CELL DEATH DURING DEVELOPMENT

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DEPT OF PATHOLOGY AND CELL BIOLOGY

April 9, 2009

KEY DEVELOPMENTAL PROCESSES

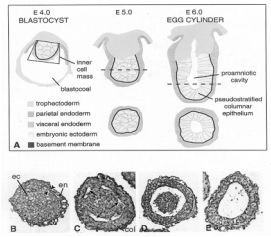
- CELL PROLIFERATION
- CELL MIGRATION
- CELL DIFFERENTIATION
- CELL DEATH

FUNCTIONS OF DEVELOPMENTAL CELL DEATH

A. MORPHOGENESIS: SCULPTING/SHAPING STRUCTURES

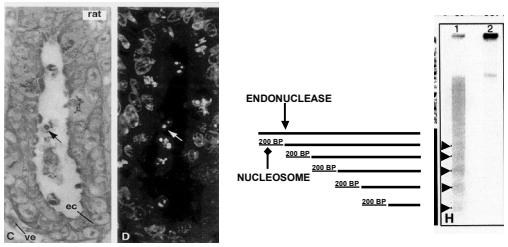
CREATION OF CAVITIES AND TUBES

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



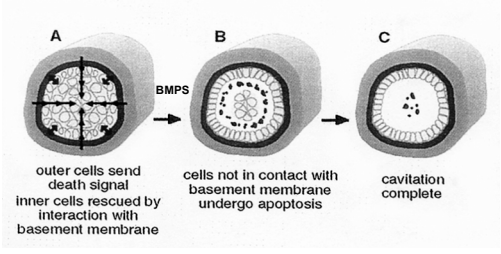
FROM: Coucouvanis and Martin. Cell 83: 279-287 (1995)

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)

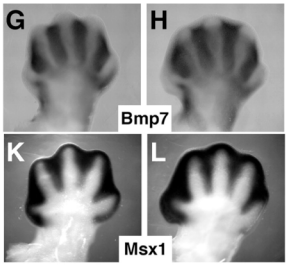
FUNCTIONS OF DEVELOPMENTAL CELL DEATH

A. MORPHOGENESIS: SCULPTING/SHAPING STRUCTURES

CREATION OF CAVITIES AND TUBES

CREATION OF FORM (DIGITS)

CELL DEATH AND FORMATION OF DIGITS 3



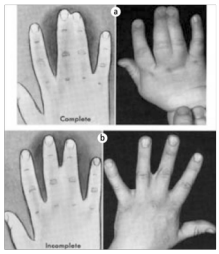
Pajni-Underwood, S. et al. Development 2007;134:2359-2368

REGULATION OF INTERDIGITAL CELL DEATH

FGFR → SURVIVAL

BMP → BMPR → MSX ⊣ FGF → DEATH

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

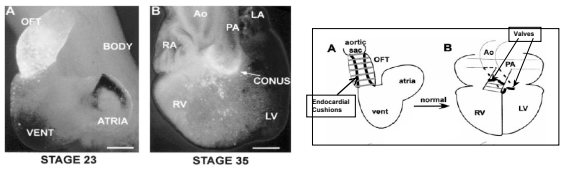
A. MORPHOGENESIS: SCULPTING/SHAPING STRUCTURES

CREATION OF CAVITIES AND TUBES

CREATION OF FORM (DIGITS)

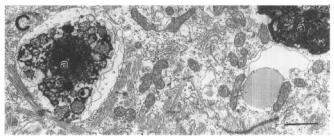
TISSUE REMODELING (CARDIAC OUTFLOW TRACT)

