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As harlequins grow old

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The harlequin (*Hq*) mouse mutant serves as a model for late-onset neurodegenerative disease. In the September 26 Nature, Jeffery Klein and colleagues define the genetic basis of the *Hq* mutant and provide a molecular link between free-radical damage, oxidative stress and neuronal cell death (*Nature*, **419:**367-374, September 26, 2002).

Klein *et al.* show that the Hq phenotype is linked to progressive neuronal apoptosis in the cerebellum and late-onset retinal degeneration. Genetic analysis revealed the presence of an ecotropic proviral insertion within the first intron of the gene encoding apoptosis-inducing factor (AIF) that results in a dramatic reduction in expression. AIF is a mitochondrial oxidoreductase that can translocate to the nucleus and induce cell death. They show that loss of AIF leads to oxidative stress and increased levels of catalase and glutathione. The granule cells from *Hq* mutant animals were sensitive to peroxides, and this sensitivity could be rescued by re-introducing AIF. Klein *et al.* also found that neurons in the *Hq* mice re-enter the cell cycle upon oxidative stress.

The harlequin mouse thus offers a model with which to decipher the links between cell-cycle re-entry, oxidative stress and neurodegenerative disorder.

References

1. *Nature*, [http://www.nature.com]

2. Essential role of the mitochondrial apoptosis-inducing factor in programmed cell death