CELL DEATH DURING DEVELOPMENT

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DEPT OF PATHOLOGY

APRIL 26, 2007

KEY DEVELOPMENTAL PROCESSES

CELL PROLIFERATION

CELL MIGRATION

CELL DIFFERENTIATION

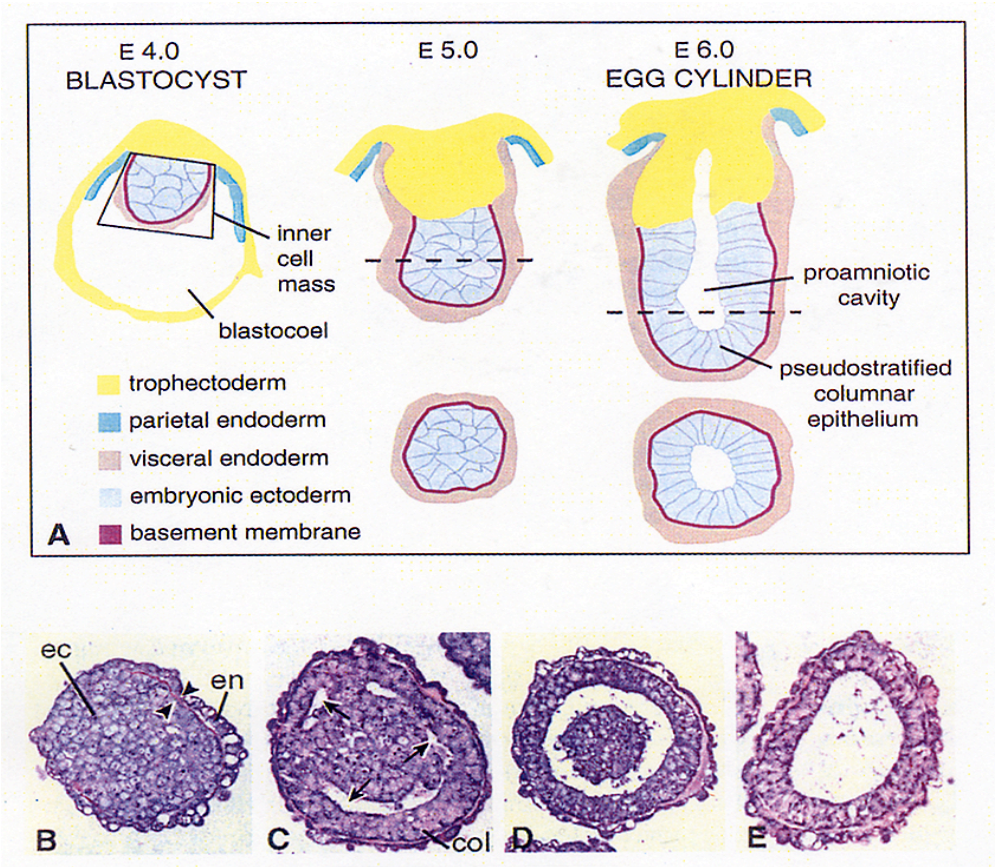
CELL DEATH

FUNCTIONS OF DEVELOPMENTAL CELL DEATH

A. **MORPHOGENESIS**: SCULPTING/SHAPING STRUCT

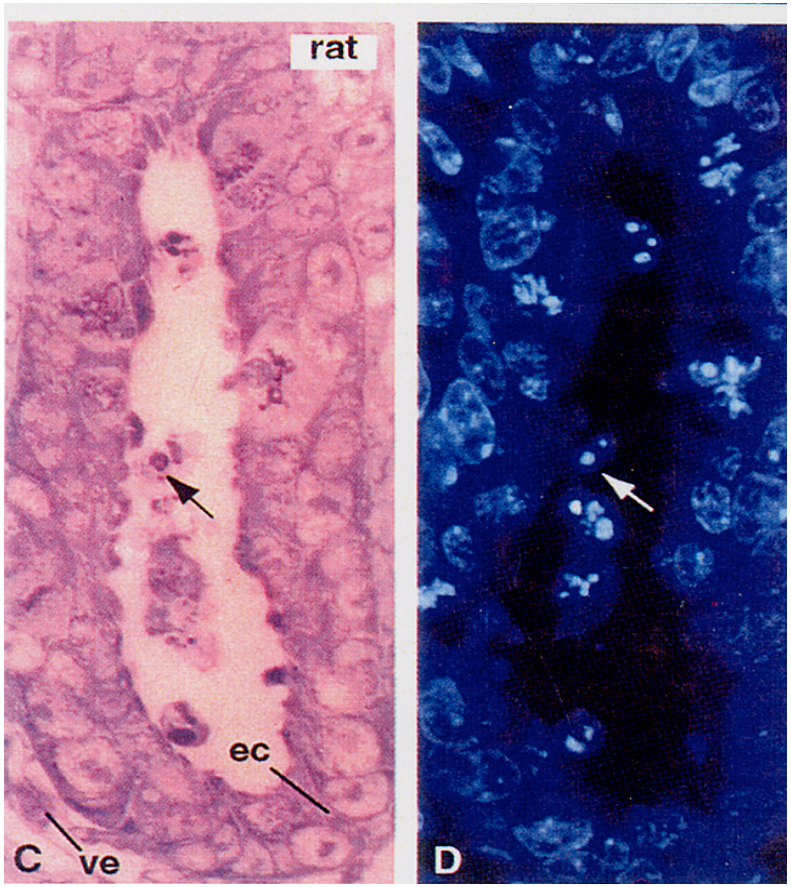
CREATION OF CAVITIES AND TUBES

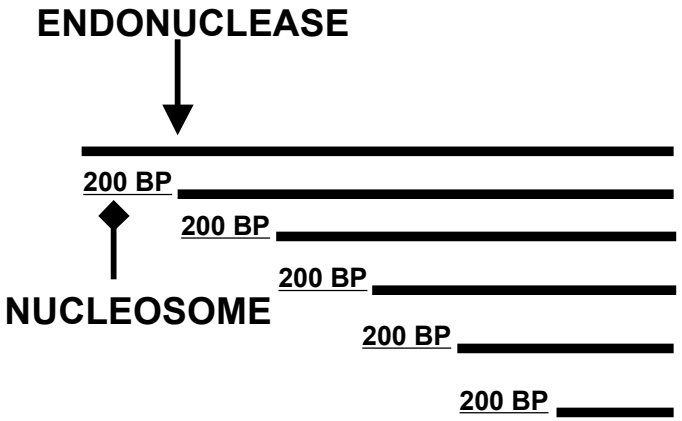
CELL DEATH AND FORMATION OF THE PROAMNIOTIC CAVITY FROM THE BLASTOCYST 1



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

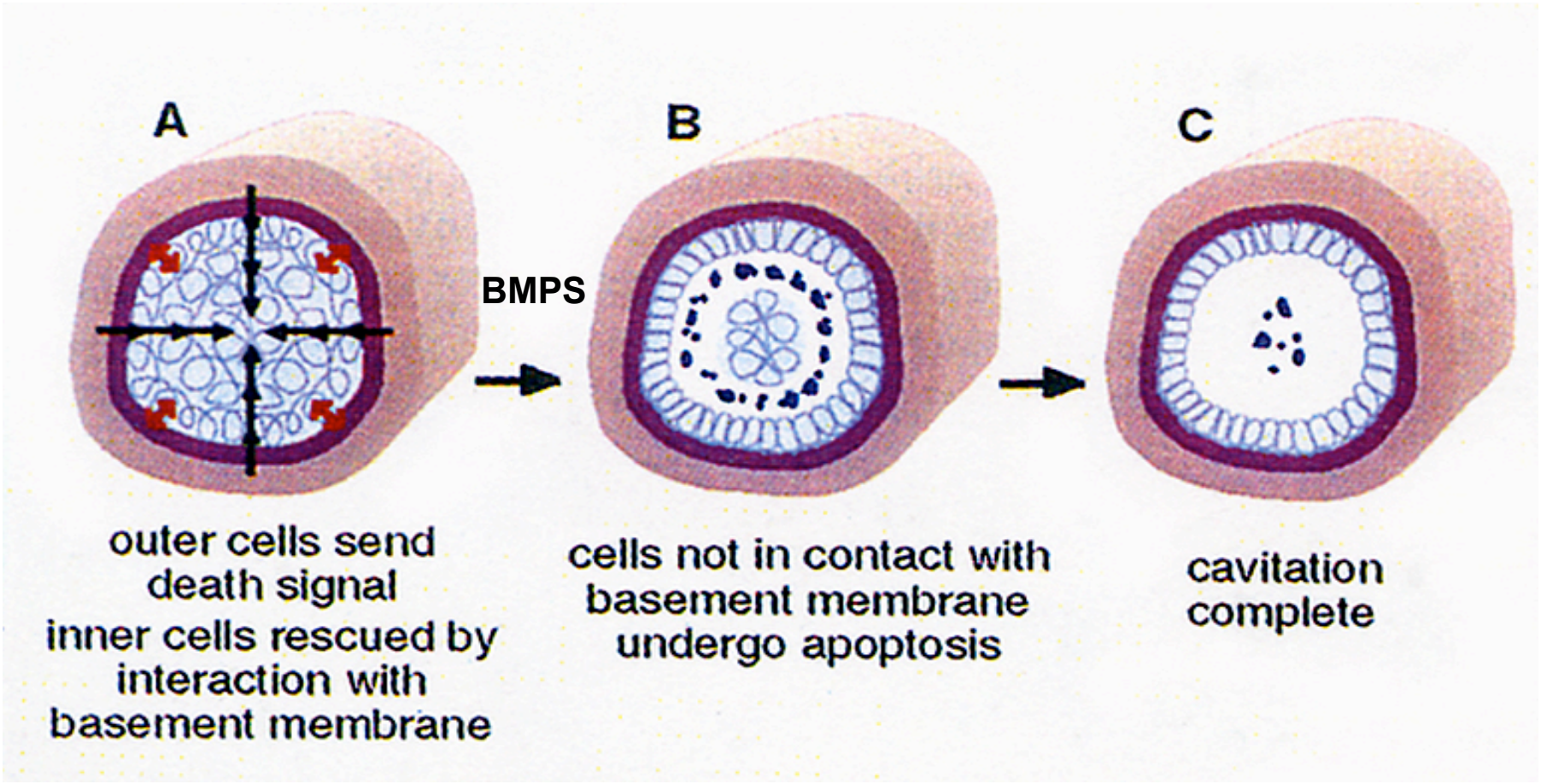
CELL DEATH AND FORMATION OF THE PROAMNIO CAVITY FROM THE BLASTOCYST 2





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

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



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

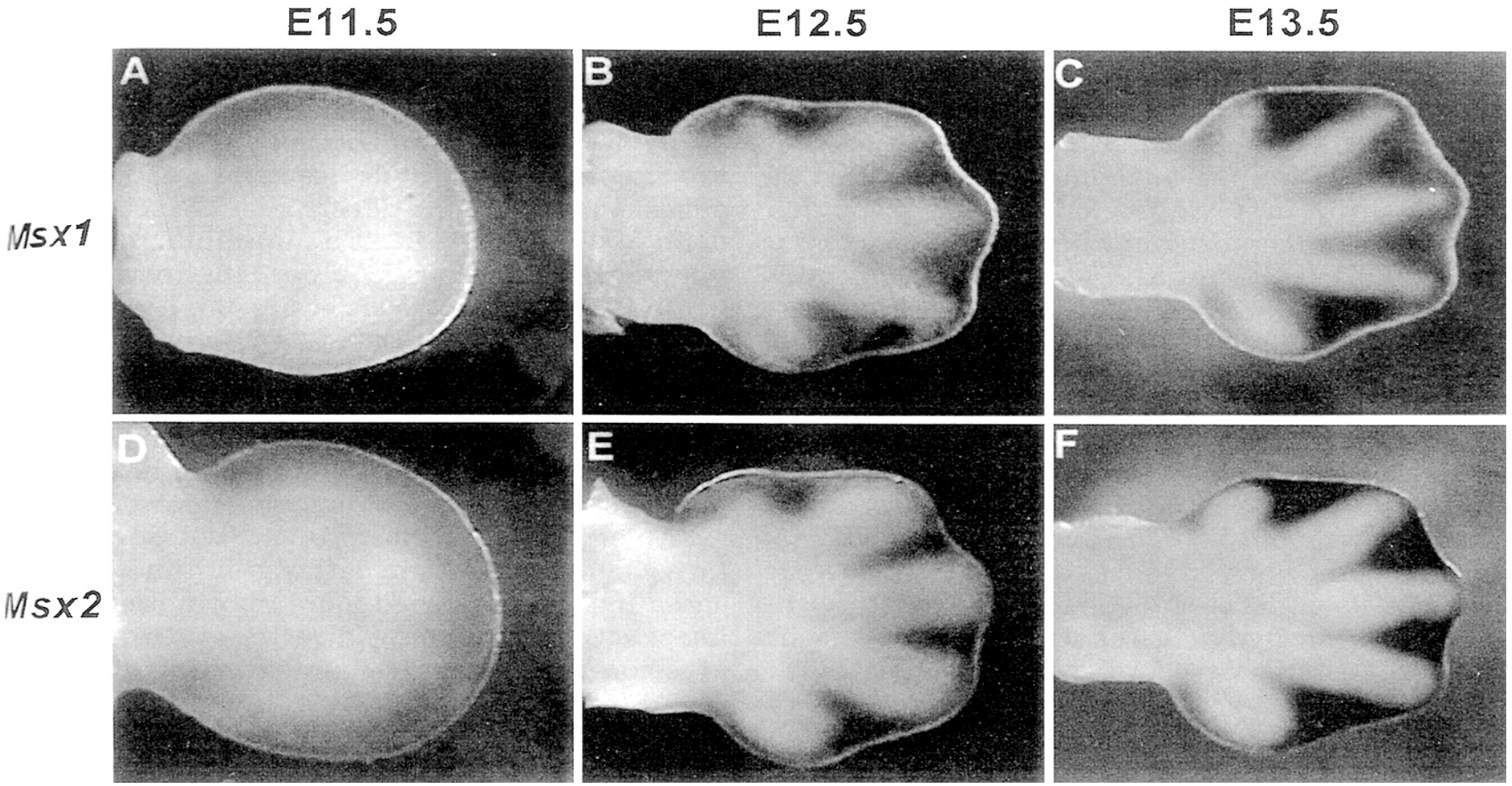
FUNCTIONS OF DEVELOPMENTAL CELL DEATH

A. MORPHOGENESIS: SCULPTING/SHAPING STRUCT

CREATION OF CAVITIES AND TUBES

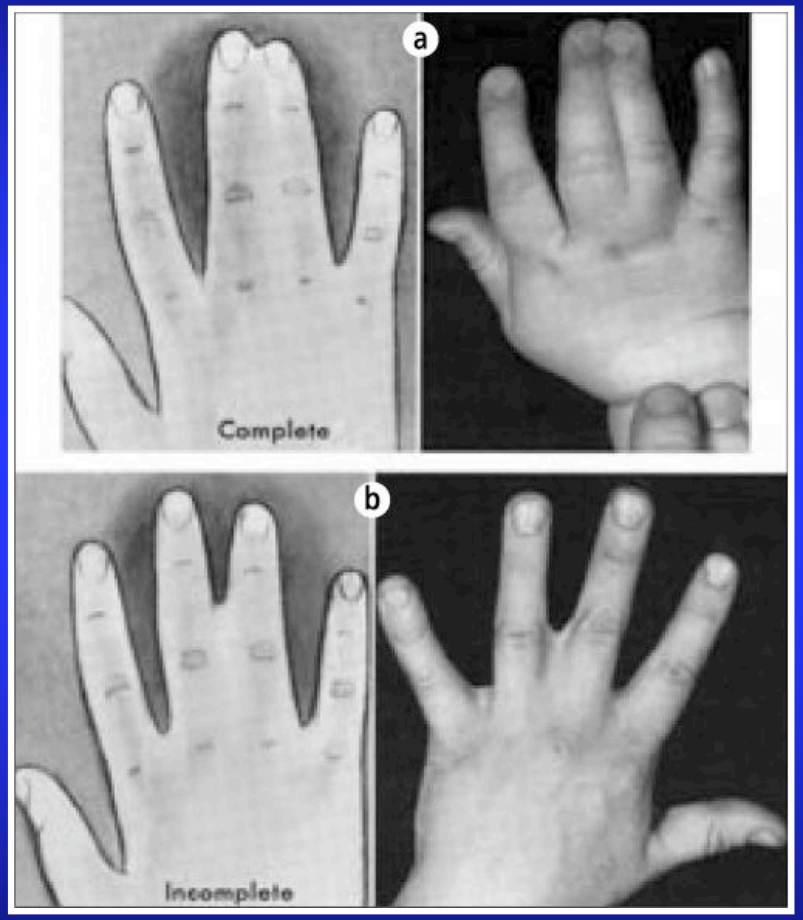
CREATION OF FORM (DIGITS)

CELL DEATH AND FORMATION OF DIGITS 3