CELL DEATH AND CARDIAC MORPHOGENESIS



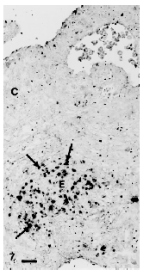
OTF = Outflow Tract
RA = Right Auricle
RV = Right Ventricle
LA = Left Auricle
LV = Left Ventricle
PA = Pulmonary Artery
Ao = Aorta

a = Apoptotic Cardiomyocyte



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

CELL DEATH AND CARDIAC MORPHOGENESIS

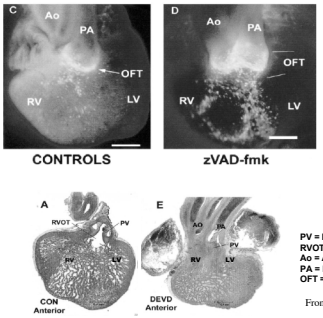


CELL DEATH IN CARDIAC OUTFLOW TRACT OF E13 MOUSE HEART AS REVEALED BY TUNEL STAINING (ARROWS)

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)



PV = Pulmonic Valve
RVOT = Right Ventricular Outflow Tract
Ao = Aorta
PA = Pulmonary Artery
OFT = Outflow Tract

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

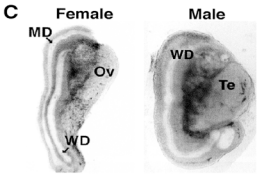
UROGENITAL SYSTEM: WOLFFIAN AND MÜLLERIAN DUCTS

REGULATION OF REPRODUCTIVE TRACT DEVELOPMENT 1

EMBRYONIC RAT GENITAL RIDGES SHOWING:

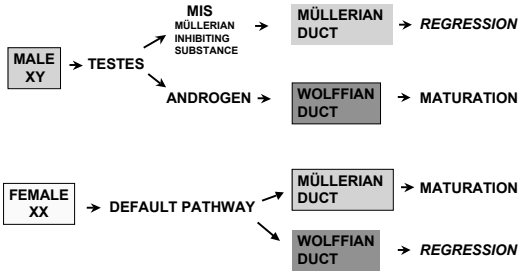
MÜLLERIAN DUCT (MD)
WOLFFIAN DUCT (WD)

OVARY (Ov)
TESTES (Te)

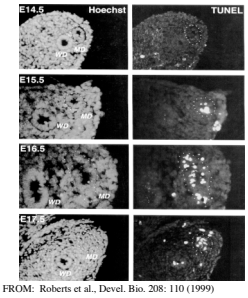


FROM: Roberts et al., Devel. Bio. 208: 110 (1999)

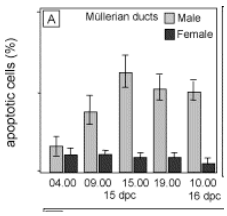
REGULATION OF REPRODUCTIVE TRACT DEVELOPMENT 2



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

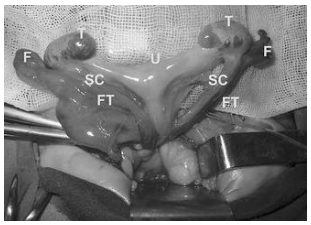


FROM: Roberts et al., Devel. Bio. 208: 110 (1999)



FROM: Xavier and Allard Mol Cell Endocrinol (2003)

FAILURE OF MÜLLERIAN DUCT REGRESSION: PERSISTENT MÜLLERIAN DUCT SYNDROME



Intraoperative appearance of a 15-month-old male with persistent mullerian 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

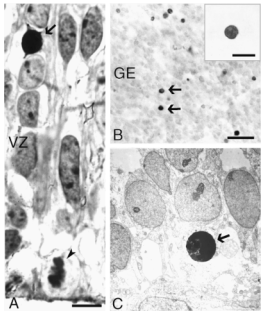
NERVOUS SYSTEM:

→ **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



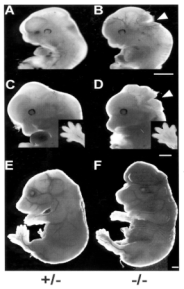
A. 4.5 gw Ventricular Zone. Apoptotic nucleus (arrow)

