

CELL DEATH DURING DEVELOPMENT

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April 9, 2009

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 3

G H
Bmp7

K L
Msx1

Pejani-Underwood, S. et al. Development 2007;134:2359-2368

REGULATION OF INTERDIGITAL CELL DEATH

BMP → Bmpr → MSX → FGF → DEATH

FGFR → SURVIVAL

↑

MSX → FGF → DEATH

HUMAN SYNDACTYLY

COMPLETE

INCOMPLETE

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

A OFT BODY VENT ATRIA

B RA RV LA LV CONUS Ao PA

C

STAGE 23 **STAGE 35**

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)

Terminal deoxynucleotidyl transferase dUTP nick end labeling

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

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

CONTROLS zVAD-fmk

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

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

EMBRYONIC RAT GENITAL RIDGES SHOWING:

MÜLLERIAN DUCT (MD)
WOLFFIAN DUCT (WD)

Ovary (Ov)
TESTES (Te)

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

REGULATION OF REPRODUCTIVE TRACT DEVELOPMENT 2

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    graph TD
      Male[MALE XY] --> Testes[TESTES]
      Testes --> MIS[MIS MÜLLERIAN INHIBITING SUBSTANCE]
      Testes --> Androgen[ANDROGEN]
      MIS --> MD[MÜLLERIAN DUCT]
      MD --> Regress[REGRESSION]
      Androgen --> WD[WOLFFIAN DUCT]
      WD --> Maturation[MATURATION]
      
      Female[FEMALE XX] --> Default[DEFAULT PATHWAY]
      Default --> MD2[MÜLLERIAN DUCT]
      MD2 --> Maturation2[MATURATION]
      Default --> WD2[WOLFFIAN DUCT]
      WD2 --> Regress2[REGRESSION]
    
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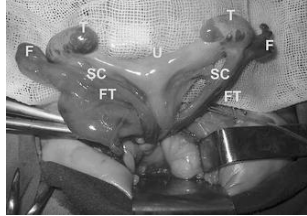
REGULATION OF REPRODUCTIVE TRACT DEVELOPMENT 3: CELL DEATH DURING MÜLLERIAN DUCT REGRESSION

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

Stage (dpc)	Male (%)	Female (%)
04:00	~10	~10
09:00	~25	~10
15:00	~45	~10
19:00	~35	~10
10:00	~35	~10

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

FAILURE OF MÜLLERIAN DUCT REGRESSION: PERSISTENT MÜLLERIAN DUCT SYNDROME



Intraoperative appearance of a 15-month-old male with persistent müllerian duct syndrome. T: Testis, SC: Spermatic cord, FT: Fallopian tube, F: Fimbria, U: Uterus

From: Boleken et al., Int Urol Nephrol. March 1, 2007

FUNCTIONS OF DEVELOPMENTAL CELL DEATH

C. REGULATION OF CELL NUMBERS

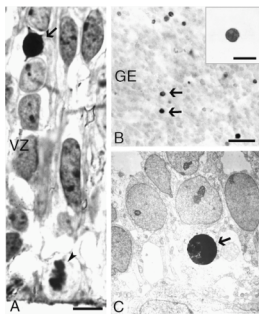
NERVOUS SYSTEM:

➔ **GENERATION OF CORRECT NEURON NUMBER**

MATCHING NEURONS AND TARGETS

MATCHING SCHWANN CELL AND OLIGODENDROCYTES WITH AXONS

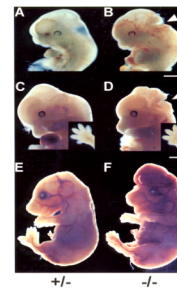
DEATH OF NEUROPROGENITOR CELLS IN DEVELOPING HUMAN NERVOUS SYSTEM



A. 4.5 gw Ventricular Zone. Apoptotic nucleus (arrow)
 B. 17 gw Ganglionic Eminence. TUNEL staining (arrow)
 C. 4.5 gw Neural Tube. EM of apoptotic cell

FROM: Rakic S and Zecevic N. Eur J Neurosci. 12:2721-34 2000.

