In the MyD88 family of cytosolic adaptor proteins, the newest member is the group’s black sheep, according to Kim et al. (page 2063). Whereas most MyD88 proteins turn on anti-pathogen responses within myeloid cells, the rebel, MyD88-5, instigates cell death within neurons.

MyD88-1–4 all respond to Toll-like receptor (TLR) activation in leukocytes and stimulate innate immune responses. MyD88-5, however, does not transmit TLR signals or induce innate response genes. Two extra domains in MyD88-5 that may allow it to interact with cytoskeletal proteins hint at an entirely different function.

Kim et al. now find that the protein is not even expressed in most leukocytes and instead is found mainly in neurons. There, MyD88-5 bound to microtubules and studded the outer membranes of mitochondria. Mitochondria formed clusters when MyD88-5 expression levels were high but were unable to group when the two protein interaction domains of MyD88-5 were removed. By linking them to the microtubules, MyD88-5 probably enables the mitochondria to get around efficiently within the neuron, where these energy stores must travel long distances. But how MyD88-5 levels are controlled within the neuron remains to be determined.

MyD88-5 also recruited JNK3, a kinase whose association with mitochondria activates apoptosis in stressed cells. The stress of UV light increased the association of JNK3 with MyD88-5, and neurons from mice lacking MyD88-5 were less vulnerable to stress-induced apoptosis. The authors are now using mouse models of brain injury to investigate whether the absence of MyD88-5 saves damaged neurons during, for example, a stroke.

T cells also expressed some MyD88-5. Because these cells lack JNK3, the adaptor probably has additional binding partners. JEM

Precursor loss triggers AIDS

HIV and its simian counterpart, SIV, replicate rapidly after infection but often take many years to subdue the immune system and cause AIDS. Okoye et al. (page 2171) now find that these slow burner viruses only cause disease after they deplete the precursor cells that give rise to pathogen-fighting effector cells.

The effector memory T (TEM) cells that battle these viruses at infection sites develop from a pool of CD4+ central memory (TCM) cells that are stored in secondary lymphoid organs. Although the virus infects both types of cells simultaneously, TEM cells are the first casualties. This early depletion of TEM cells is not completely devastating; the TCM population quickly cranks out more TEM cells. But this defensive strategy is obviously not foolproof: infected individuals eventually develop AIDS.

Okoye et al. now identify the glitch in the strategy by tracking disease progression in SIV-infected rhesus macaques. Newly generated TEM cells were short lived, they found, as persistent activation by the virus induced their death. And unlike in earlier stages of infection, TEM cells no longer came to the rescue, as they were also crippled by viral infection. The virus thus tampered the immune system by stimulating one population to death and destroying its back-up.

Based on these results, stabilizing the TCM pool may be a more effective way to prevent the onset of AIDS than controlling viral load—the goal of current vaccination strategies. Rising viral loads might not be the trigger for AIDS, as viral loads remained constant while CD4+ T cell levels declined during the later stages of disease.

Recent studies from other groups show that survival of patients with AIDS correlates with more circulating TEM cells, supporting the idea that protecting the TCM niche might keep AIDS at bay. The team is now trying to identify the factors that bolster TCM cell levels and how HIV/SIV dismantles them. JEM