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**

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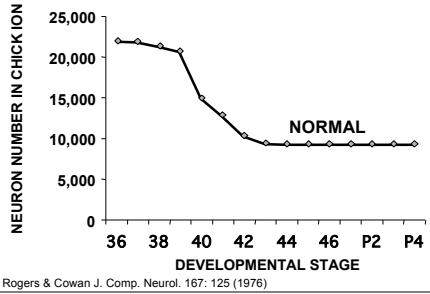
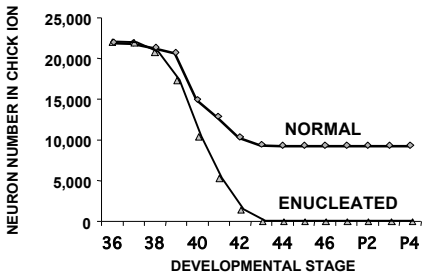
NORMAL DEVELOPMENTAL NEURONAL DEATH OCCURS AND IS REGULATED BY TARGET DERIVED TROPHIC FACTORS



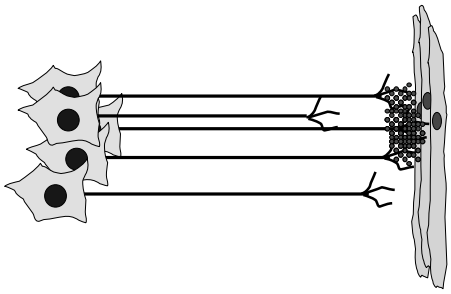
Clarke, Rogers & Cowan J. Comp. Neurol. 167: 125 (1976)

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



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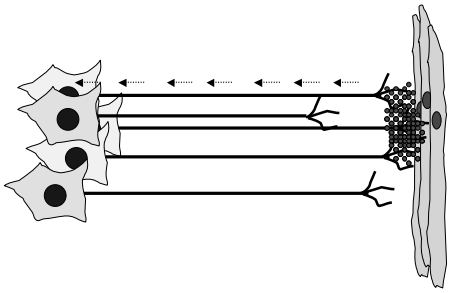
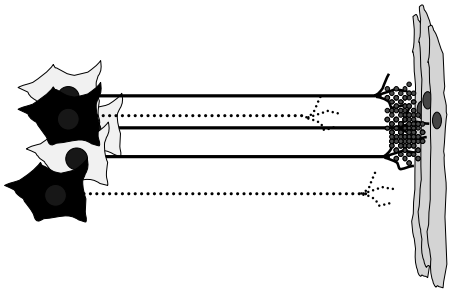
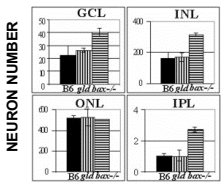


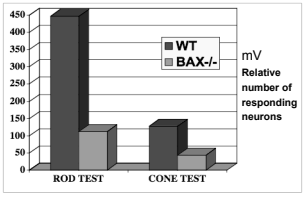
NEURONAL CULLING AS REGULATED BY COMPETITION FOR TARGET-SUPPLIED TROPHIC FACTOR



RETINAL NEURON RESPONSES TO LIGHT CHANGE IN ABSENCE OF NORMAL DEVELOPMENTAL CELL DEATH



GCL=ganglion cell layer
INL=inner nuclear layer
ONL=outer nuclear layer
IPL=inner plexiform layer