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

HUMAN SYNDACTYLY



SIMPLE

C0MPLEX

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

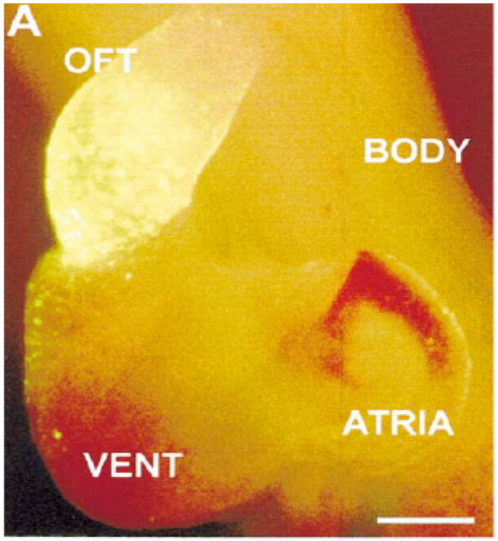
A. MORPHOGENESIS: SCULPTING/SHAPING STRUCT

CREATION OF CAVITIES AND TUBES

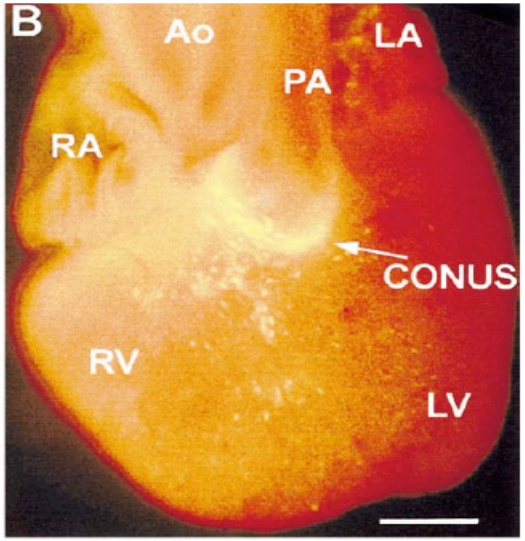
CREATION OF FORM (DIGITS)

TISSUE REMODELING (CARDIAC OUTFLOW TRAC

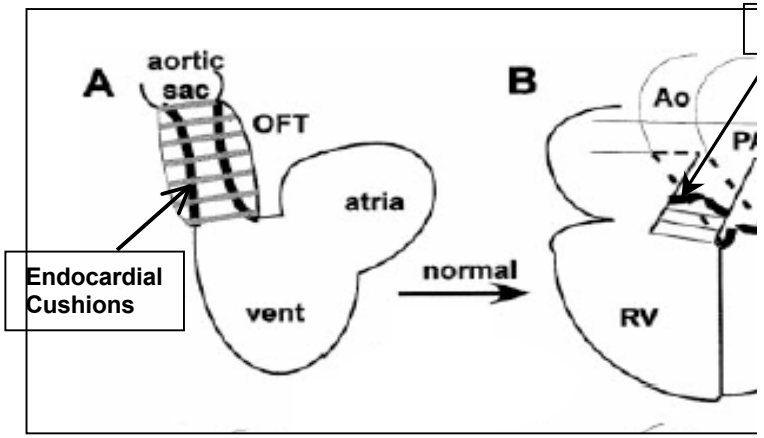
CELL DEATH AND CARDIAC MORPHOGENESIS



STAGE 23

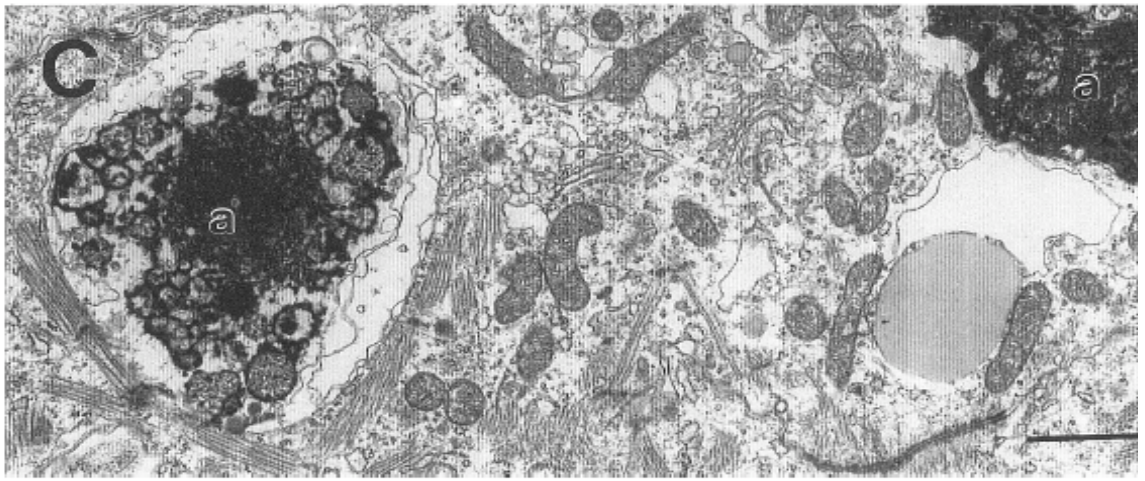


STAGE 35



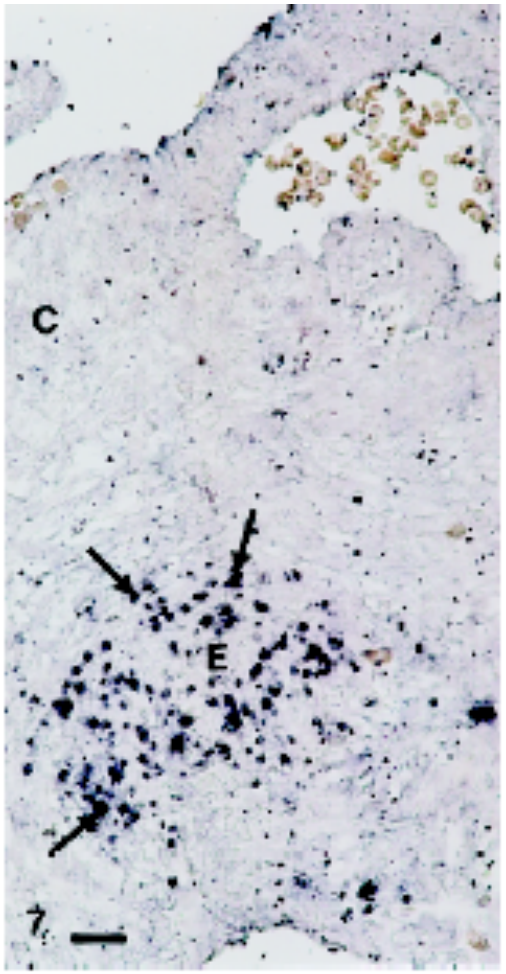
OTF = Outflow Tract
RA = Right Auricle
RV = Right Ventricle
LA = Left Auricle
LV = Left Ventricle
PA = Pulmonary Artery
Ao = Aorta

a = Apoptotic Cardiomyocyte



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

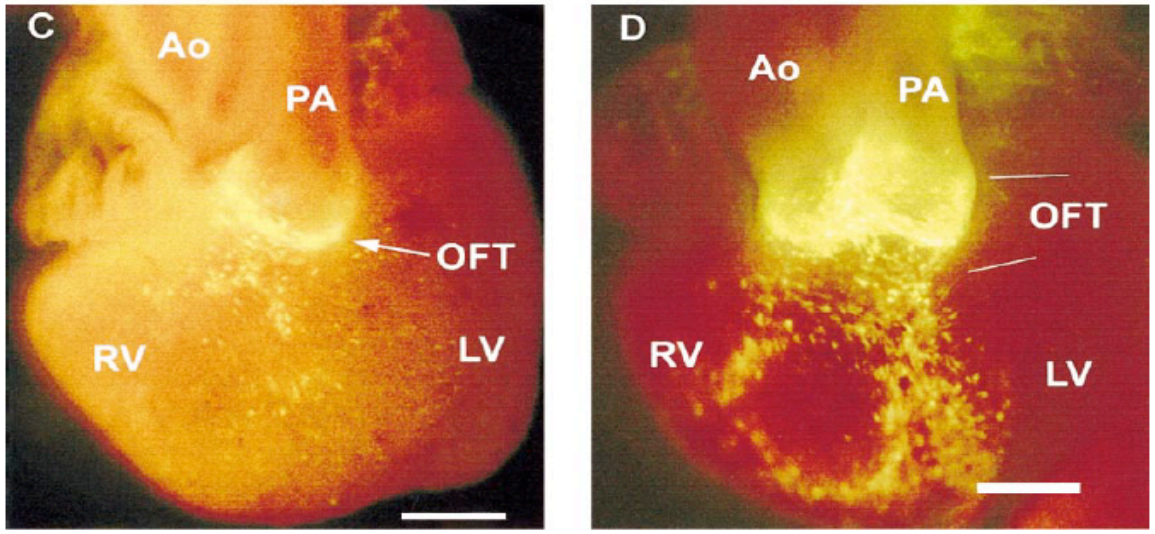
CELL DEATH AND CARDIAC MORPHOGENESIS



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

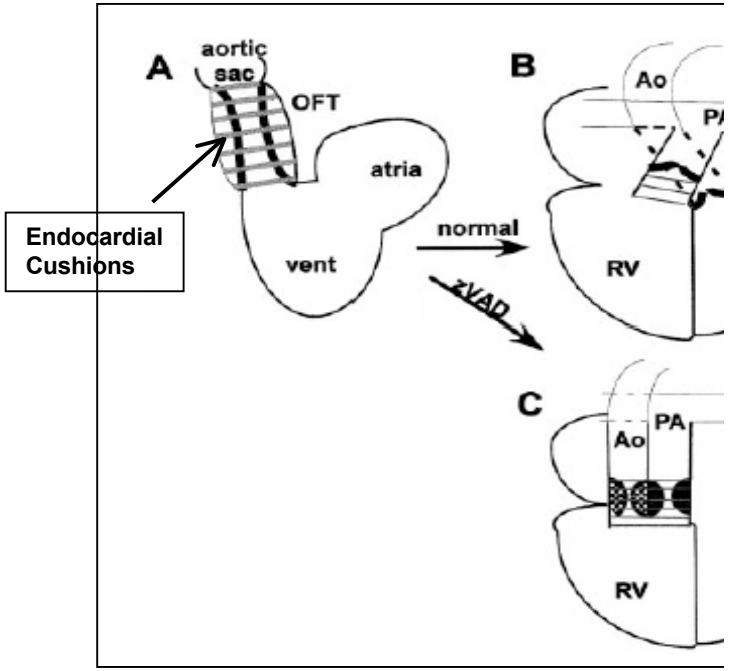
From: Abdelwahid et al., Microscopy Res Tech. 58: 2002

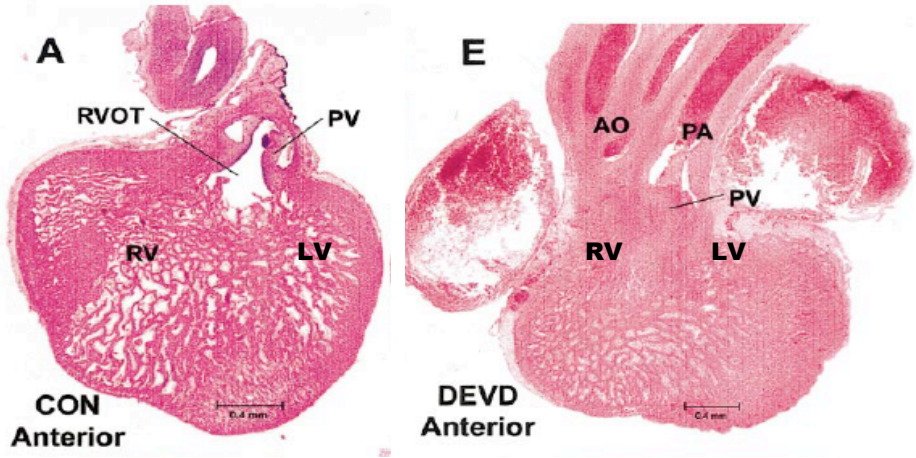
BLOCKADE OF DEATH IN DEVELOPING HEART OFT LEADS TO DOUBLE OUTLET RIGHT VENTRICLE (DORV)