EMBRYOGENIC DEFECTS IN A MOUSE LACKING CASPASE-9



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

FUNCTIONS OF DEVELOPMENTAL CELL DEATH

C. REGULATION OF CELL NUMBERS

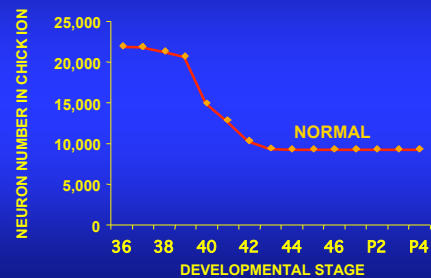
NERVOUS SYSTEM:

GENERATION OF CORRECT NEURON NUMBER

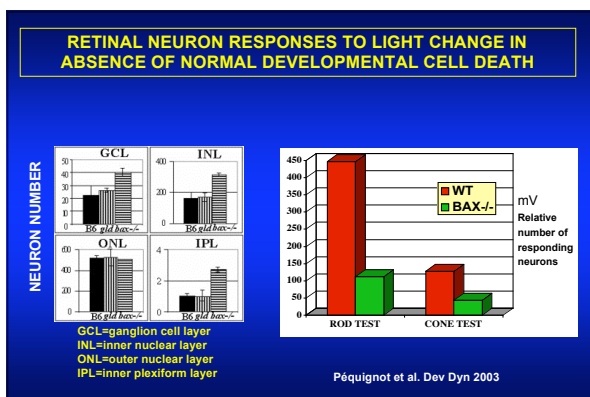
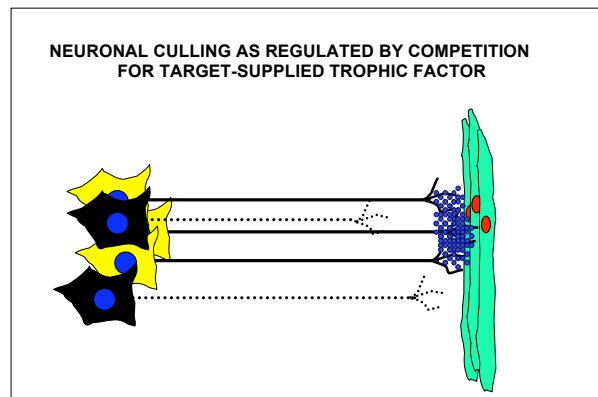
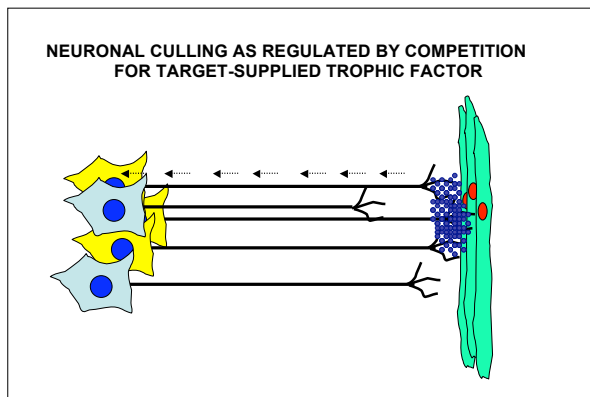
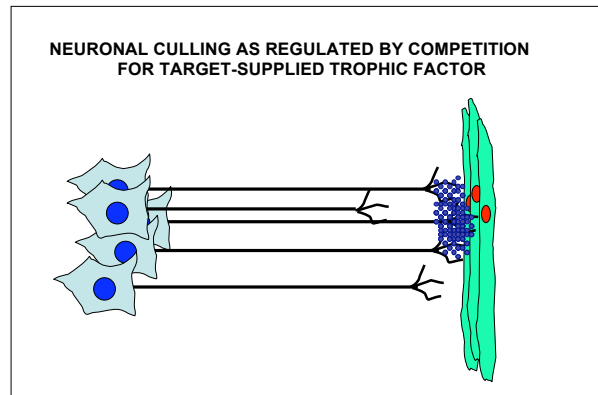
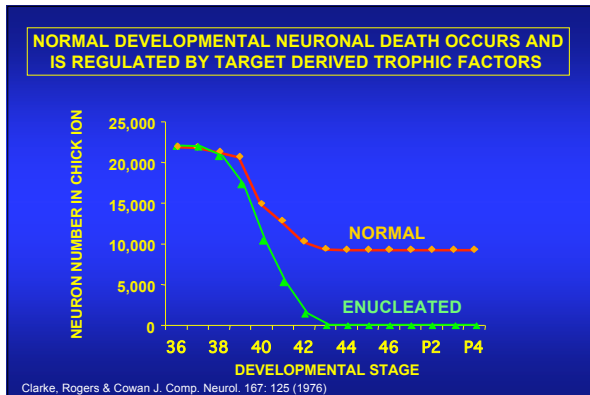
➔ **MATCHING NEURONS AND TARGETS**