Péquignot et al. Dev Dyn 2003

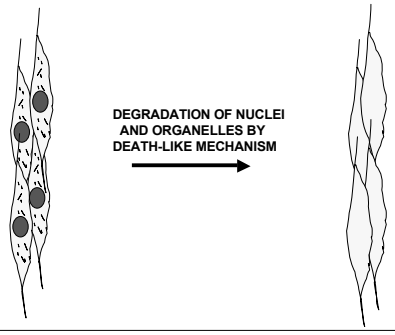
FUNCTIONS OF DEVELOPMENTAL CELL DEATH

D. PRODUCTION OF STRUCTURES WITHOUT ORGANELLES

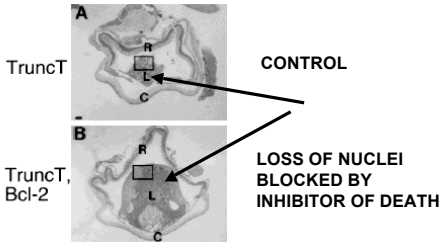
SQUAMOUS EPITHELIUM FROM KERATINOCYTES

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

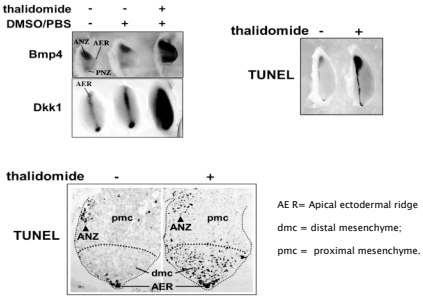


FROM: Fromm et al., Dev Genetics 20: 296 (1997)

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)

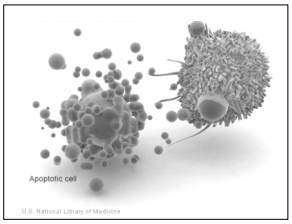
TERATOGENS AND CELL DEATH



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

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

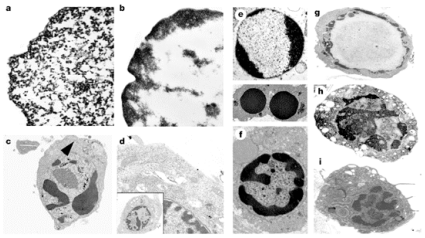
HOW DOES DEVELOPMENTAL CELL DEATH OCCUR?



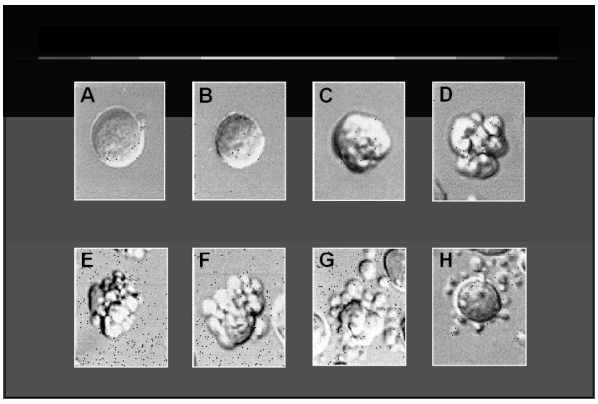
APOPTOTIC DEATH	vs	NECROTIC DEATH
PRESENT IN DEVELOPING TISSUES		RESPONSE TO CELL INJURY, TOXINS
CYTOPLASMIC BLEBBING		
CELLULAR & NUCLEAR PYKNOSIS		CELL & NUCLEAR SWELLING
CHROMATIN CONDENSATION		
DNA DEGRADATION BY ENDONUCLEASES (FORMATION OF DNA LADDER)		RANDOM DNA DEGRADATION
FORMATION OF MEMBRANE-LIMITED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

Kerr, Wylie and Currie

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

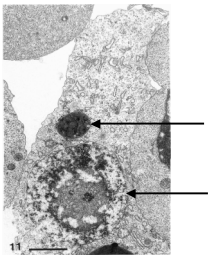


Nature Reviews | Molecular Cell Biology



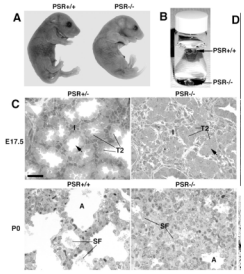
APOPTOTIC BODIES AND NUCLEI ARE CLEARED BY PHAGOCYTOSIS

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)

MICE MUTANT FOR PHAGOCYTOSIS SHOW DEFECTIVE LUNG DEVELOPMENT AND RESPIRATORY SYMPTOMS SIMILAR TO THOSE IN HUMAN RESPIRATORY DISTRESS SYNDROME (RDS))



From: Li et al., Science: 302 (2003)

WHAT ARE THE MECHANISMS BY WHICH CELLS DIE DURING DEVELOPMENT?