CONTROLS

zVAD-fmk





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 (200

FUNCTIONS OF DEVELOPMENTAL CELL DEATH

B. DELETION OF UNNEEDED STRUCTURES

KIDNEY: PRONEPHROS AND MESONEPHROS

BRAIN: CORTICAL SUBPLATE NEURONS

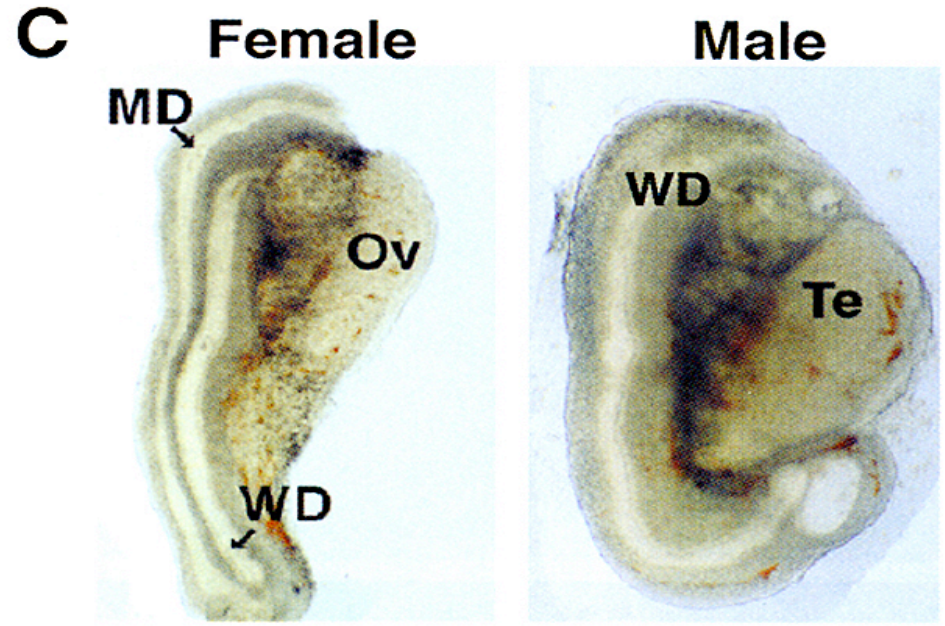
UROGENITAL SYSTEM: WOLFFIAN AND MÜLLER DUCTS

REGULATION OF REPRODUCTIVE TRACT DEVELOPMENT 1

EMBRYONIC RAT GENITAL RIDGES SHOWING:

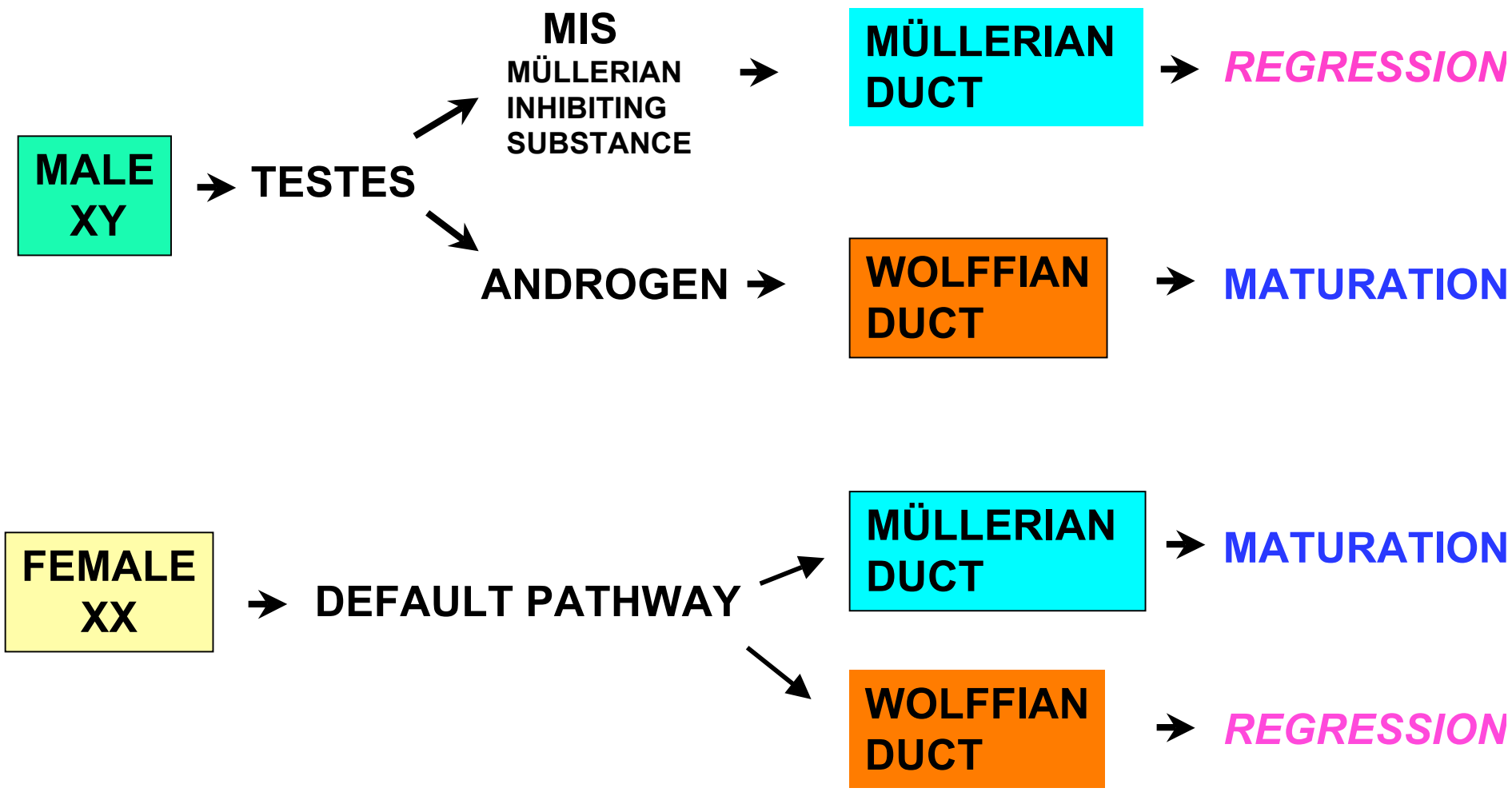
MÜLLERIAN DUCT (MD)
WOLFFIAN DUCT (WD

OVARY (Ov)
TESTES (Te)

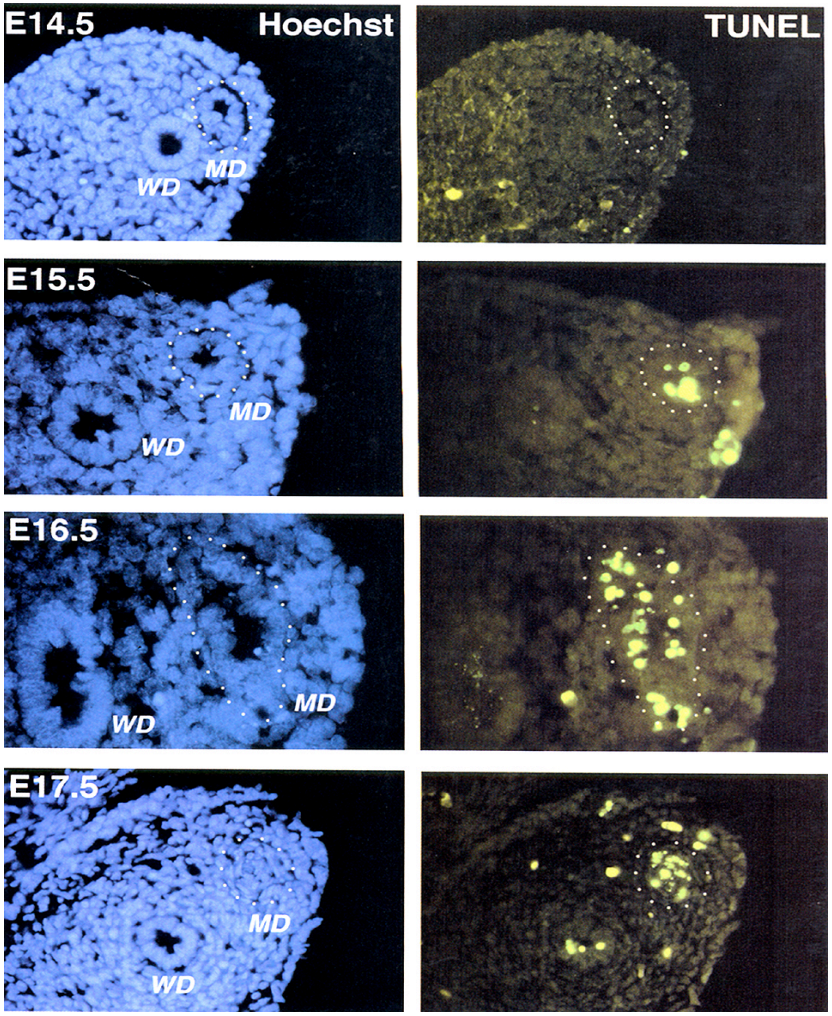


FROM: Roberts et al., Devel. Bio. 208: 110 (1999)

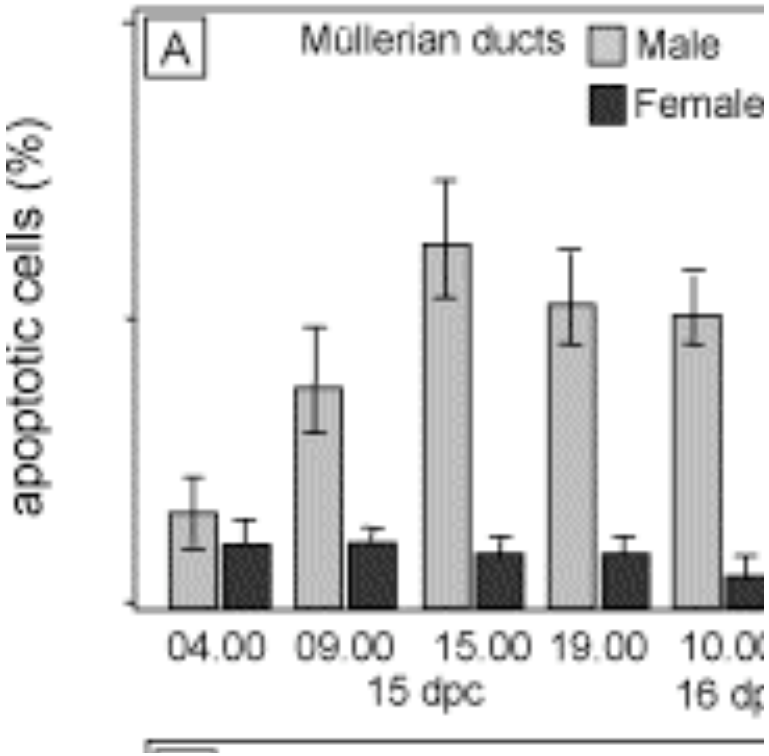
REGULATION OF REPRODUCTIVE TRACT DEVELOPMENT 2



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

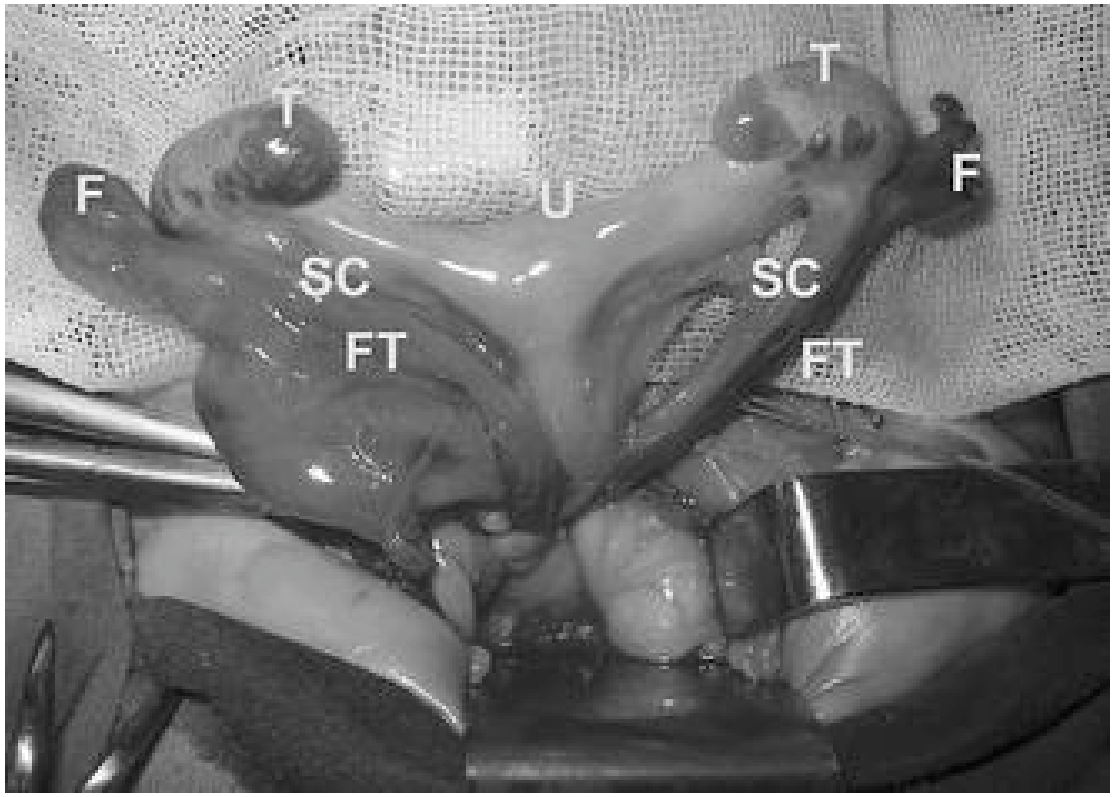


FROM: Roberts et al., Devel. Bio. 208: 110 (1999)



