

CELL DEATH DURING DEVELOPMENT

LLOYD A. GREENE

FEBRUARY 23, 2006

KEY DEVELOPMENTAL PROCESSES

CELL PROLIFERATION

CELL MIGRATION

CELL DIFFERENTIATION

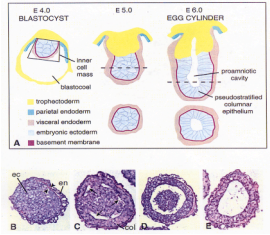
CELL DEATH

FUNCTIONS OF DEVELOPMENTAL CELL DEATH

A. MORPHOGENESIS: SCULPTING/SHAPING STRUCTURES

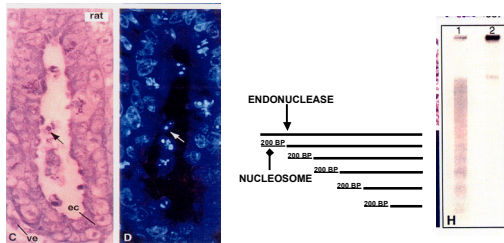
CREATION OF CAVITIES AND TUBES

CELL DEATH AND FORMATION OF THE PROAMNIOTIC CAVITY FROM THE BLASTOCYST 1



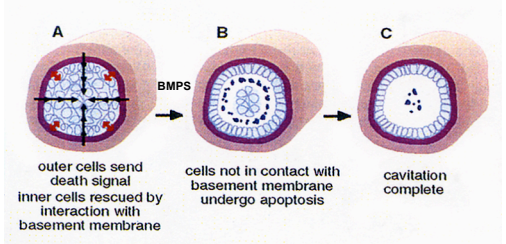
FROM: Coucouvanis and Martin. Cell 83: 279-287 (1995)

CELL DEATH AND FORMATION OF THE PROAMNIOTIC CAVITY FROM THE BLASTOCYST 2



FROM: Coucouvanis and Martin. Cell 83: 279-287 (1995)

CELL DEATH AND FORMATION OF THE PROAMNIOTIC CAVITY FROM THE BLASTOCYST 3



FROM: Coucouvanis and Martin. Cell 83: 279-287 (1995)

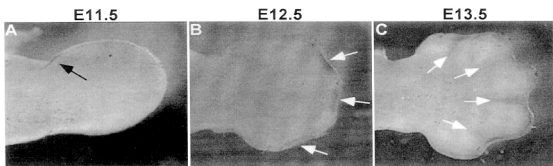
FUNCTIONS OF DEVELOPMENTAL CELL DEATH

A. MORPHOGENESIS: SCULPTING/SHAPING STRUCTURES

CREATION OF CAVITIES AND TUBES

CREATION OF FORM (DIGITS)

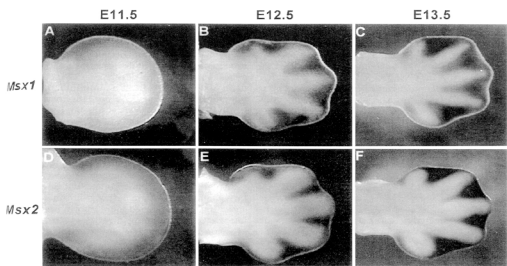
CELL DEATH AND FORMATION OF DIGITS 1



DYING CELLS ARE VISUALIZED BY NILE BLUE STAINING

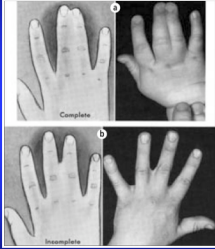
FROM: Chen and Zhao, J. Exp. Zool. 282:691 (1998).

CELL DEATH AND FORMATION OF DIGITS 3



FROM: Chen and Zhao, J. Exp. Zool. 282:691 (1998).

HUMAN SYNDACTYLY



SIMPLE

COMPLEX

FOR EXAMPLE: ONE
FEATURE APERT
SYNDROME - CAUSED BY
ACTIVATING MUTATIONS IN
FGF2 RECEPTORS)

From: Flatt AE. Proc (Bayl Univ Med Cent). 2005 Jan;18(1):26-37.

