No exit for Ca\(^{2+}\)

Overexcited neurons go to their death because of a Ca\(^{2+}\) overdose, say Daniele Bano, Pierlugi Nicotera (University of Leicester, UK), and colleagues. The overdose is induced by a calpain protease, which chops up the exchanger that normally ferries Ca\(^{2+}\) out of the cell.

Neurons that are cut off from a blood supply and thus from oxygen fail to clear the neurotransmitter glutamate from their synapses. The result is overstimulation, including an excessive dose of intracellular calcium. Nicotera and colleagues show that this initial increase can subsequently be translated into a larger and potentially deadly overdose of Ca\(^{2+}\). The overdose occurs downstream of a calpain cleavage of the Na\(^+\)/Ca\(^{2+}\) exchanger NCX3. The Ca\(^{2+}\) overload is blocked and necrotic cell death is reduced after inhibition of calpain or expression of the alternative NCX2 exchanger. Reduction of NCX3 function by siRNA results, however, in the opposite effect: treated neurons are sensitized to Ca\(^{2+}\)-induced necrotic death.

NCX3 is a low affinity but high capacity exchanger, and thus is well suited to ferrying large amounts of Ca\(^{2+}\) out of the cell. It is not clear whether calpain’s action to stop this restorative function is a form of deliberate suicide or of pathology. The calpain may be acting to eliminate defective cells and thus save the organism from potential damage, or it may be overdoing a normal calpain function, such as regulation of membrane protein turnover, resulting in an accidental pathology.

Reference: Bano, D., et al. 2005. Cell. 120:275–285.

Diet affects DNA

Mitochondria apparently adjust their DNA inheritance strategies when faced with different metabolic conditions, based on results from Xin Jie Chen, Ronald Butow, and colleagues (UTSW, Dallas, TX). The key to the change is a metabolic protein called aconitase.

When grown in glucose, budding yeast rely on glycolytic fermentation. The result is overstimulation, including an excessive dose of intracellular calcium. Nicotera and colleagues show that this initial increase can subsequently be translated into a larger and potentially deadly overdose of Ca\(^{2+}\). The overdose occurs downstream of a calpain cleavage of the Na\(^+\)/Ca\(^{2+}\) exchanger NCX3. The Ca\(^{2+}\) overload is blocked and necrotic cell death is reduced after inhibition of calpain or expression of the alternative NCX2 exchanger. Reduction of NCX3 function by siRNA results, however, in the opposite effect: treated neurons are sensitized to Ca\(^{2+}\)-induced necrotic death.

NCX3 is a low affinity but high capacity exchanger, and thus is well suited to ferrying large amounts of Ca\(^{2+}\) out of the cell. It is not clear whether calpain’s action to stop this restorative function is a form of deliberate suicide or of pathology. The calpain may be acting to eliminate defective cells and thus save the organism from potential damage, or it may be overdoing a normal calpain function, such as regulation of membrane protein turnover, resulting in an accidental pathology.

Reference: Bano, D., et al. 2005. Cell. 120:275–285.