FROM: Xavier and Allard Mol Cell Endocrir

FAILURE OF MÜLLERIAN DUCT REGRESSION: PERSISTENT MÜLLERIAN DUCT SYNDROME



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

From: Boleken et al., Int Urol Nephrol. March 1, 2

FUNCTIONS OF DEVELOPMENTAL CELL DEATH

C. REGULATION OF CELL NUMBERS

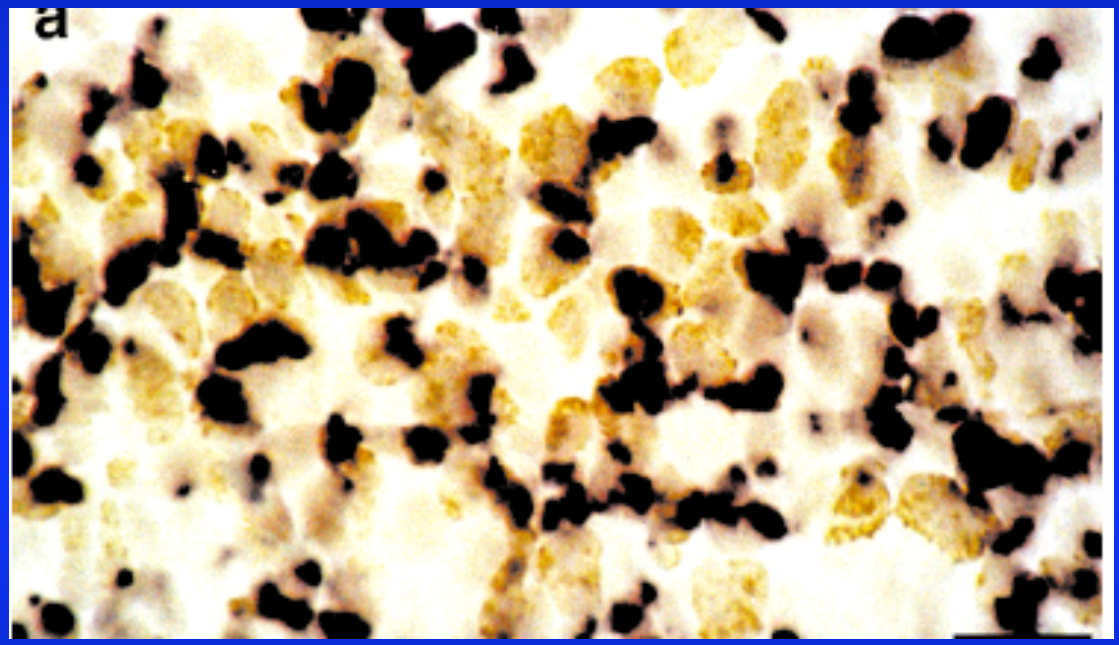
NERVOUS SYSTEM:

GENERATION OF CORRECT NEURON NUMBER

MATCHING NEURONS AND TARGETS

MATCHING SCHWANN CELL AND OLIGODENDROCYTES WITH AXONS

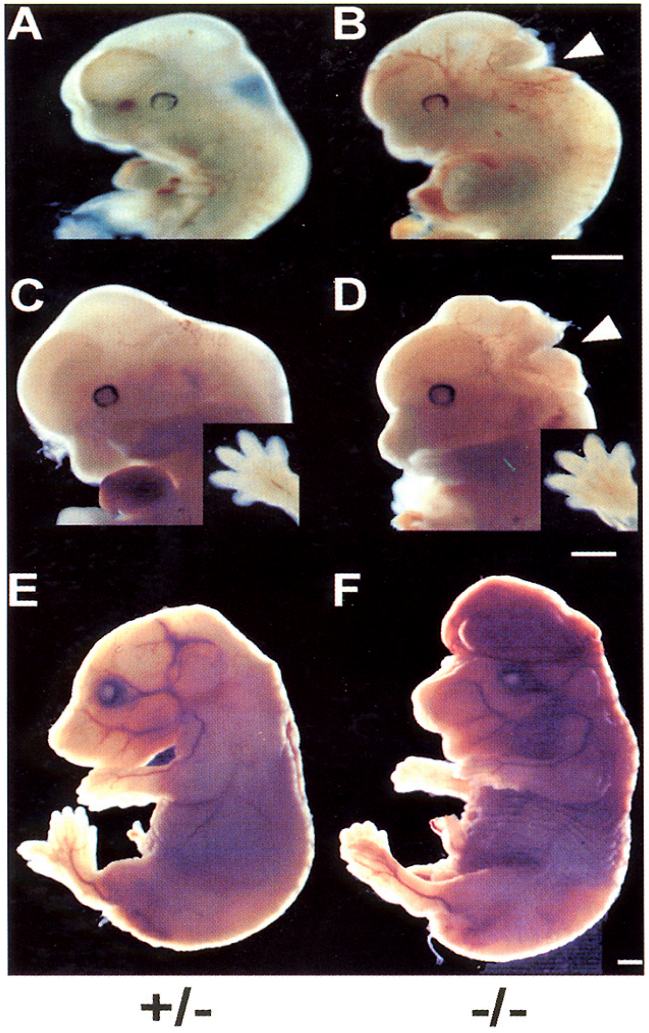
DEATH OF PROLIFERATING VZ CELLS IN E14 MOUSE CEREB



Tan = BrDU; Purple = ISEL/dying

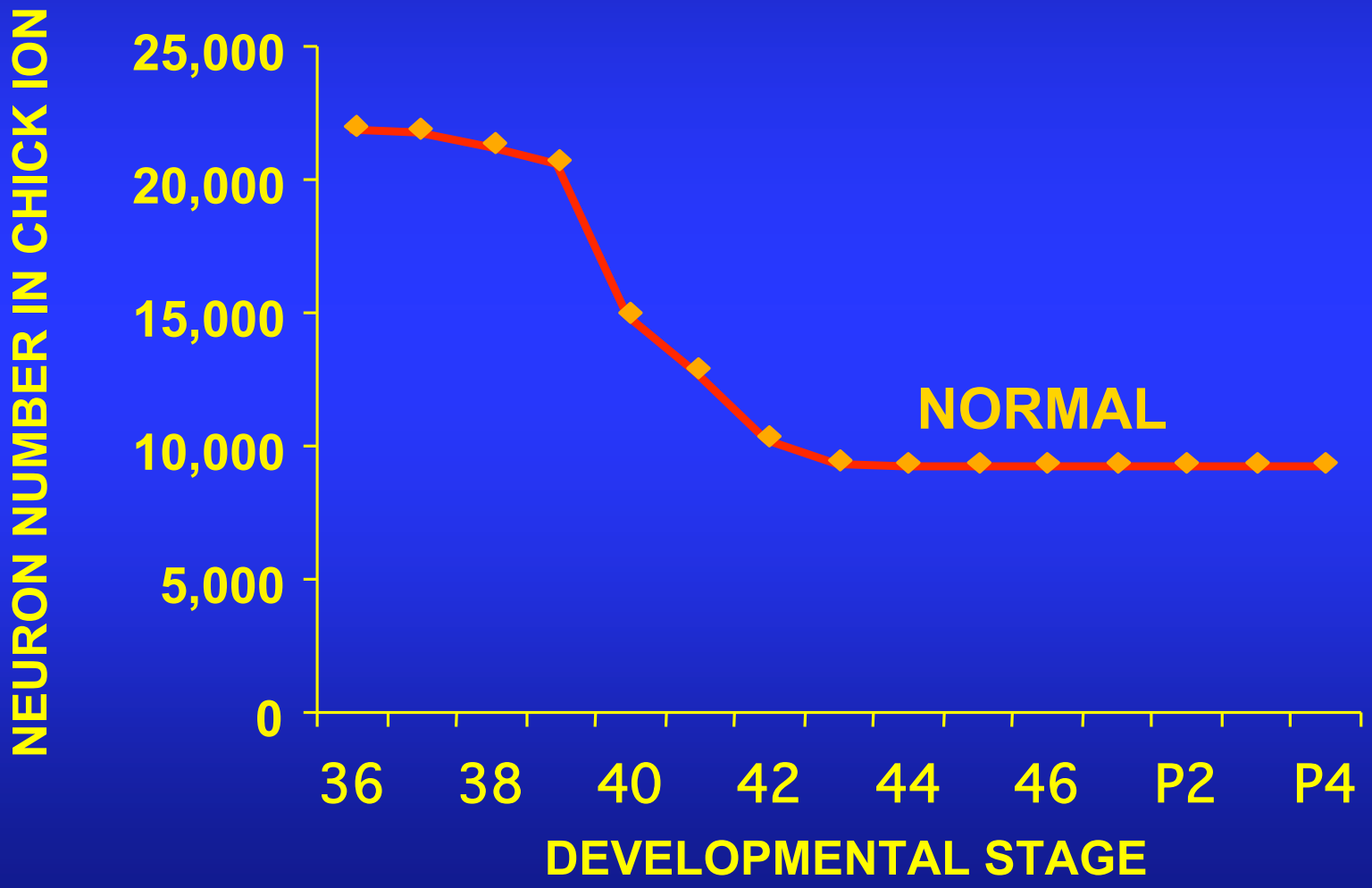
Blaschke et al J Comp Neurol 1998

EMBRYOGENIC DEFECTS IN A MOUSE LACKING CASPASE-



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

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



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

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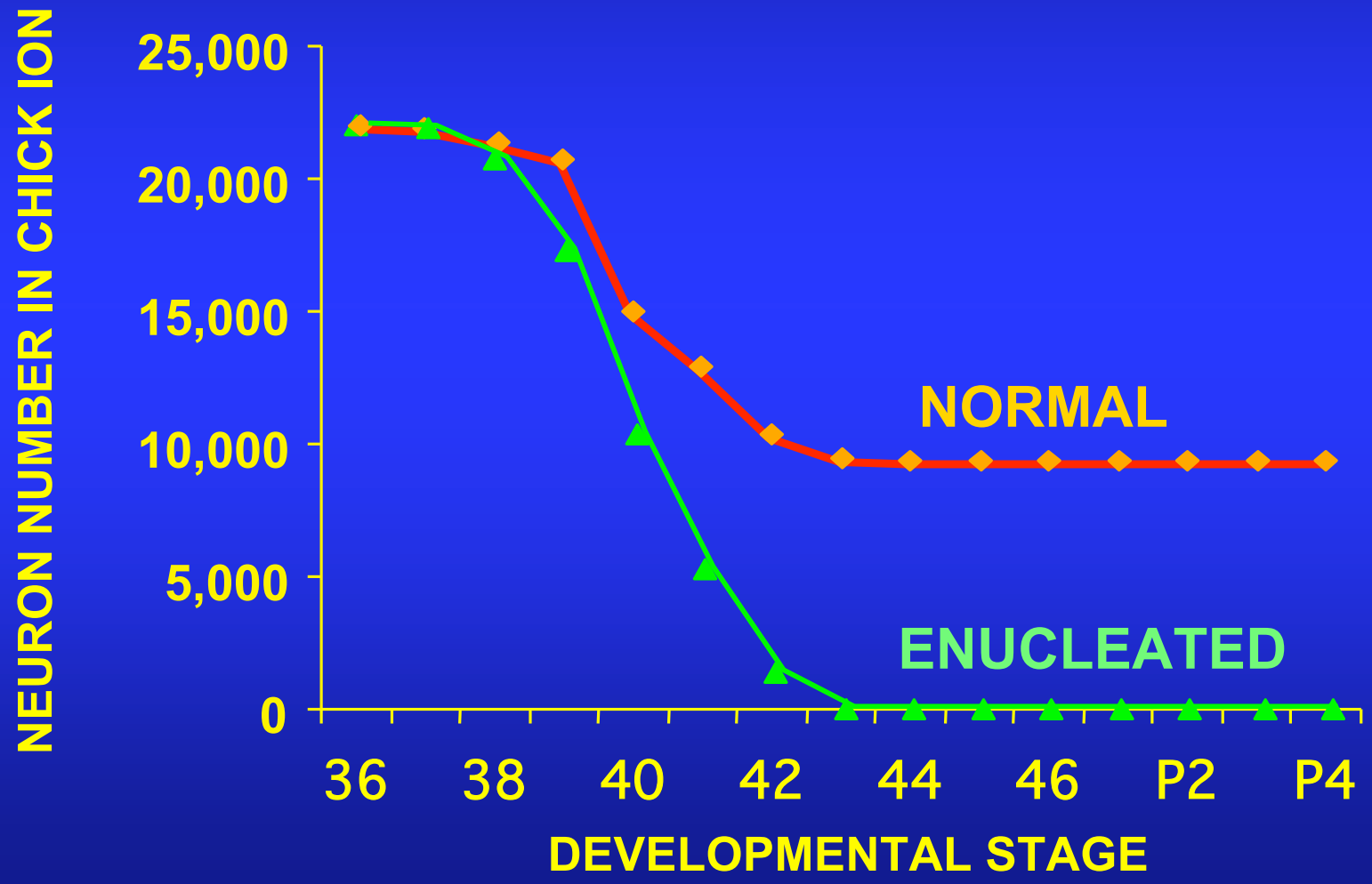
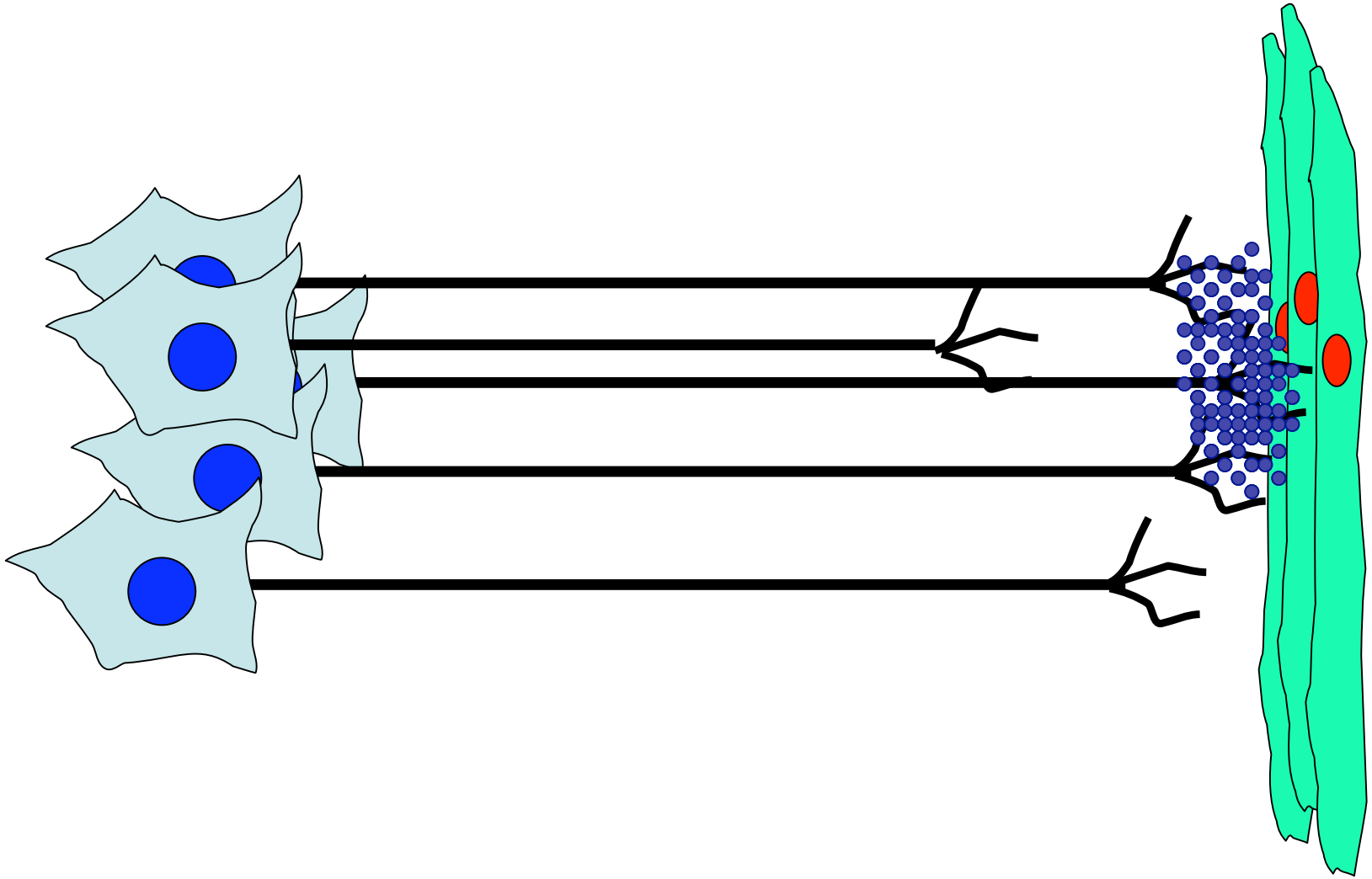