MATCHING SCHWANN CELL AND OLIGODENDROCYTES WITH AXONS

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



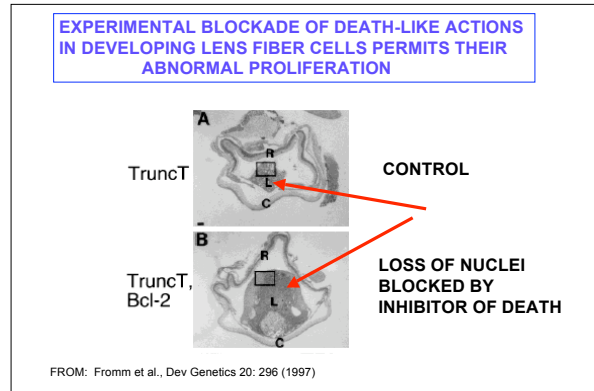
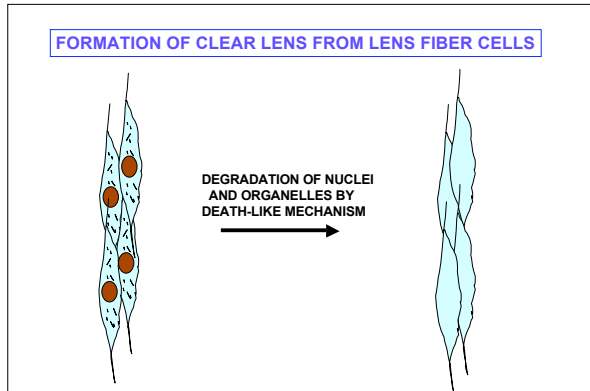
Clarke, Rogers & Cowan J. Comp. Neurol. 167: 125 (1976)



FUNCTIONS OF DEVELOPMENTAL CELL DEATH

D. PRODUCTION OF STRUCTURES WITHOUT ORGANELLES

- SQUAMOUS EPITHELIUM FROM KERATINOCYTES
- FORMATION OF LENS FROM LENS FIBER CELLS



TERATOGENS AND CELL DEATH

THALIDOMIDE: USED TO TREAT MORNING SICKNESS IN EUROPE, CANADA, JAPAN AND AUSTRALIA IN 1950'S RESULTING IN 10,000 BABIES BORN WITH BIRTH DEFECTS INCLUDING MALFORMED LIMBS (PHOCOMELIA)

TERATOGENS AND CELL DEATH

thalidomide	-	-	+
DMSO/PBS	-	+	+

Bmp4

Dkk1

TUNEL

thalidomide - +

AE R= Apical ectodermal ridge
dmc = distal mesenchyme;
pmc = proximal mesenchyme.

