Lecture 13
Cell Death

1. Introduction

Cell death is a widespread and regulated phenomenon

Regulated form of cell death = apoptosis
e.g. Thymocytes die if too reactive to self = negative selection

Phenotypes of apoptosis versus necrotic cell death (injury)

Apoptosis: cells do not lyse/rapidly phagocytosed
chromatin condenses and DNA fragments
inhibited by protein synthesis or RNA synthesis inhibitors

Necrosis: Cells lyse cell contents leak out into intercellular space
inflammation follows lysis

Reasons for cell death
reshape body plan during development
selection of cells having optimal function (neuronal connections)

2. Cell Death in C. elegans and Drosophila

Cells in particular lineages die

Mutants exist affecting cell death
ced-3 and ced-4 loss of function block cell death
ced-9 loss of function increases cell death
gain of function blocks cell death
egl-1 loss of function blocks cell death

- egl1-1, ced-9 double mutants -> excessive cell death
egl1-1 normally functions to block the action of ced-9.

- ced-3; ced-9 or ced-4; ced-9 double mutants —> no cell death
ecd-9 normally functions to block the action of ced-3 and ced-4.

egl1-1 ced9-1 ced3, ced4 -> apoptosis

Cell death is poised to occur in most or all cells and is actively repressed
Hamlet is central part of life

Reaper and hin control cell death in Drosophila
loss of function no cell death
Vertebrate homologues of cell death genes (see figure 7.26 of Sanes, Reh, and Harris book):

- *egl-1* = Bax/Bcl-x – I Bcl-2
- *ced-9* = Bcl 2 gene: over expression of Bcl 2 blocks cells death -> cancer
  Bcl 2 can substitute for ced-9 in worms to block cell death
- *ced-3* = Caspase 3: over-expression of ced-3 or Caspase 3 in vertebrate cells –> cell death (can be blocked by simultaneous over-expression of bcl 2).
- *ced-4* = Apaf-1 (complexes with cytochrome C -> initiates Caspase cascade)

Cell death is common in *Drosophila* patterning mutants
Cells die only in regions affected by mutation
If cells are confused they die - living requires that all is well
Mechanism for insuring proper function - screw up and die

3. **Cell death during vertebrate neurogenesis**

Cell death is common in vertebrate neurogenesis
30-75% of cells formed may die in various regions of the nervous system
Cell death is regulated - apoptosis

Reasons for cell death:
  - match size of presynaptic neuronal population to target size
  - permit appropriate cells to innervate target (specific presynaptic cell survival)
  - select for functional connections (others die)

Experiments demonstrating cell death and target dependence
Can count cells before and after innervation
  - frequent result: many cells die at time of synaptogenesis

Remove normal target (remove limb bud - chicks): increased cell death
Add extra target (graft on additional limb bud): decreased cell death
Diversion of both chick isthmo-optic nuclei to innervate one eye (enucleate other eye) leads to increased cell death
Remove a large fraction of cells in presynaptic pool (chick cilliary ganglion): decreased cell death among remaining ganglion cells

Conclusion: competition among presynaptic cells for survival factor produced in target