Clarke, Rogers & Cowan J. Comp. Neurol. 167: 125 (1976)

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



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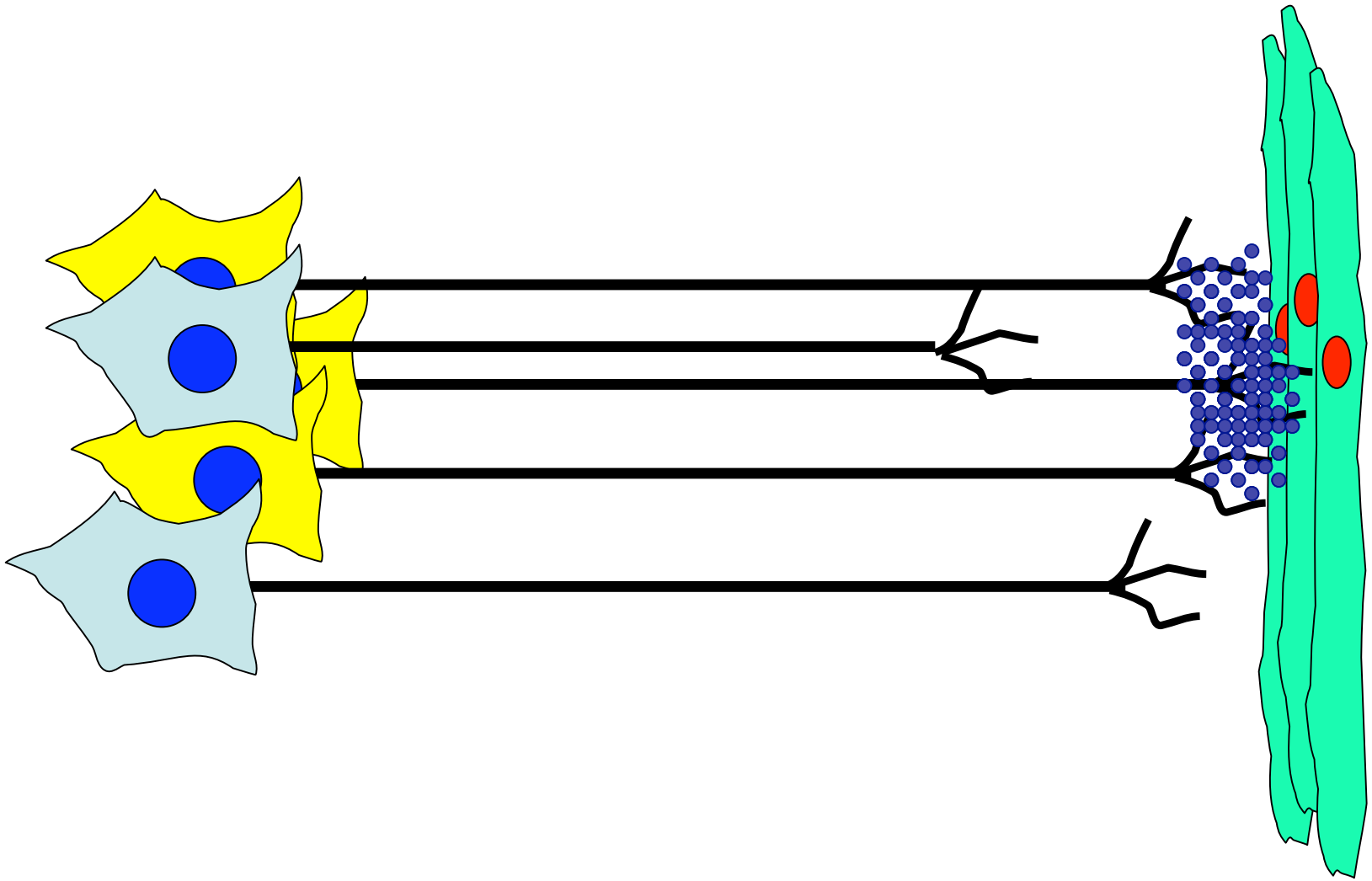

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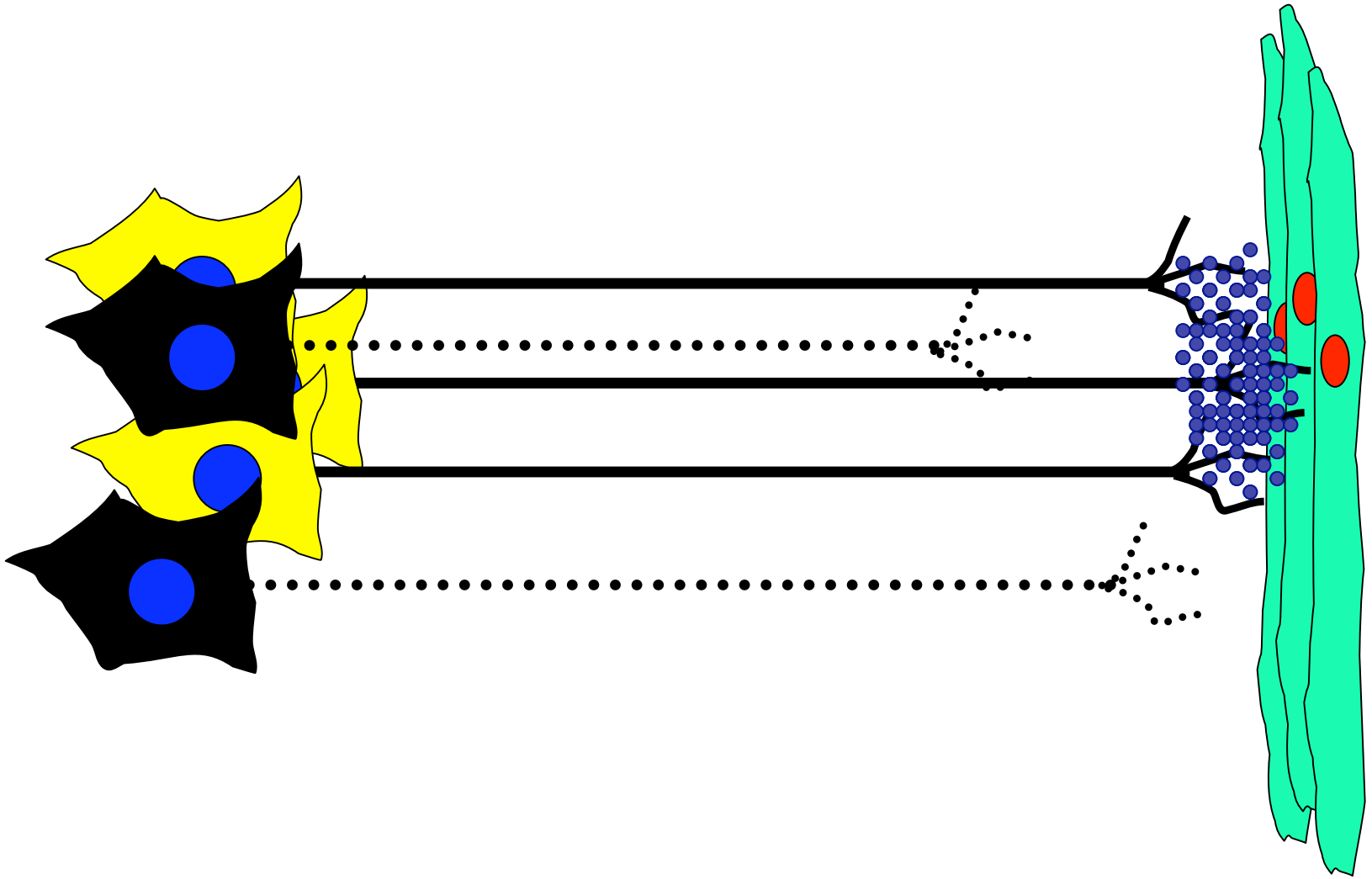
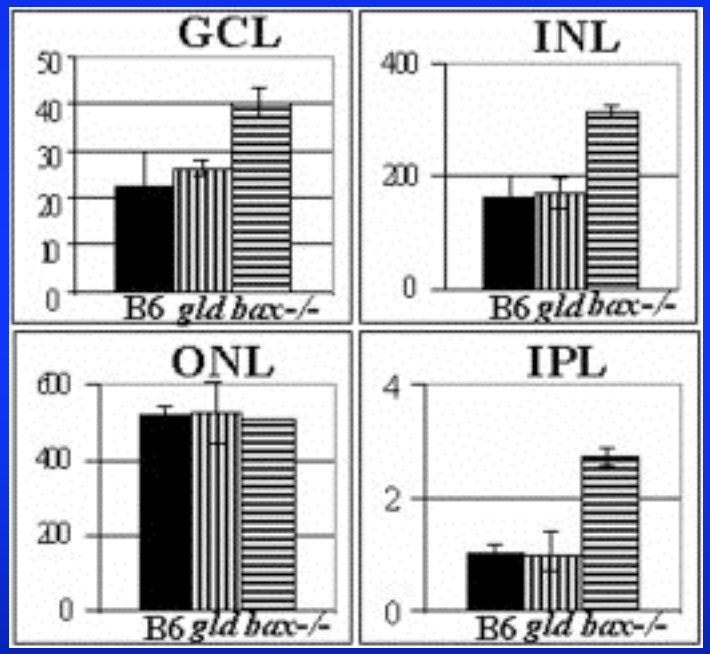
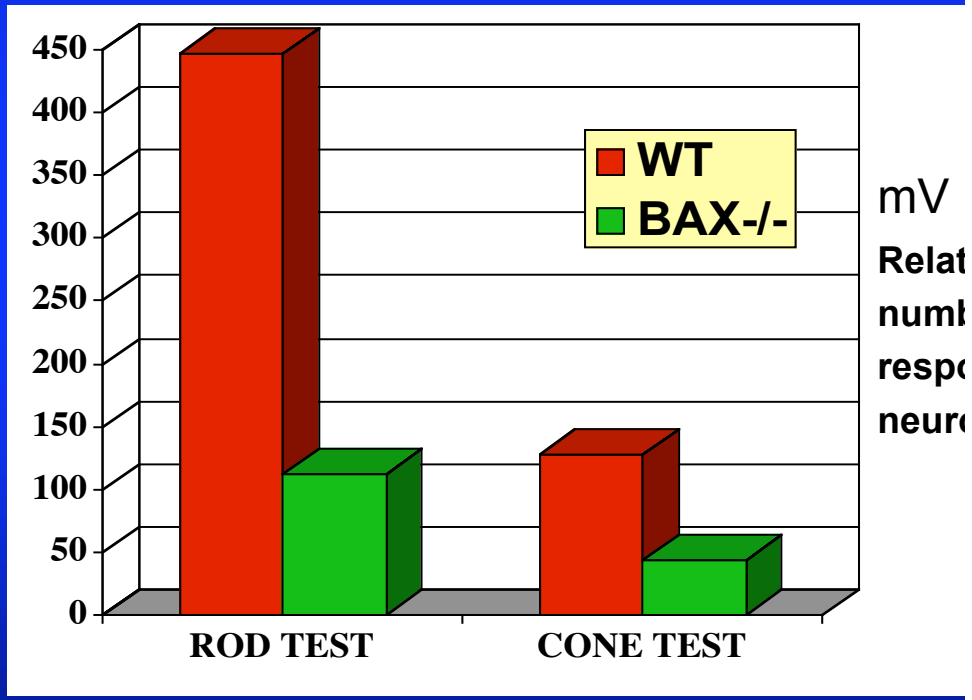


