death promotors (eg, BAX and BAK). Interaction between these proteins determines if the cell will survive or undergo apoptosis. A preponderance of proapoptotic proteins leads to destabilization of the mitochondrial membrane, which releases cytochrome c into the cytosol, activating a proteolytic cascade that leads to the cell’s intrinsic destruction (Figure 2).

The extrinsic apoptotic pathways can begin with death receptors in the tumor necrosis factor family on the cell, leading to the activation of caspases. There are various points where the cell death pathway can be interrupted by either activation of anti-apoptotic proteins within the cell or artificially introducing anti-apoptotic molecules. Voila! Cannon’s canon law of homeostasis.

An exquisite balance is maintained between pro-apoptotic and anti-apoptotic proteins. This balance can be tipped by several factors. For example, in glaucoma increased intraocular pressure results in ganglion cell stress, which activates apoptotic pathways. However, cell death can be staved off by the presence of extratrophic factors.

**Figure 2.** Apoptosis pathway for programmed cell death.

Survival or death, autophagy or apoptosis—that is often the question. Autophagic markers appear in the cut ends of the optic nerve within a few hours after optic nerve crush and autophagic signals appear in retinal ganglion cells within a few days. In experimental glaucoma, an autophagic signal appears within a day, leading one to conclude that autophagic signals precede the signals for apoptosis. Under certain conditions, autophagy may promote cell death by the catabolism of too many cell components, particularly mitochondria. This may then activate intrinsic apoptotic pathways.

Control of the molecular players in the processes of autophagy and apoptosis will, in the future, be useful to control pathologic states. For example, in experimental neurodegenerative disease, increasing autophagy has cleared protein aggregates, allowing the neurons to survive longer in amyotrophic lateral sclerosis and/or Huntington’s disease models. Retinal cells are ripe for manipulation, and in various conditions show either up- or down-regulation of autophagic genes.

And the balancing act continues.

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