FUNCTIONS OF DEVELOPMENTAL CELL DEATH

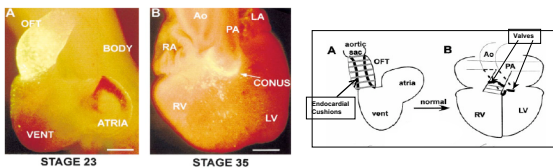
A. MORPHOGENESIS: SCULPTING/SHAPING STRUCTURES

CREATION OF CAVITIES AND TUBES

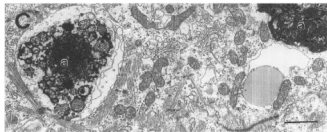
CREATION OF FORM (DIGITS)

TISSUE REMODELING (CARDIAC OUTFLOW TRACT)

CELL DEATH AND CARDIAC MORPHOGENESIS

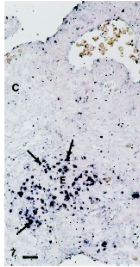


OTF = Outflow Tract
RA = Right Auricle
RV = Right Ventricle
LA = Left Auricle
LV = Left Ventricle
PA = Pulmonary Artery
Ao = Aorta
a = Apoptotic Cardiomyocyte



From: Watanabe et al. Dev. Bio. 240: 274-288 (2001)

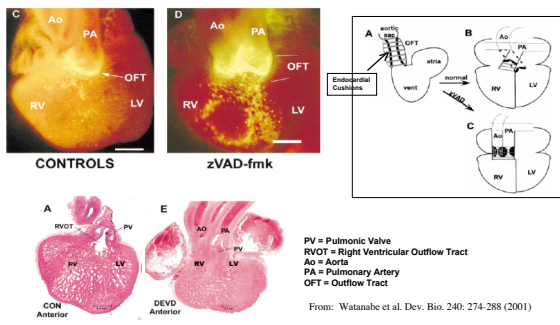
CELL DEATH AND CARDIAC MORPHOGENESIS



CELL DEATH IN CARDIAC
OUTFLOW TRACT OF E13 MOUSE
HEART AS REVEALED BY
TUNEL STAINING (ARROWS)

From: Abdelwahid et al., Microscopy Res Tech. 58: 2002

**BLOCKADE OF DEATH IN DEVELOPING HEART OFT
LEADS TO DOUBLE OUTLET RIGHT VENTRICLE (DORV)**



FUNCTIONS OF DEVELOPMENTAL CELL DEATH

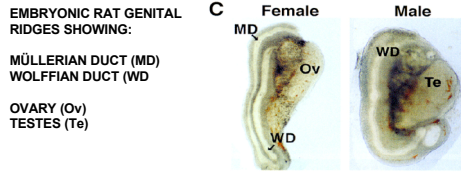
B. DELETION OF UNNEEDED STRUCTURES

KIDNEY: PRONEPHROS AND MESONEPHROS

BRAIN: CORTICAL SUBPLATE NEURONS

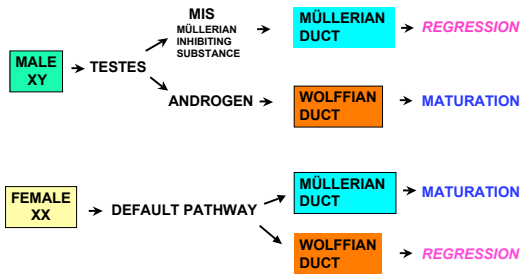
UROGENITAL SYSTEM: WOLFFIAN AND MÜLLERIAN DUCTS

REGULATION OF REPRODUCTIVE TRACT DEVELOPMENT 1

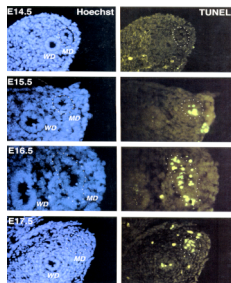


FROM: Roberts et al., *Devel. Bio.* 208: 110 (1999)

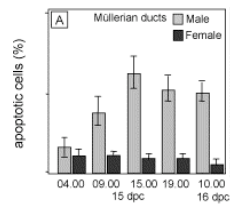
REGULATION OF REPRODUCTIVE TRACT DEVELOPMENT 2



REGULATION OF REPRODUCTIVE TRACT DEVELOPMENT 3: CELL DEATH DURING MÜLLERIAN DUCT REGRESSION



FROM: Roberts et al., *Devel. Bio.* 208: 110 (1999)



FROM: Xavier and Allard *Mol Cell Endocrinol* (2003)

**REGULATION OF REPRODUCTIVE TRACT DEVELOPMENT 4:
CELL DEATH DURING MÜLLERIAN DUCT REGRESSION**

**WHAT HAPPENS IF MIS SIGNALING IS DEFECTIVE
AND THE MULLERIAN DUCT DOES NOT REGRESS
BY APOPTOSIS?**

PERSISTANT MULLERIAN DUCT SYNDROME

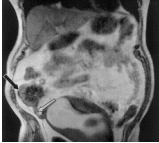


Figure 5. Coronal T1-weighted MR image demonstrates the right fallopian tube(open arrow) and right testis (solid arrow), both with low signal intensity.