RETINAL NEURON RESPONSES TO LIGHT CHANGE IN ABSENCE OF NORMAL DEVELOPMENTAL CELL DEATH



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



(Péquignot et al. Dev Dyn 2003

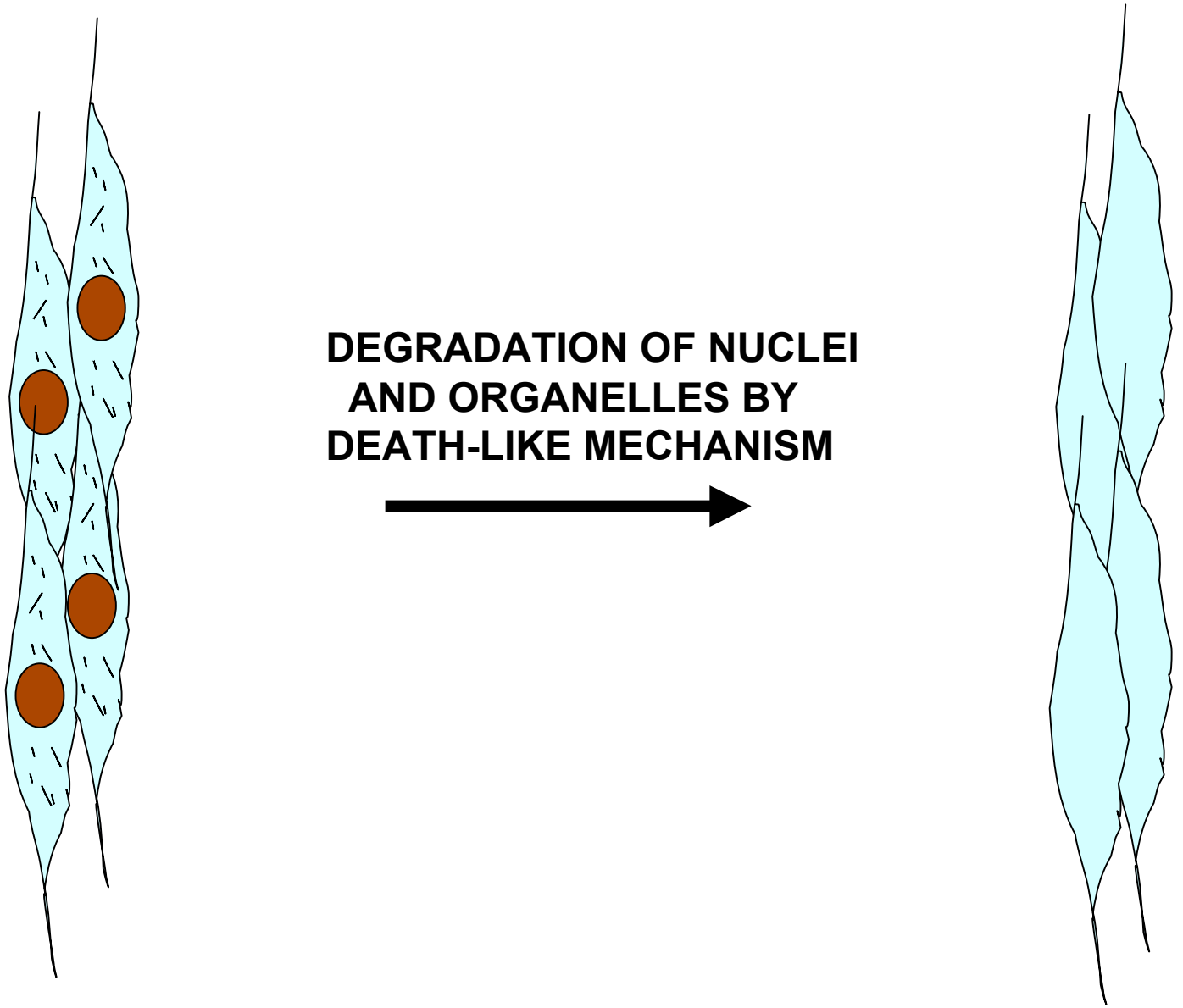
FUNCTIONS OF DEVELOPMENTAL CELL DEATH

E. PRODUCTION OF STRUCTURES WITHOUT ORGANELLES

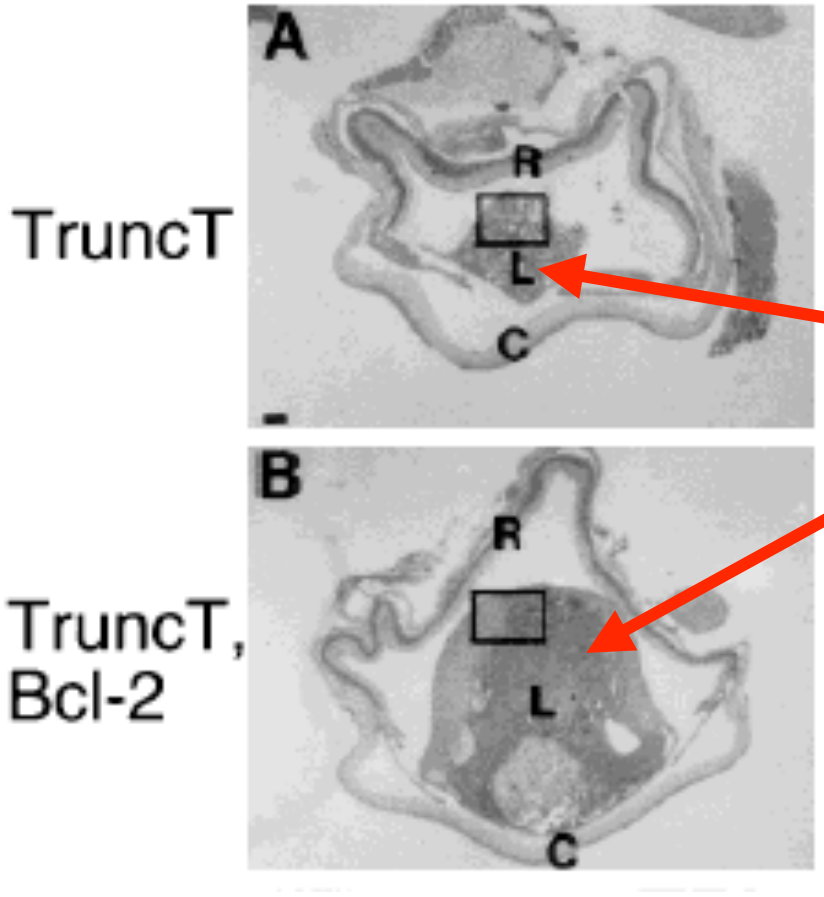
SQUAMOUS EPITHELIUM FROM KERATINOCYTES

FORMATION OF LENS FROM LENS FIBER CEL

FORMATION OF CLEAR LENS FROM LENS FIBER CELLS



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

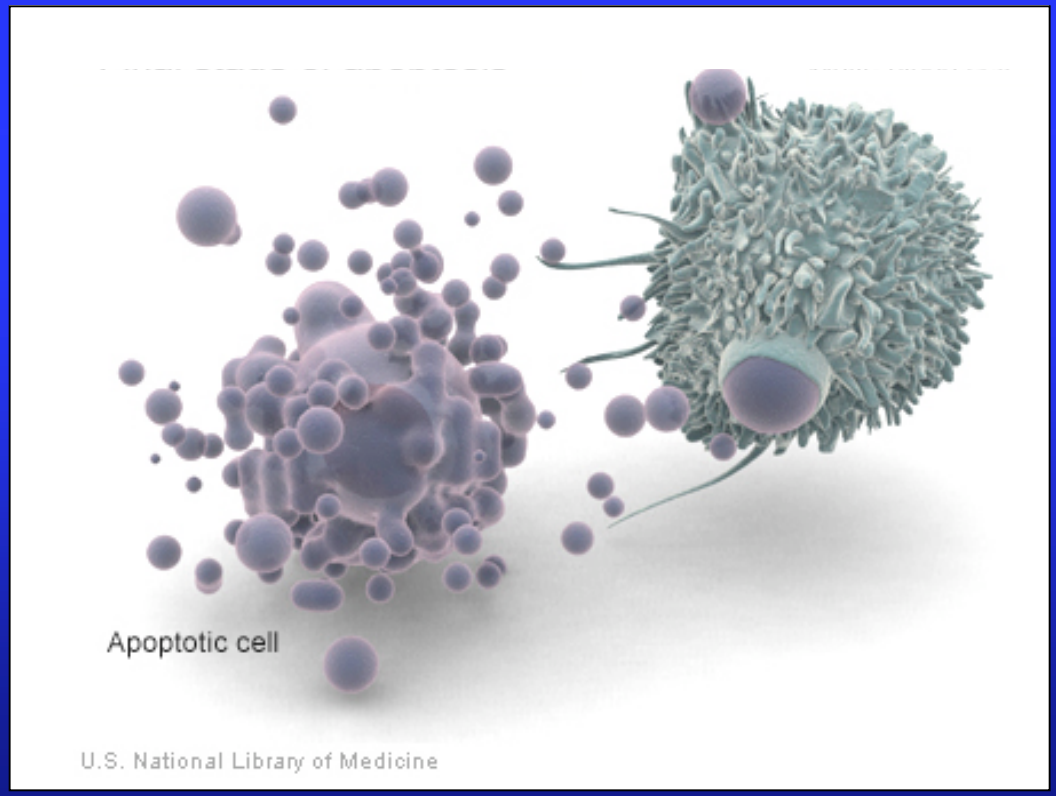


CONTROL

LOSS OF NUCLEI BLOCKED BY INHIBITOR OF DEAT

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

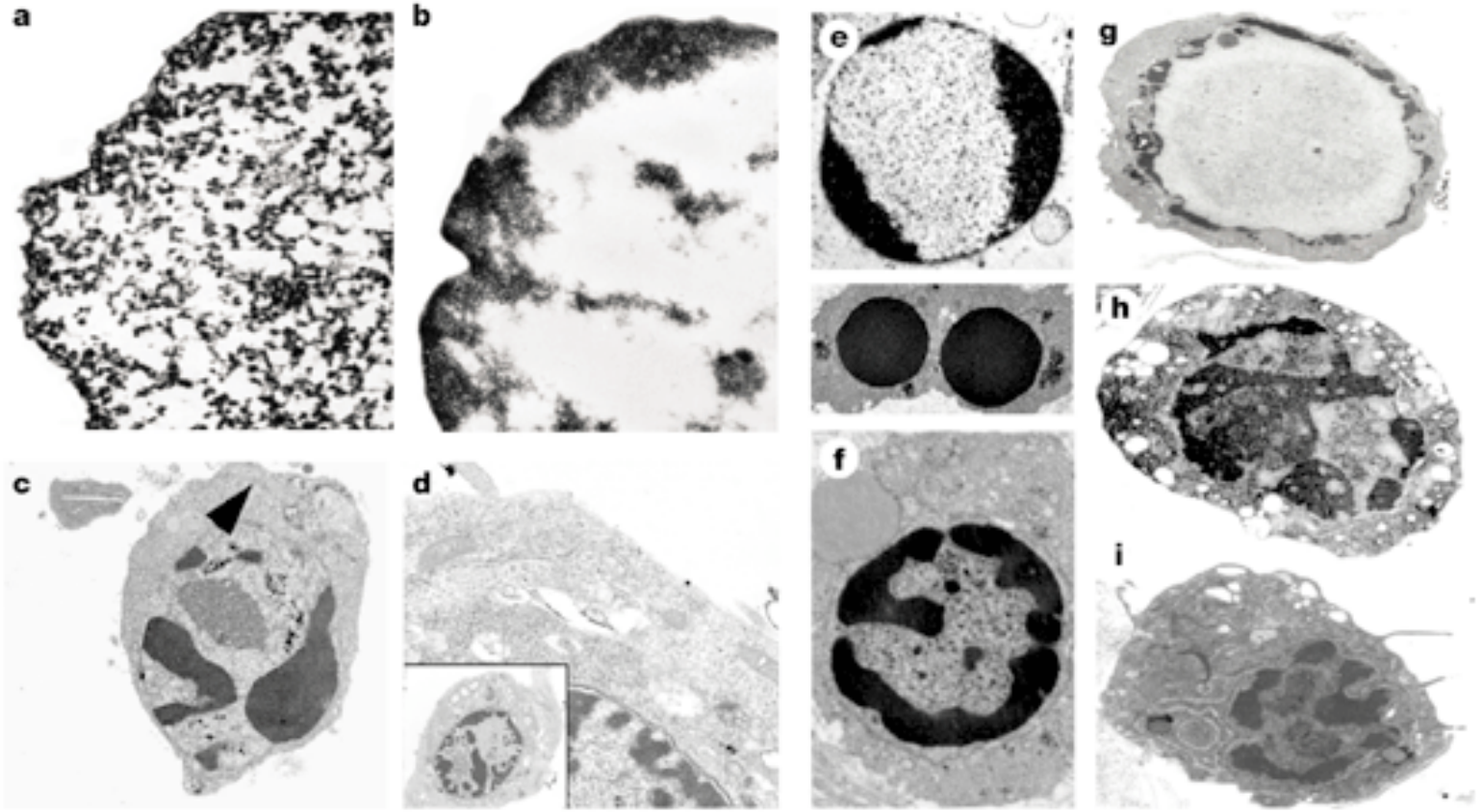
HOW DOES DEVELOPMENTAL CELL DEATH OCCUR?



APOPTOTIC DEATH	vs	NECROTIC DEATH
PRESENT IN DEVELOPING TISSUES		RESPONSE TO CELL INJURY, T
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 INTEGRIT & LOSS OF CYTOPLASMIC CON
PHAGOCYTOSIS OF APOPTOTIC BODIES		
ABSENCE OF INFLAMMATORY RESPONSE		INFLAMMATORY RESPONSE