From: Knobloch J, et al., FASEB J. 7:1410-21 (2007)

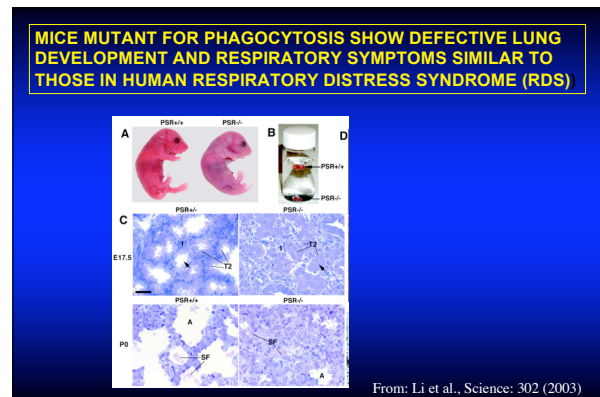
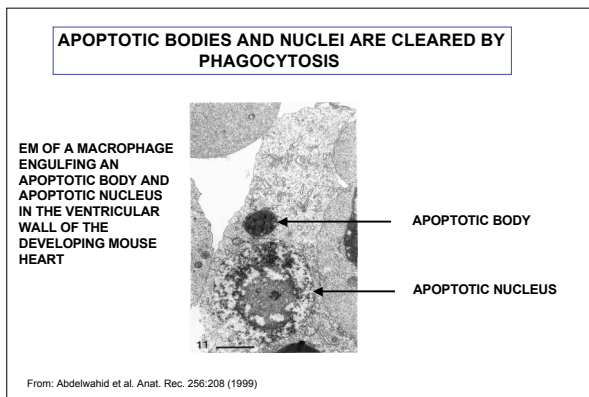
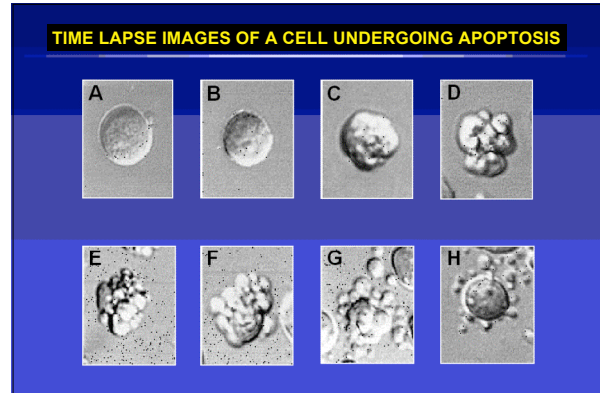
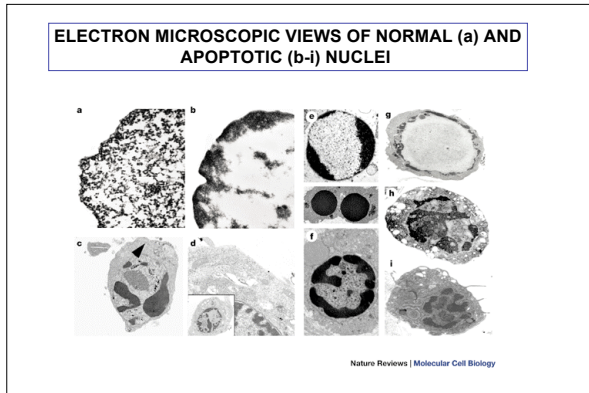
HOW DOES DEVELOPMENTAL CELL DEATH OCCUR?

Apoptotic cell

U.S. National Library of Medicine

APOPTOTIC DEATH	vs	NECROTIC DEATH
PRESENT IN DEVELOPING TISSUES		RESPONSE TO CELL INJURY, TOXINS
CYTOPLASMIC BLEBBING		CELL & NUCLEAR SWELLING
CELLULAR & NUCLEAR PYKNOSIS		CELL & NUCLEAR SWELLING
CHROMATIN CONDENSATION		RANDOM DNA DEGRADATION
DNA DEGRADATION BY ENDONUCLEASES (FORMATION OF DNA LADDER)		LOSS OF MEMBRANE INTEGRITY & LOSS OF CYTOPLASMIC CONTENTS
FORMATION OF MEMBRANE-LIMITED APOPTOTIC BODIES		INFLAMMATORY RESPONSE
PHAGOCYTOSIS OF APOPTOTIC BODIES		
ABSENCE OF INFLAMMATORY RESPONSE		