FROM: Dekker et al. Radiographics 23:309 (2003)

FUNCTIONS OF DEVELOPMENTAL CELL DEATH

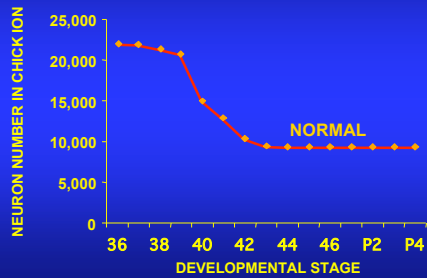
C. CULLING: REGULATION OF CELL NUMBERS

NERVOUS SYSTEM:

MATCHING NEURONS WITH TARGETS

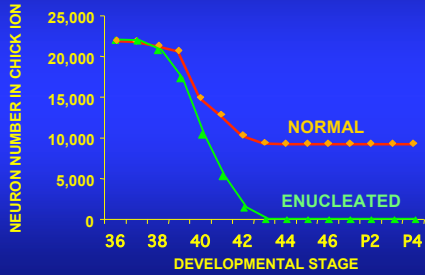
**MATCHING SCHWANN CELL AND
OLIGODENDROCYTES WITH AXONS**

**NORMAL DEVELOPMENTAL NEURONAL DEATH OCCURS AND
IS REGULATED BY TARGET DERIVED TROPHIC FACTORS**



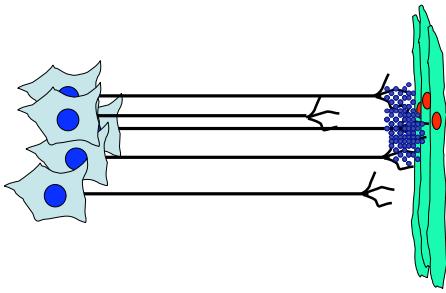
Clarke, Rogers & Cowan J. Comp. Neurol. 167: 125 (1976)

NORMAL DEVELOPMENTAL NEURONAL DEATH OCCURS AND IS REGULATED BY TARGET DERIVED TROPHIC FACTORS

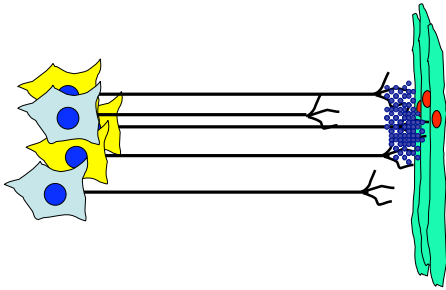


Clarke, Rogers & Cowan J. Comp. Neurol. 167: 125 (1976)

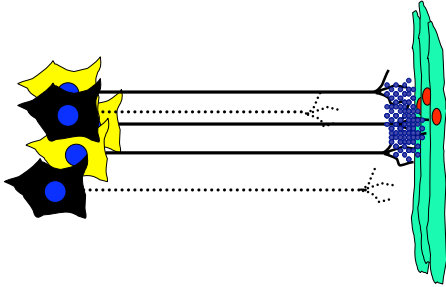
NEURONAL CULLING AS REGULATED BY COMPETITION FOR TARGET-SUPPLIED TROPHIC FACTOR



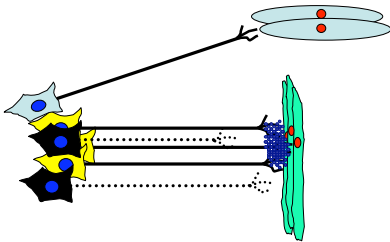
NEURONAL CULLING AS REGULATED BY COMPETITION FOR TARGET-SUPPLIED TROPHIC FACTOR



NEURONAL CULLING AS REGULATED BY COMPETITION FOR TARGET-SUPPLIED TROPHIC FACTOR

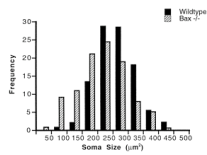
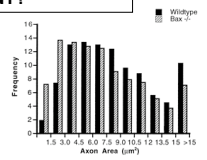
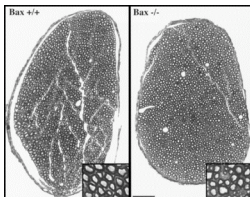


ELIMINATION OF ECTOPIC NEURONS



WHAT HAPPENS IF NEURONS DO NOT DIE DURING DEVELOPMENT?