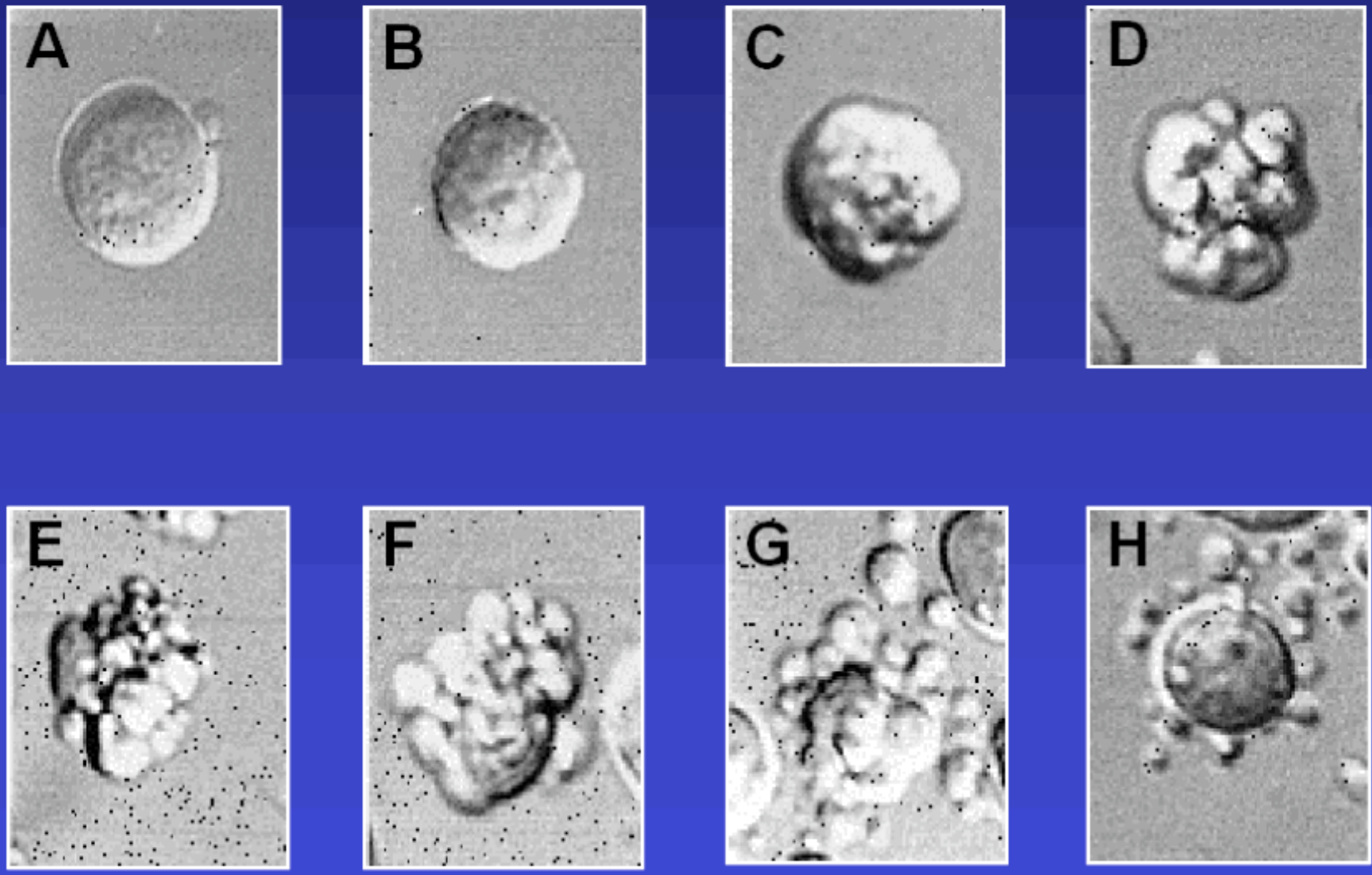
Kerr, Wylie and Currie

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



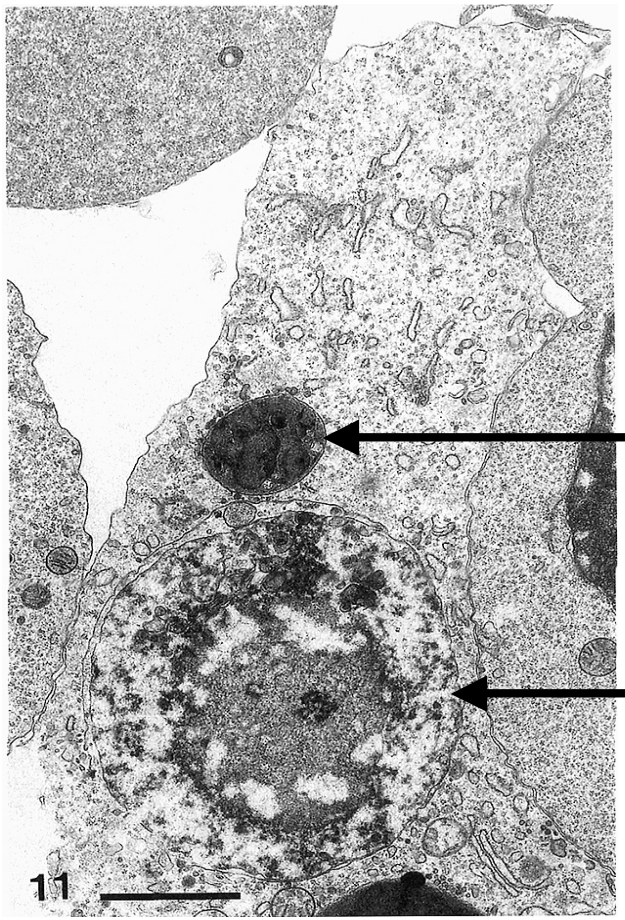
Nature Reviews | Molecular Cell Biology

TIME LAPSE IMAGES OF A CELL UNDERGOING APOPTOSI



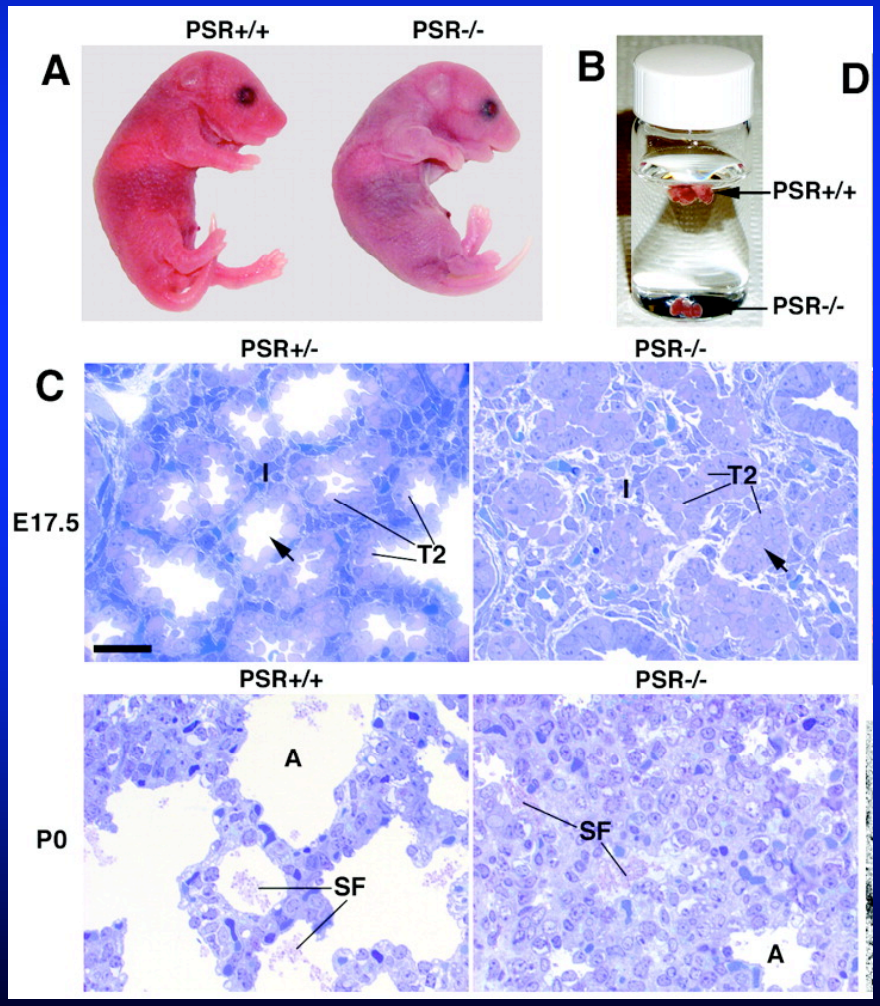
APOPTOTIC BODIES AND NUCLEI ARE CLEARED BY PHAGOCYTOSIS

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 LUN DEVELOPMENT AND RESPIRATORY SYMPTOMS SIMILAR TO THOSE IN HUMAN RESPIRATORY DISTRESS SYNDROME (RD



From: Li et al., Science: 302 (

WHAT ARE THE MECHANISMS BY WHICH CEL

DIE DURING DEVELOPMENT?

THERE ARE EVOLUTIONARILY CONSERVED MECHANISM

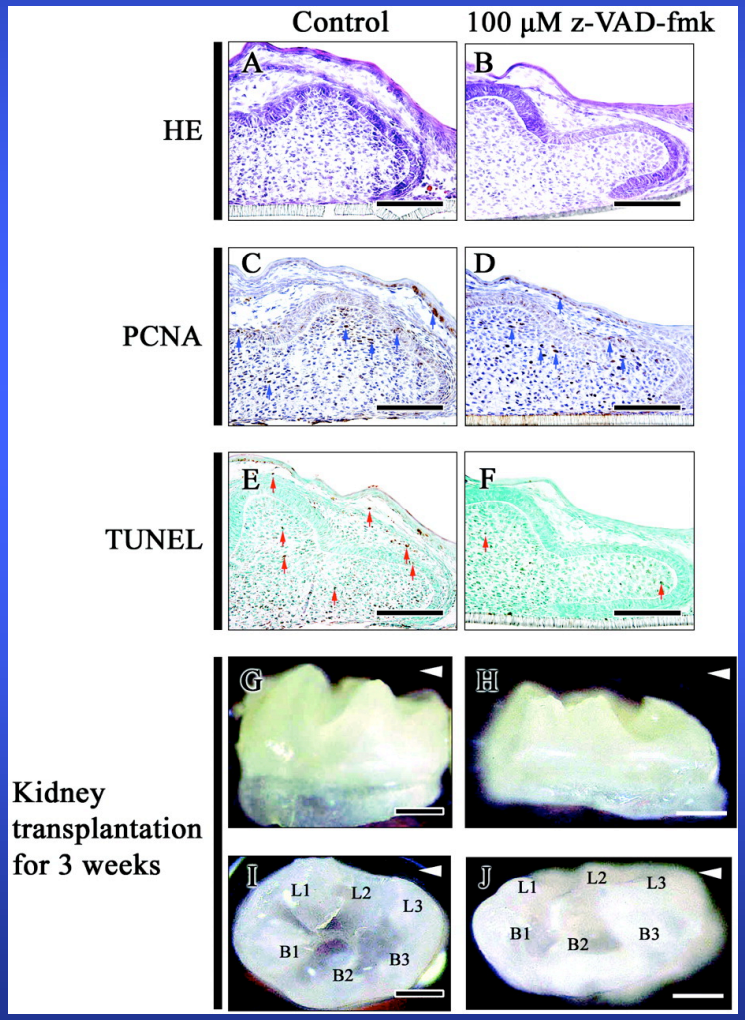
THAT GOVERN DEVELOPMENTAL CELL DEATH

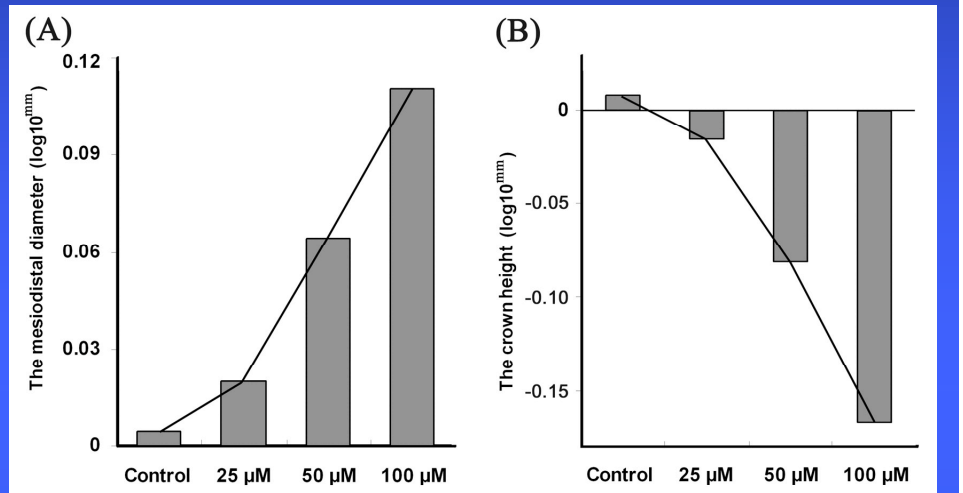
Robert Horvitz

CASPASES

- FAMILY OF EXECUTORS OF APOPTOTIC DEATH
- CYSTEINE PROTEASES THAT CLEAVE AFTER ASP
- CONSTITUTIVELY PRESENT AS INACTIVE FORMS
- ACTIVATED BY CLEAVAGE 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





(C)

	Control (N=19)		25μM Z-VAD-fmk (N=15)		50μM Z-VAD-fmk (N=15)		100μM Z-VAD-fmk (N=15)	
	Diameter	Height	Diameter	Height	Diameter	Height	Diameter	Height
Length (mm)	1.01	1.02	1.05	0.97	1.16	0.83	1.29	0.68
S.D.(±)	±0.10	±0.09	±0.11	±0.10	±0.10	±0.10	±0.11	±0.11

(D)

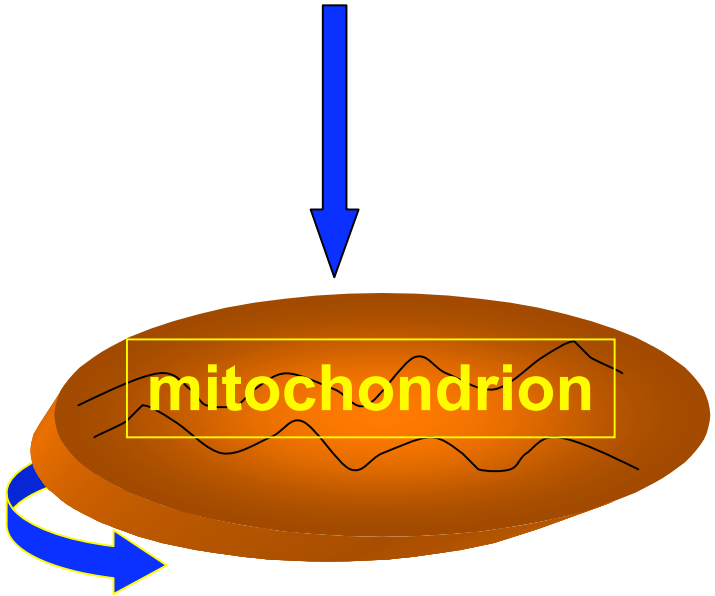
Numbers of PCNA and TUNEL positive cells per 100 μm^2

	PCNA	TUNEL
Control (N=15)	14.5 ± 5.5	4.5 ± 3.8*
100 μM z-VAD-fmk (N=15)	16.2 ± 5.8	0.9 ± 0.9*

