endogenous and exogenous TRF2 in primary human fibroblasts, which indicates that these proteins interact *in vivo*. Pulldown experiments using fusion proteins that comprised different fragments of ATM showed that TRF2 bound to a specific domain of ATM, close to serine 1981 — the main site of autophosphorylation. Finally, immunofluorescence of IR-treated primary fibroblasts that overexpressed TRF2 detected the protein at telomeric foci, but not at chromosomal sites of DNA damage.

Based on these results, the authors propose a model in which TRF2 binds to ATM and inhibits its activation by preventing phosphorylation at S1981. Importantly, the subnuclear location of TRF2 indicates that this inhibition is restricted to telomeres, which would allow ATM to mediate vital DNA repair elsewhere in the nucleus.

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References and links

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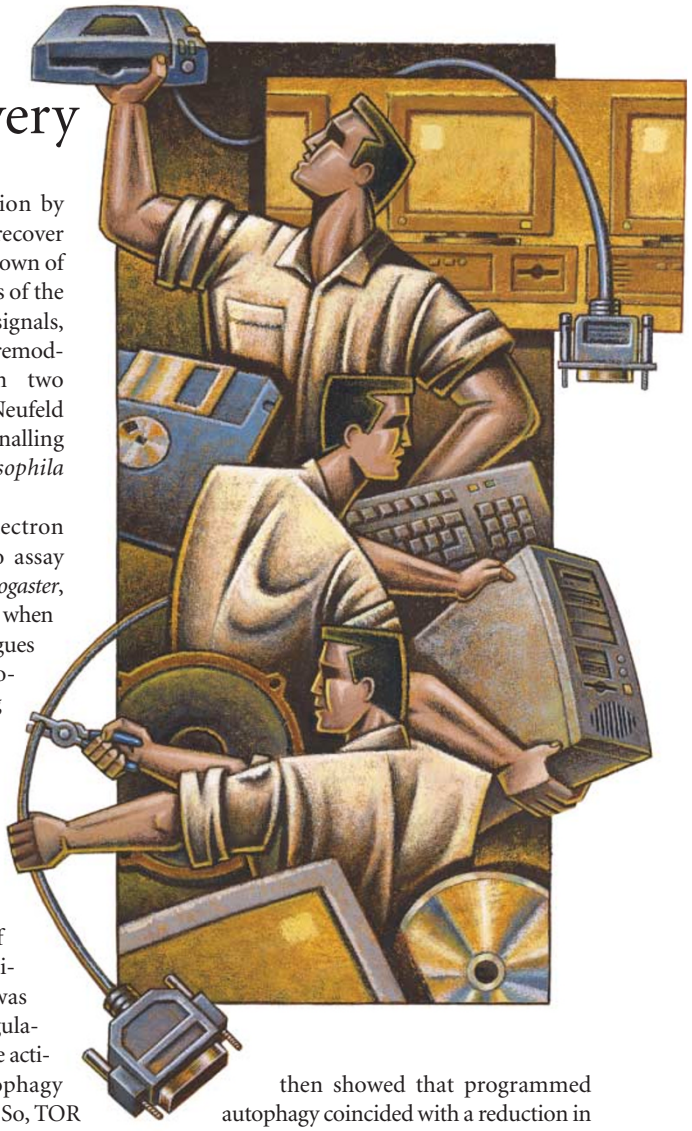
AUTOPHAGY

Breakdown recovery



Eukaryotic cells can respond to starvation by autophagy — a process whereby the cells recover essential nutrients by the lysosomal breakdown of organelles, proteins and other components of the cytoplasm. In response to developmental signals, 'programmed' autophagy promotes tissue remodelling and cell death. Reporting in two *Developmental Cell* papers, the groups of Neufeld and Stenmark have now uncovered the signalling pathways that control autophagy in *Drosophila melanogaster*.

Both groups used a combination of electron and fluorescent confocal microscopy to assay autophagy in the larval fat body of *D. melanogaster*, which showed a strong autophagic response when deprived of nutrients. Stenmark and colleagues also studied the various phases of programmed autophagy in the fat body during the final larval stage.

TOR (target of rapamycin) kinases, the central components of a conserved nutrient-sensing pathway, were suspected to function in the regulation of autophagy. To find out more, Neufeld and co-workers studied *TOR*-null flies and showed that the loss of TOR activity causes the induction of autophagy, regardless of the nutrient conditions. The same autophagic phenotype was observed when they expressed negative regulators of TOR in fat-body cells. Conversely, the activation of TOR signalling suppressed autophagy under conditions of nutrient deprivation. So, TOR signalling is both necessary and sufficient to suppress starvation-induced autophagy.

Components of the phosphatidylinositol 3-kinase (PI3K) signalling pathway, when overexpressed, also suppressed autophagy. However, overexpression of PI3K was unable to inhibit autophagy that was caused by the loss of TOR function, which indicates that PI3K signalling requires TOR activity to suppress autophagy.

Surprisingly, Neufeld and colleagues found that the inactivation of S6K, which is a central downstream effector of TOR, did not induce autophagy. In fact, the autophagy phenotype of starved *S6K*-mutant cells was significantly reduced compared with starved wild-type cells. This implies not only that the suppression of autophagy by the TOR pathway is independent of S6K, but that S6K is a positive regulator of autophagy.

The Stenmark group also studied the signalling pathways that are responsible for programmed autophagy, and found that the ecdysone hormone, which is important for larval development, triggered this event in the *D. melanogaster* fat body. Using a marker for PI3K activity, Stenmark and colleagues then showed that programmed autophagy coincided with a reduction in PI3K activity and could be blocked by the overexpression of components of the PI3K pathway. So, the authors propose that ecdysone signalling downregulates PI3K signalling, thereby inducing autophagy.

These new insights into the pathways that regulate autophagy raise new questions about its physiological role. For example, does autophagy contribute to the reduced cell growth that occurs when TOR activity is low? The answer seems to be no, as the inhibition of autophagy increased the severity of the phenotype that is caused by the loss of TOR signalling in *TOR*-mutant flies, which included reductions in cell size, growth rate and survival. Neufeld and colleagues concluded that, when TOR signalling is reduced, autophagy is required mainly for survival and normal cell metabolism. It will also be interesting to probe the role of TOR during programmed autophagy.

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