PublisherInfo		
PublisherName	:	BioMed Central
PublisherLocation	:	London
PublisherImprintName	:	BioMed Central

A caspase-independent apoptosis pathway

ArticleInfo		
ArticleID	:	4037
ArticleDOI	:	10.1186/gb-spotlight-20010403-02
ArticleCitationID	:	spotlight-20010403-02
ArticleSequenceNumber	:	108
ArticleCategory	:	Research news
ArticleFirstPage	:	1
ArticleLastPage	:	2
ArticleHistory	:	RegistrationDate : 2001–04–03 OnlineDate : 2001–04–03
ArticleCopyright	:	BioMed Central Ltd2001
ArticleGrants	:	
ArticleContext	:	130592211

Kenneth Lee
Email: kenlee_fr@yahoo.fr

In animals the process of programmed cell death, or apoptosis, is thought to be mediated by caspases, a family of cysteine proteases that cleave one another and key intracellular proteins, killing the cell in a controlled way. In 29 March Nature, Nicholas Joza and colleagues at the Amgen Institute, Toronto, Canada provide genetic evidence that the first wave of apoptosis in the early mouse embryo requires a molecule called apoptosis-inducing factor (AIF) and not caspases (*Nature* 2001, **410**:549-554).

Joza *et al* deleted exon 3 of the *aif* gene in mouse embryonic stem (ES) cells. This exon encodes the amino terminus of the protein, and because the *aif* gene is on the X chromosome, mutation of one *aif* allele resulted in a complete knockout in male ES cells. The resulting mutant cells were defective in apoptosis. In the absence of serum normal cells in culture commit suicide, but *aif*-/Y ES cells remained viable.

During mammalian development, the first wave of apoptosis occurs when the embryo is a solid ball of cells. Cells at the core of the ball commit suicide, resulting in a cavity. This process can be mimicked *in vitro* by growing ES cells in ball-like aggregates called embryoid bodies. Joza *et al* report that embryoid bodies formed from wild-type ES cells, or from ES cells lacking components of the caspase-mediated apoptotic machinery, all undergo cavitation. Embryoid bodies aggregated from *aif*-/Y ES cells did not undergo cavitation.

The results suggest the existence of a second, caspase-independent, pathway for triggering apoptosis.

References

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