From: Kim et al., J Dent Res 85: 530 (200

THE MITOCHONDRIAL PATHWAY OF APOPTOTIC DEATH -

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



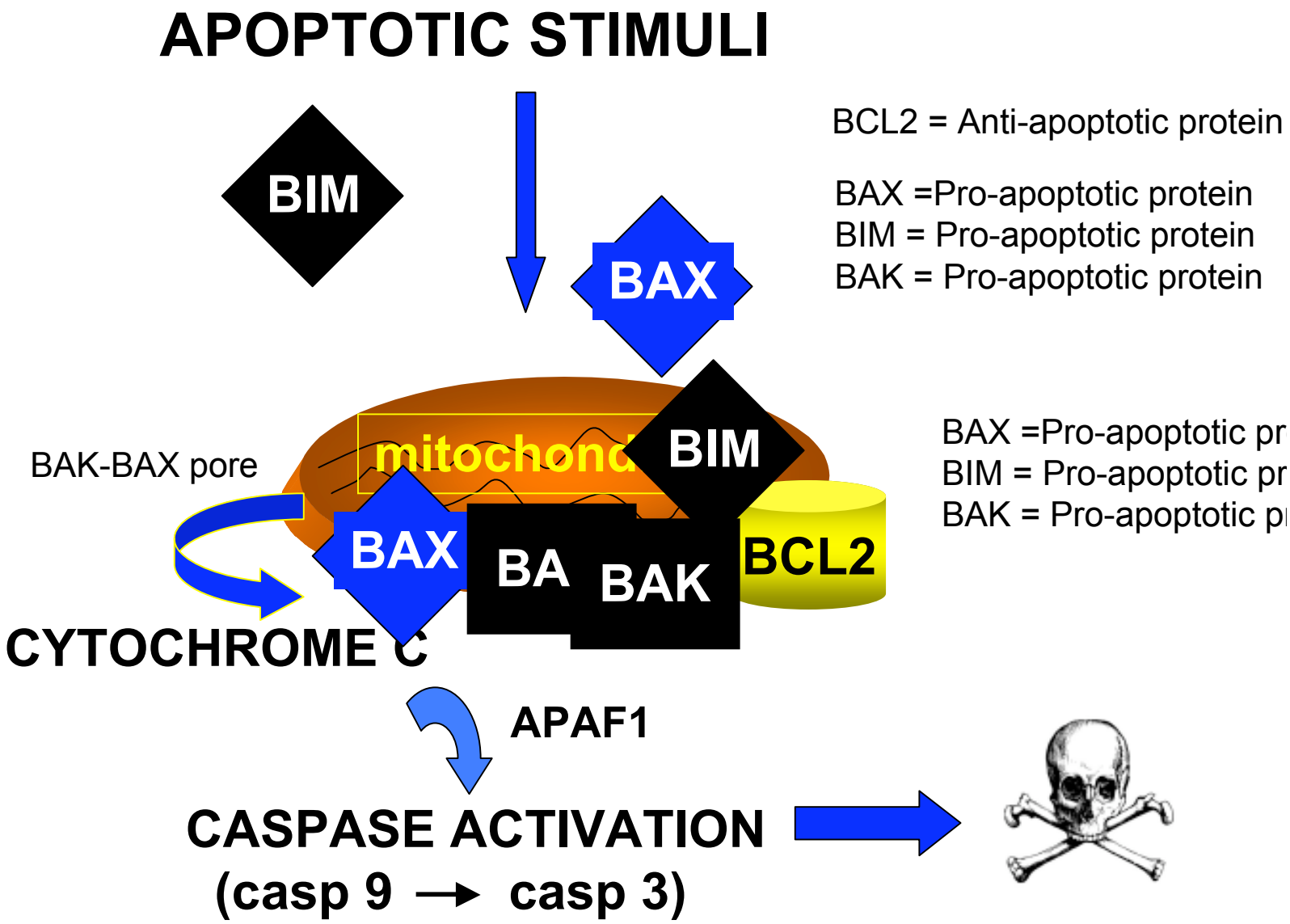
CYTOCHROME C

APAF1

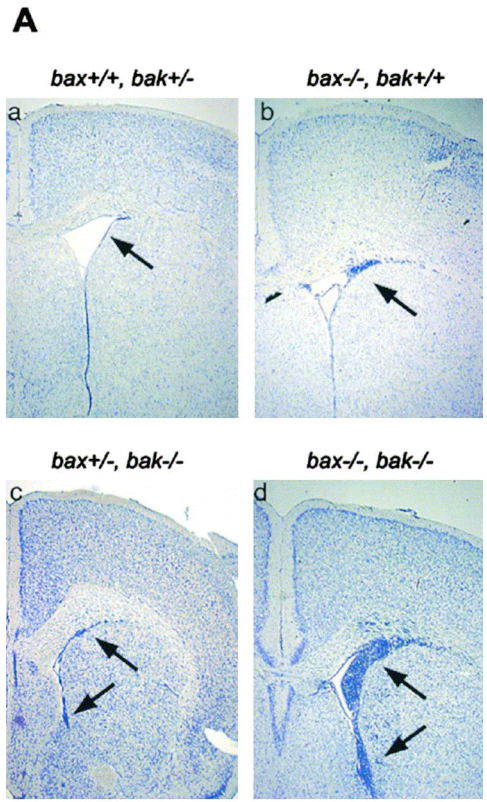
CASPASE ACTIVATION

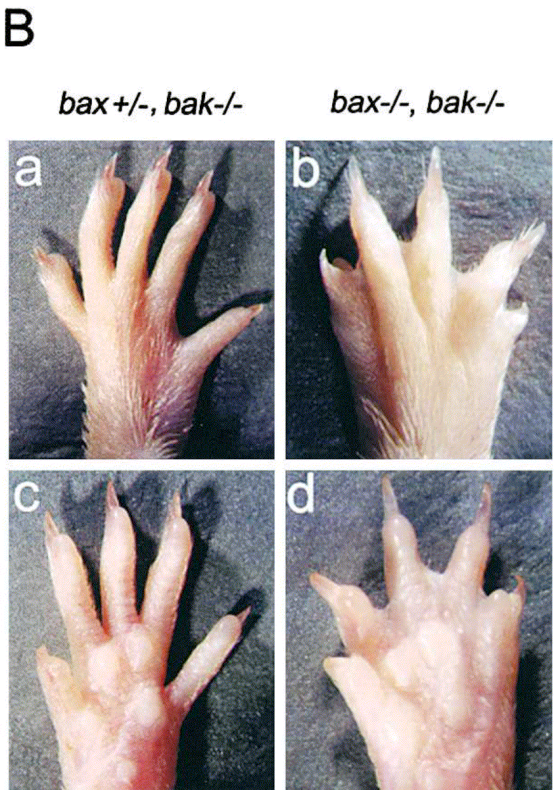
(casp 9 → casp 3)

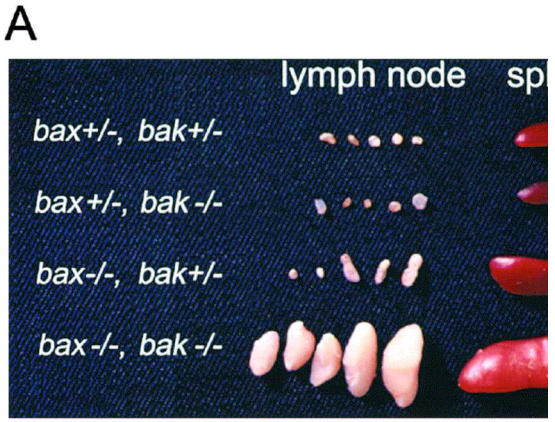
THE MITOCHONDRIAL PATHWAY OF APOPTOTIC DEATH -



ABNORMALITIES IN MICE LACKING BAX AND BAK







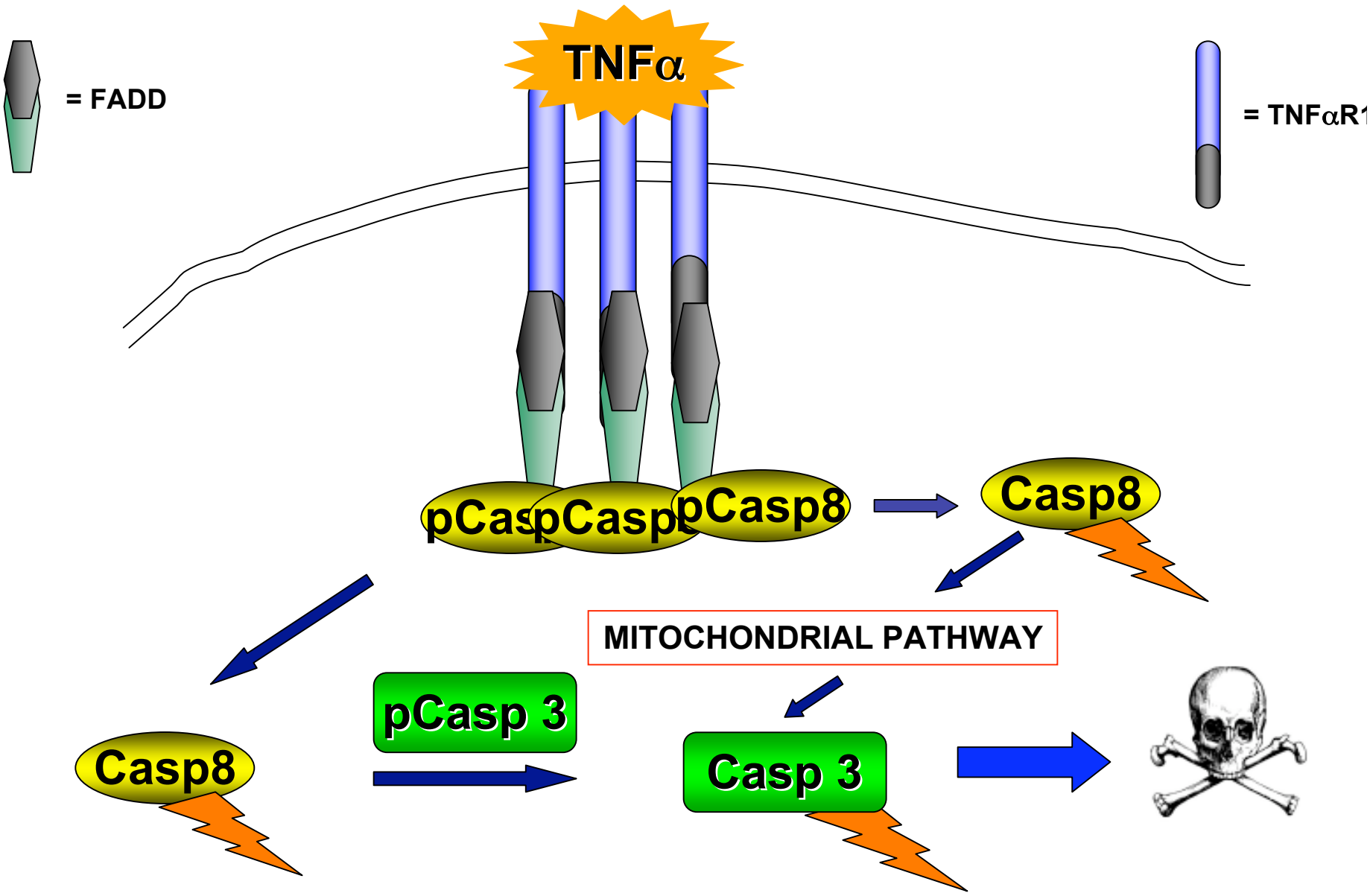
Arrow shows neuroprogenitors
in ventricular zone of embryonic brain

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

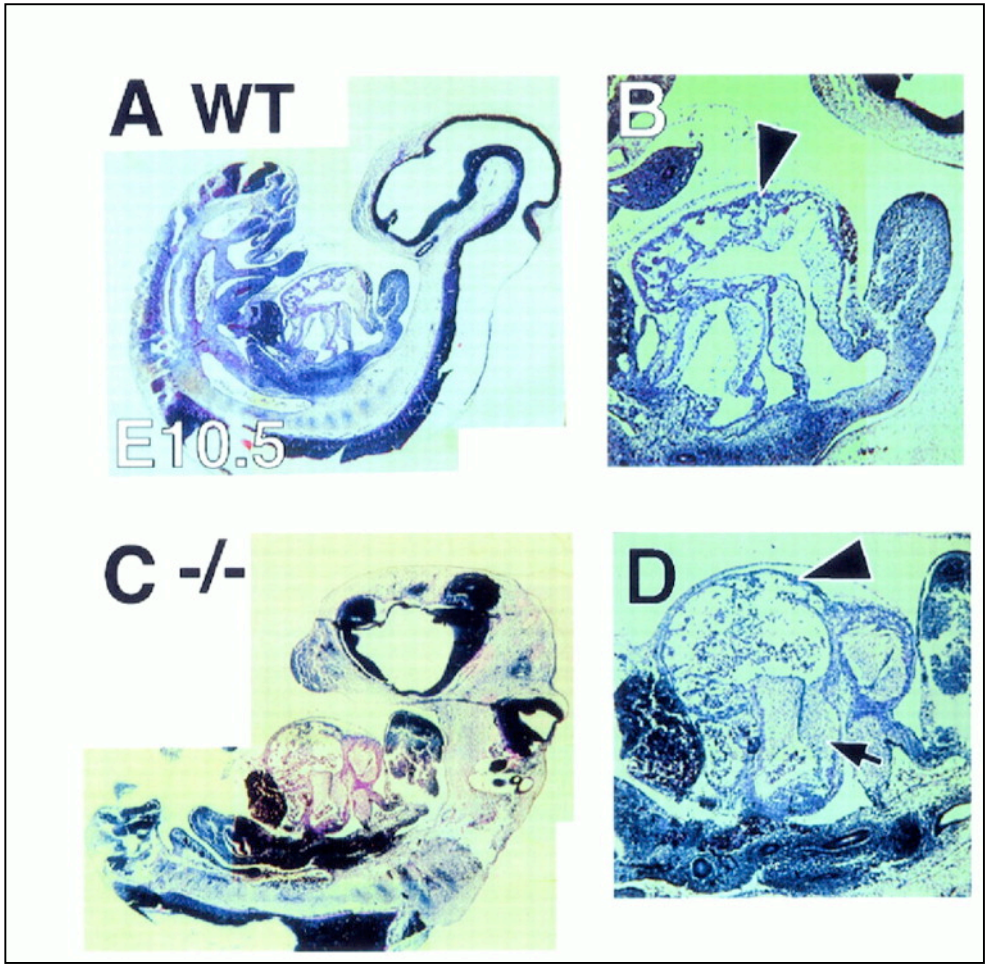
DEATH PROMOTING RECEPTORS AND LIGANDS
THE EXTRINSIC PATHWAY TO APOPTOTIC DEAT

LIGAND	RECEPTOR
TNFα	TNFαR1
FAS ligand	FAS
TRAIL	TRAIL-R

THE RECEPTOR-MEDIATED PATHWAY OF APOPTOTIC DEA



MICE LACKING FADD DIE DURING EMBRYOGENESIS AND HAVE MULTIPLE DEFECTS



Low power view:
A,C

B,D: Ventricul
Myocardium

Arrowhead sh
abnormal deve
trabeculae; ar
normal endoca
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
- MUTATION OF SPECIFIC APOPTOTIC GENES LEADS TO DEVELOPMENTAL ABNOMALITIES