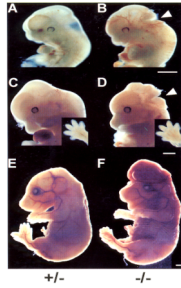
Facial nerve cross section



FROM: White et al., J Neurosci: 18: 1428 (1998)

Facial nucleus

EMBRYOGENIC DEFECTS IN A MOUSE LACKING CASPASE-9



From: Kuida et al Cell: 94: 325-337, 1998

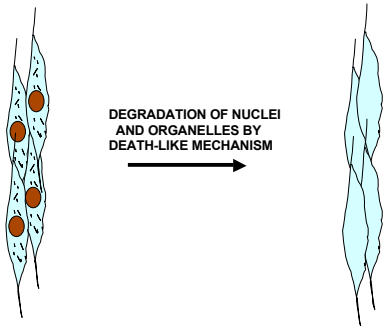
FUNCTIONS OF DEVELOPMENTAL CELL DEATH

E. PRODUCTION OF STRUCTURES WITHOUT ORGANELLES

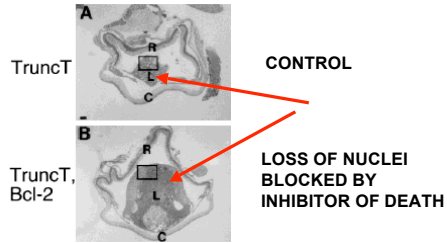
SQUAMOUS EPITHELIUM FROM KERATINOCYTES

FORMATION OF LENS FROM LENS FIBER CELLS

FORMATION OF CLEAR LENS FROM LENS FIBER CELLS



**EXPERIMENTAL BLOCKADE OF DEATH-LIKE ACTIONS
IN DEVELOPING LENS FIBER CELLS PERMITS THEIR
ABNORMAL PROLIFERATION**



FROM: Fromm et al., Dev Genetics 20: 296 (1997)

**HOW DOES DEVELOPMENTAL CELL DEATH
OCCUR?**

APOPTOTIC DEATH

vs

NECROTIC DEATH

PRESENT IN DEVELOPING TISSUES

RESPONSE TO CELL INJURY, TOXINS

CYTOPLASMIC BLEBBING

CELL & NUCLEAR SWELLING

CELLULAR & NUCLEAR PYKNOSIS

CHROMATIN CONDENSATION

DNA DEGRADATION BY ENDONUCLEASES
(FORMATION OF DNA LADDER)

RANDOM DNA DEGRADATION

FORMATION OF MEMBRANE-LIMITED
APOPTOTIC BODIES

LOSS OF MEMBRANE INTEGRITY
& LOSS OF CYTOPLASMIC CONTENTS

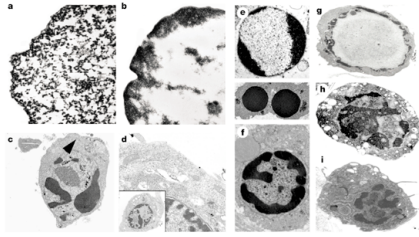
PHAGOCYTOSIS OF APOPTOTIC BODIES

ABSENCE OF INFLAMMATORY RESPONSE

INFLAMMATORY RESPONSE

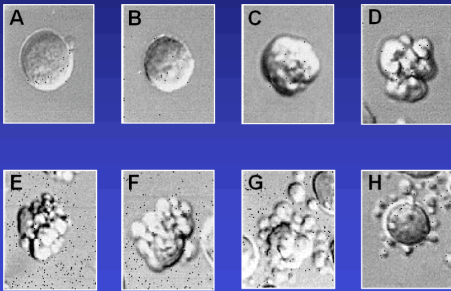
Kerr, Wyllie and Currie

ELECTRON MICROSCOPIC VIEWS OF NORMAL (a) AND APOPTOTIC (b-i) NUCLEI



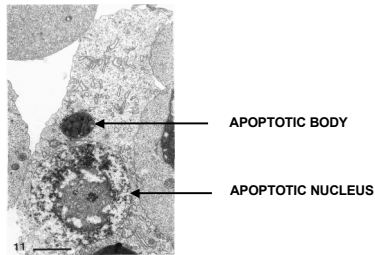
Nature Reviews | Molecular Cell Biology

TIME LAPSE IMAGES OF A CELL UNDERGOING APOPTOSIS



APOPTOTIC BODIES AND NUCLEI ARE CLEARED BY PHAGOCYTOSIS

EM OF A MACROPHAGE ENGULFING AN APOPTOTIC BODY AND APOPTOTIC NUCLEUS IN THE VENTRICULAR WALL OF THE DEVELOPING MOUSE HEART



From: Abdelwahid et al. Anat. Rec. 256:208 (1999)

WHAT ARE THE MECHANISMS BY WHICH CELLS DIE DURING DEVELOPMENT?

