Survival after executioner caspase activation during recovery from apoptotic stress

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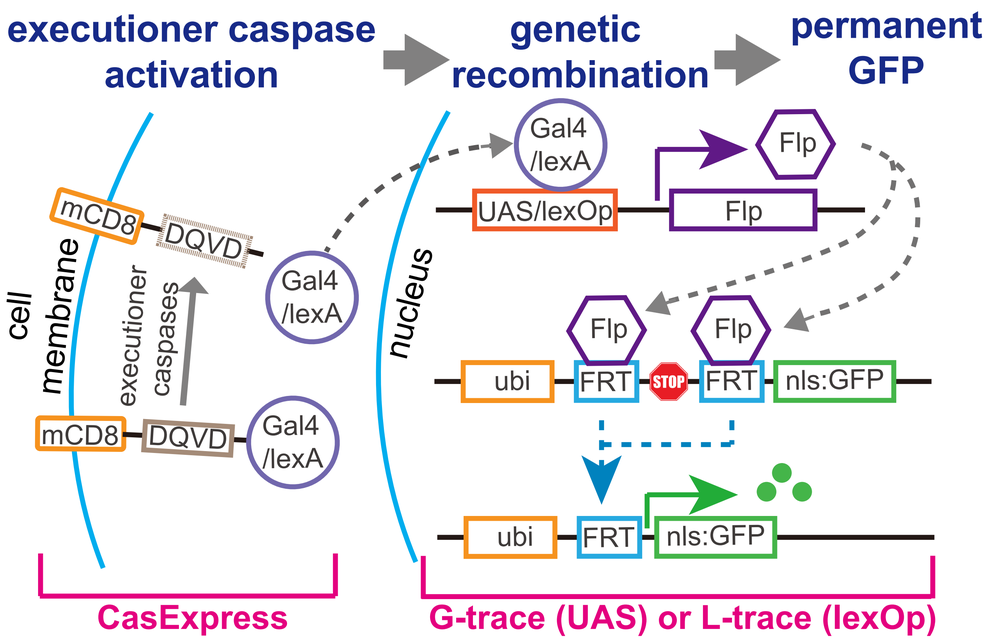
Abstract

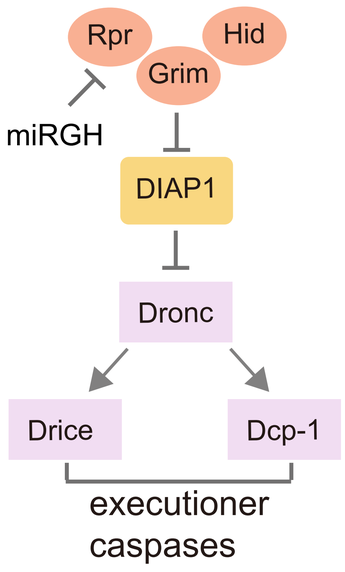
Apoptosis is an ancient and evolutionarily conserved cell suicide program. During apoptosis, executioner caspase activation has been considered a point of no return. However, emerging evidence suggests that some cells can survive executioner caspase activation following exposure to apoptosis-inducing stresses, raising questions as to the physiological significance and underlying molecular mechanisms of this unexpected phenomenon. Here, we show that, following severe tissue injury, Drosophila wing disc cells that survive executioner caspase activation contribute to tissue regeneration. We also demonstrate that apoptotic stress exists in tissues bearing oncogenic mutations (*pten RNAi*, *ras^{V12}*) and these mutations promote cells to survive the induced executioner caspase activation to achieve tissue overgrowth.