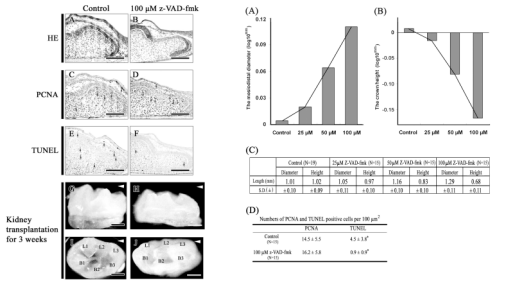
THERE ARE EVOLUTIONARILY CONSERVED MECHANISMS THAT GOVERN DEVELOPMENTAL CELL DEATH

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**

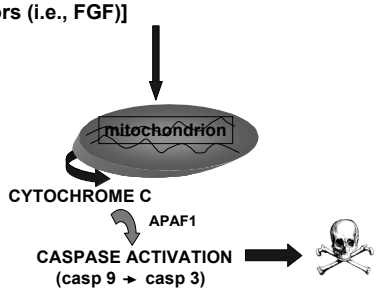
BLOCKING CELL DEATH WITH CASPASE INHIBITORS AFFECTS TOOTH DEVELOPMENT



From: Kim et al., J Dent Res 85: 530 (2006)

THE MITOCHONDRIAL PATHWAY OF APOPTOTIC DEATH - 1

APOPTOTIC STIMULI [absence of survival factors (i.e., FGF)]

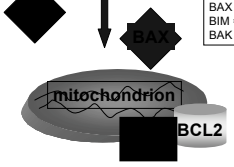


THE MITOCHONDRIAL PATHWAY OF APOPTOTIC DEATH - 2

APOPTOTIC STIMULI

BCL2 = Anti-apoptotic protein

BAX =Pro-apoptotic protein
BIM = Pro-apoptotic protein
BAK = Pro-apoptotic protein



THE MITOCHONDRIAL PATHWAY OF APOPTOTIC DEATH - 2

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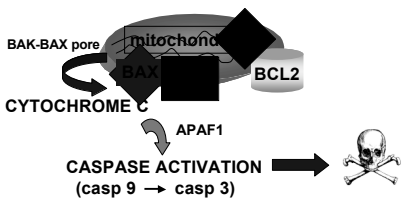
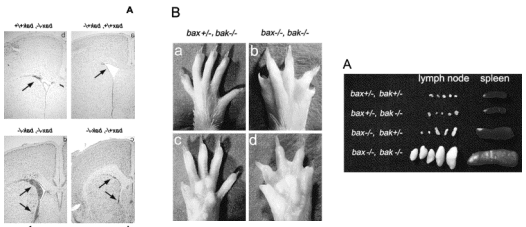


ABNORMALITIES IN MICE LACKING BAX AND BAK



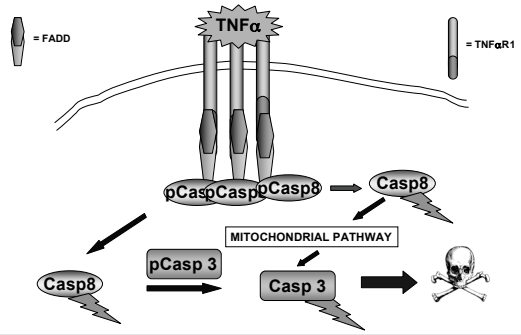
Arrow shows neuroprogenitors
in ventricular zone of embryonic brain

From: Lindsten et al. Mol Cell 6:1389 (2000)

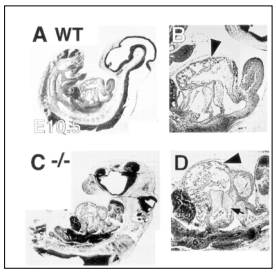
DEATH PROMOTING RECEPTORS AND LIGANDS THE EXTRINSIC PATHWAY TO APOPTOTIC DEATH

LIGAND	RECEPTOR
TNFα	TNFαR1
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)

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 ABNOMALITIES