Kerr, Wyllie and Currie



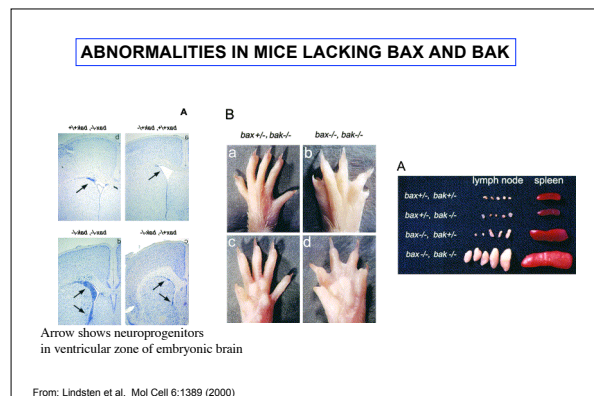
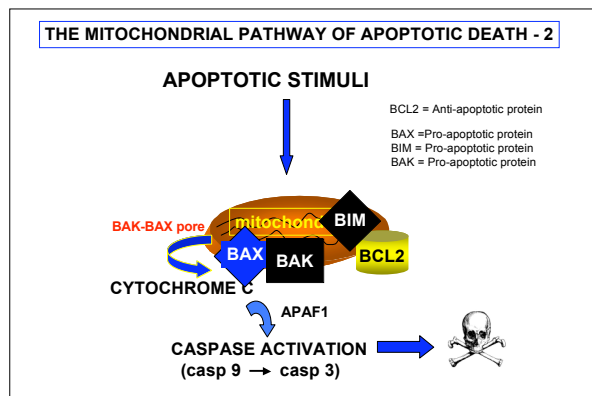
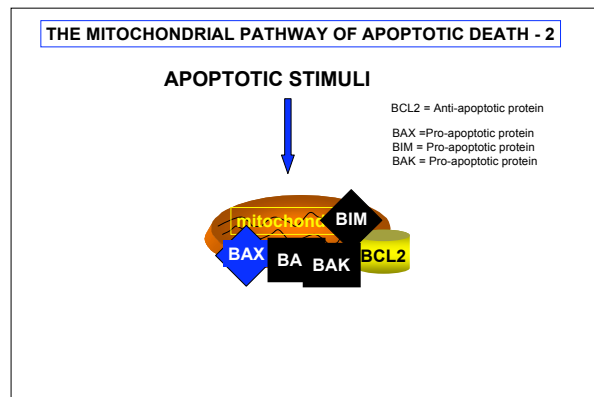
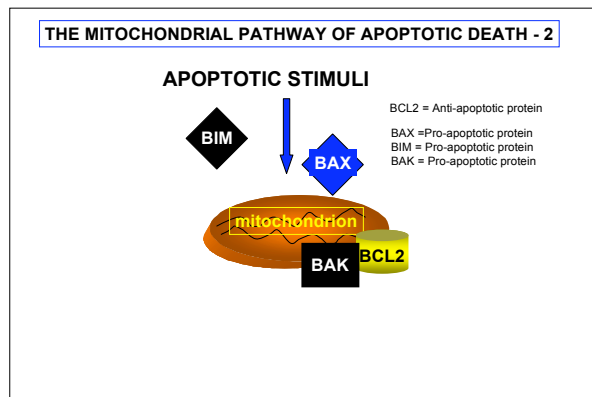
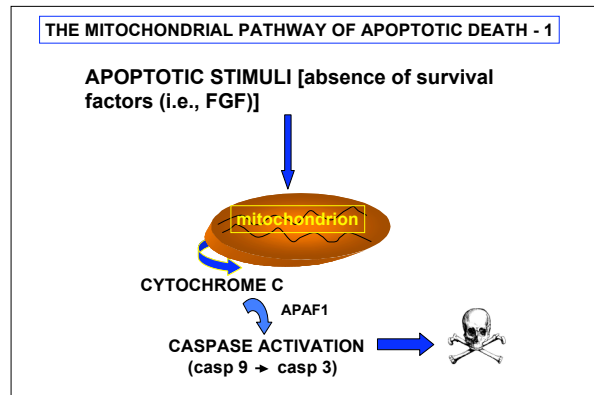
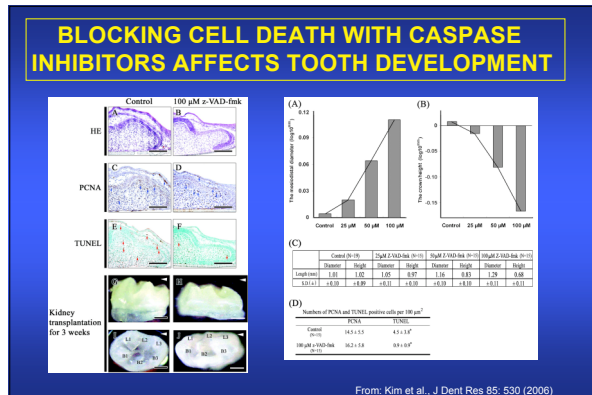
WHAT ARE THE MECHANISMS BY WHICH CELLS DIE DURING DEVELOPMENT?