CasExpress: a reporter to track cell survival after executioner caspase activation in *Drosophila*

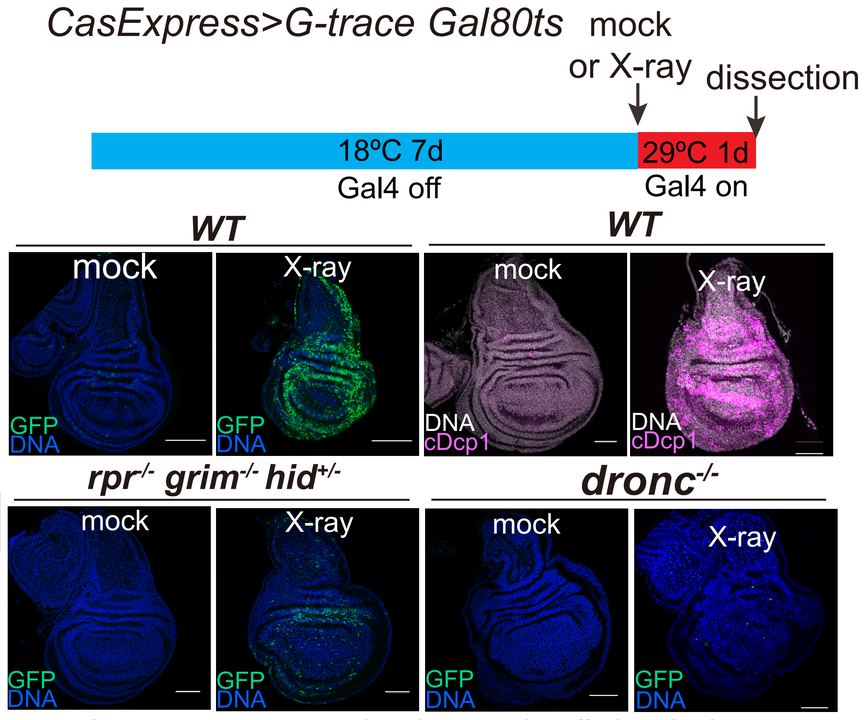


Epithelial cells in wing discs can survive radiation -induced executioner caspase activation.

Apoptosis pathway



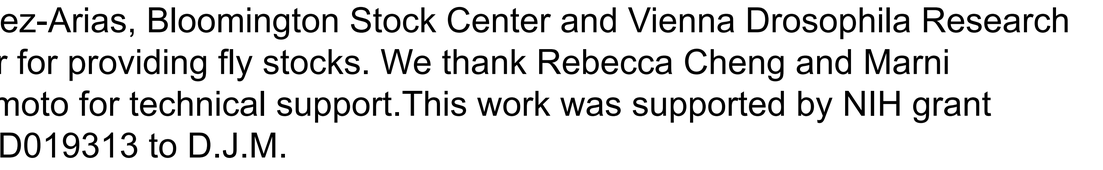
CasExpress>G-trace Gal80ts



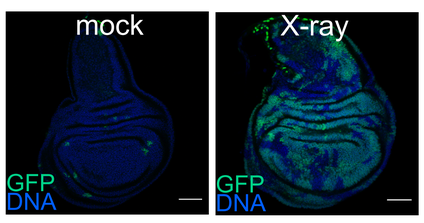
(X-ray induces strong executioner caspase activation and cell death, but many cells manage to survive. GFP: CasExpress activation, marks cells survive executioner caspase activation and their daughter cells. cDcp1: activated Dcp-1.)

Cells that survive radiation-induced executioner caspase activation participate in regeneration.

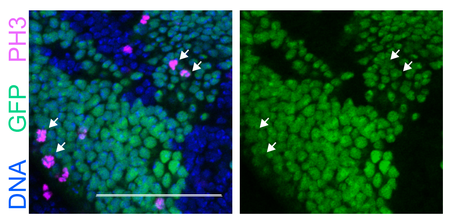
CasExpress>G-trace Gal80ts



1. A large portion of regenerated discs are CasExpress+.



2. Cells survive executioner caspase activation can proliferate.



(GFP: CasExpress activation, marks cells survive executioner caspase activation and their daughter cells. PH3: labels mitotic cells. White arrows: examples of colocalized GFP and PH3.)