THERE ARE EVOLUTIONARILY CONSERVED MECHANISMS THAT GOVERN DEVELOPMENTAL CELL DEATH



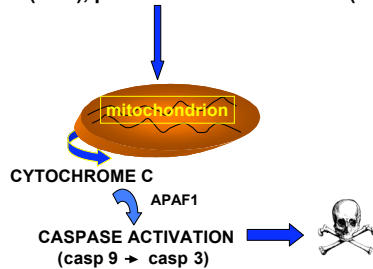
Robert Horvitz

CASPASES

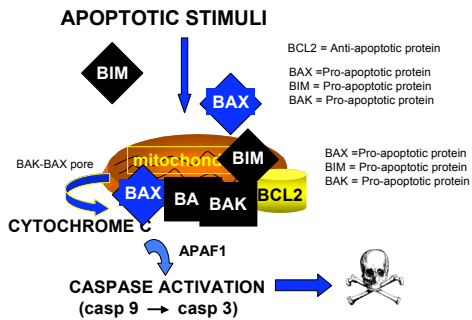
- FAMILY OF EXECUTORS OF APOPTOTIC DEATH
- CYSTEINE PROTEASES THAT CLEAVE AFTER ASP
- CONSTITUTIVELY PRESENT AS INACTIVE FORMS
- ACTIVATED BY CLEAVAGE OR BY INTERACTION WITH COFACTORS SUCH AS APAF1 AND CYTOCHROME C
- WHEN ACTIVATED, CLEAVE CELLULAR SUBSTRATES, LEADING TO APOPTOTIC DEATH

THE MITOCHONDRIAL PATHWAY OF APOPTOTIC DEATH - 1

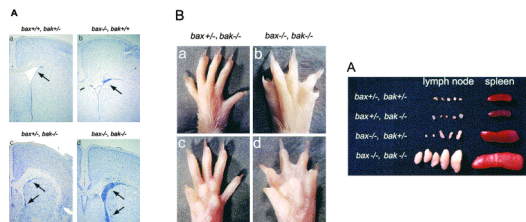
APOPTOTIC STIMULI (absence of survival factors (FGF), presence of death factors (BMPs))



THE MITOCHONDRIAL PATHWAY OF APOPTOTIC DEATH - 2



ABNORMALITIES IN MICE LACKING BAX AND BAK

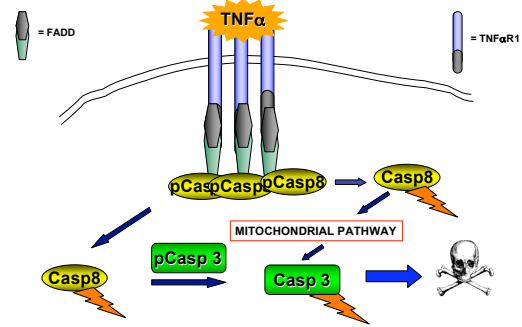


Arrow shows neuroprogenitors in ventricular zone of embryonic brain
 From: Lindsten et al. Mol Cell 6:1389 (2000)

DEATH PROMOTING RECEPTORS AND LIGANDS THE EXTRINSIC PATHWAY TO APOPTOTIC DEATH

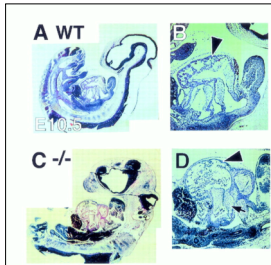
LIGAND	RECEPTOR
TNF α	TNF α R1
FAS ligand	FAS
TRAIL	TRAIL-R

THE RECEPTOR-MEDIATED PATHWAY OF APOPTOTIC DEATH



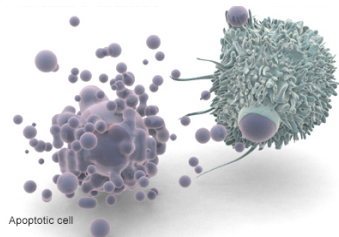
MICE LACKING FADD DIE DURING EMBRYOGENESIS AND HAVE MULTIPLE DEFECTS

Low power view:
A,C



B,D: Ventricular Myocardium
Arrowhead shows abnormal developing trabeculae; arrow normal endocardial cushion.

From: YEH et al. Science 279: 1954 (1998)



Apoptotic cell

U.S. National Library of Medicine