THERE ARE EVOLUTIONARILY CONSERVED MECHANISMS THAT GOVERN DEVELOPMENTAL CELL DEATH

Robert Horvitz

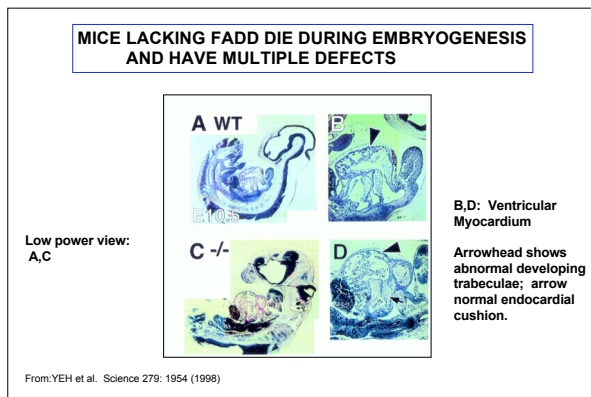
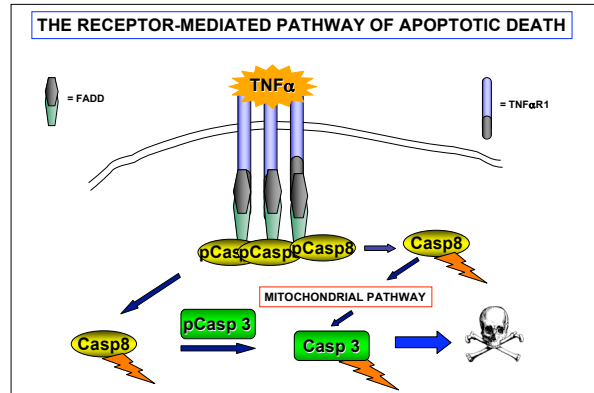
CASPASES

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



DEATH PROMOTING RECEPTORS AND LIGANDS THE EXTRINSIC PATHWAY TO APOPTOTIC DEATH

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



- CONCLUSIONS**
- CELL DEATH IS A MAJOR REGULATOR OF NORMAL EMBRYOGENESIS
 - IT OCCURS AT ALL STAGES OF EMBRYONIC DEVELOPMENT AND IN MULTIPLE ORGAN SYSTEMS AND PLAYS A VARIETY OF ROLES
 - FAILURE OF NORMAL CELL DEATH DURING EMBRYOGENESIS LEADS TO A VARIETY OF DEVELOPMENTAL DEFECTS
 - DEVELOPMENTAL CELL DEATH IS GENERALLY APOPTOTIC IN NATURE
 - THE GENERAL MECHANISMS OF APOPTOTIC CELL DEATH ARE BECOMING UNDERSTOOD AND ARE EVOLUTIONARILY CONSERVED
 - MUTATION OF SPECIFIC APOPTOTIC GENES LEADS TO DEVELOPMENTAL ABNORMALITIES