Acknowledgement

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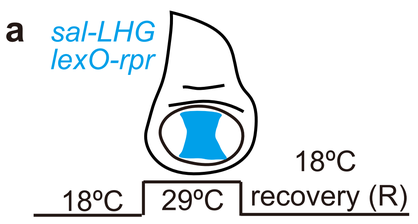
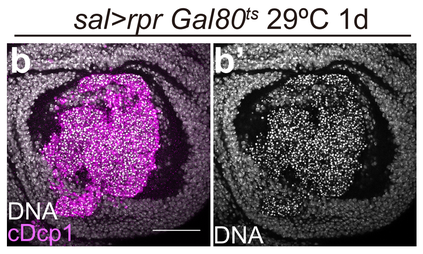
Epithelial cells can survive *rpr*-induced executioner caspase activation.

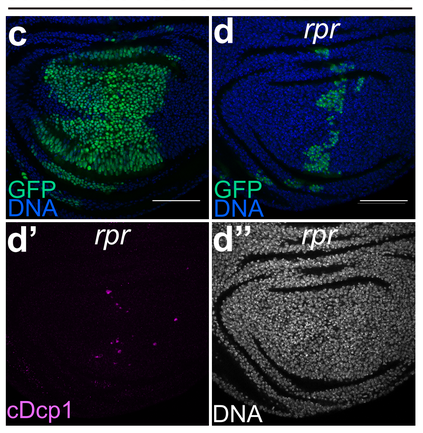
1. Cells can survive transient *rpr* overexpression.



sal>rpr Gal80^{ts} 29ºC 1d

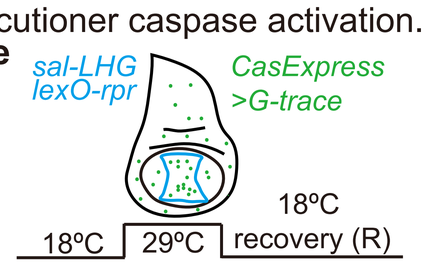


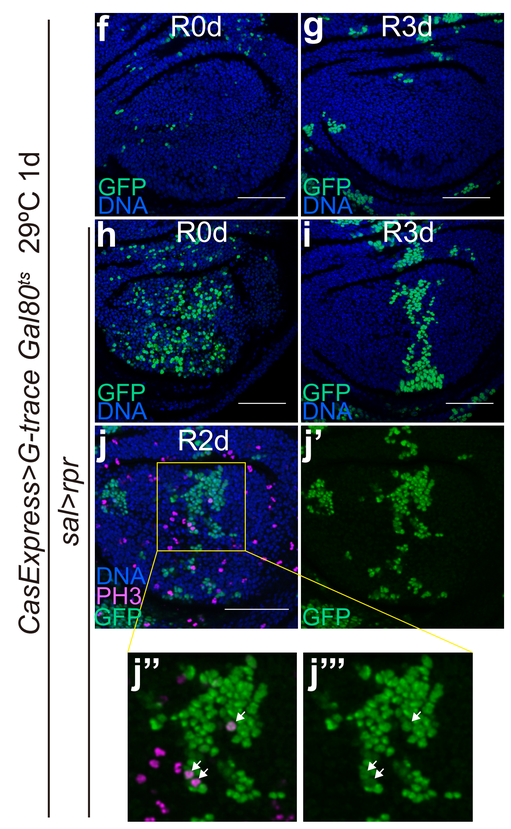
sal>L-trace Gal80^{ts} 29ºC 1d R3d



(GFP in c and d marks cells that transiently overexpressed *rpr* and their daugther cells. Transient *rpr* overexpression ablated a large fraction of *sal* domain, but a small fraction of cells survived and remained in the regenerated disc.)

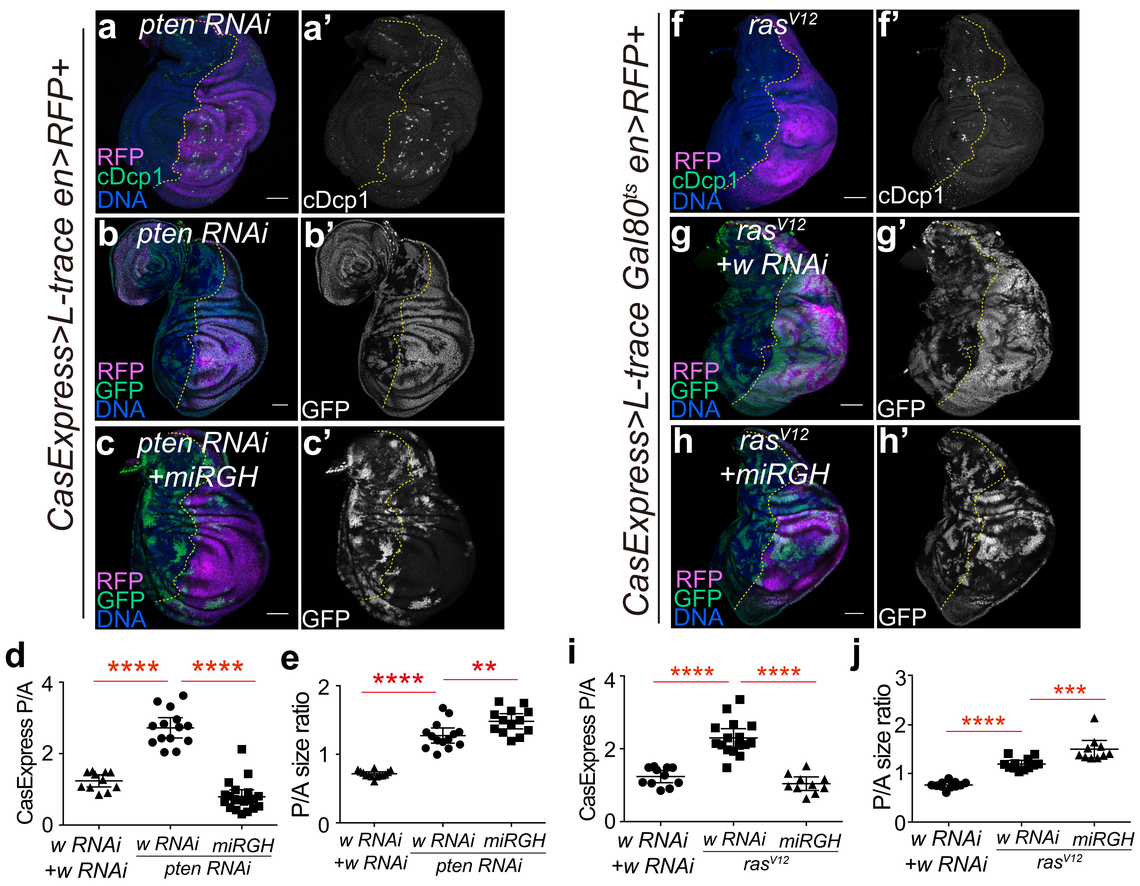
2. Cells can survive *rpr*-induced executioner caspase activation.





(GFP: CasExpress activation. Cells survive transient *rpr* overexpression has experienced executioner caspase activation. CasExpress+ cells can proliferate.)

Survival of executioner caspase activation contributes to oncogenic overgrowth.



(*pten RNAi* or *ras^{V12}* induces executioner caspase activation and overgrowth. Increased CasExpress activation (GFP+) in *pten RNAi* or *ras^{V12}*-expressing compartment indicates the transgenes promote survival after executioner caspase activation. Inhibition of apoptosis initiation by *miRGH* suppresses CasExpress activation and increases overgrowth, indicating apoptotic stress exists in these compartments to restrain growth.)