

A microscopic image of a neuron, showing a dark, circular nucleus in the center, surrounded by a dense network of radiating processes in shades of red and orange. The text is overlaid on this image.

Apoptosis in Neurons

Jingjing Zang

3.10.2018

University of Zurich



Apoptosis in Neurons

Apoptosis

Apoptotic Machinery : Caspases & Bcl-2 family

The Neurotrophin Hypothesis

The Discovery of Nerve Growth Factor

The Neurotrophin Family

Neurotrophin Receptors

Developing NGF-dependent Sympathetic Neurons as Model

Reexamine Neurotrophin Hypothesis in CNS

Why do Neurons Die during Development?



Apoptosis

Spatially and temporally reproducible and species-specific loss of large numbers of individual cells during development



Br. J. Cancer (1972) **26**, 239

APOPTOSIS: A BASIC BIOLOGICAL PHENOMENON WITH WIDE-RANGING IMPLICATIONS IN TISSUE KINETICS

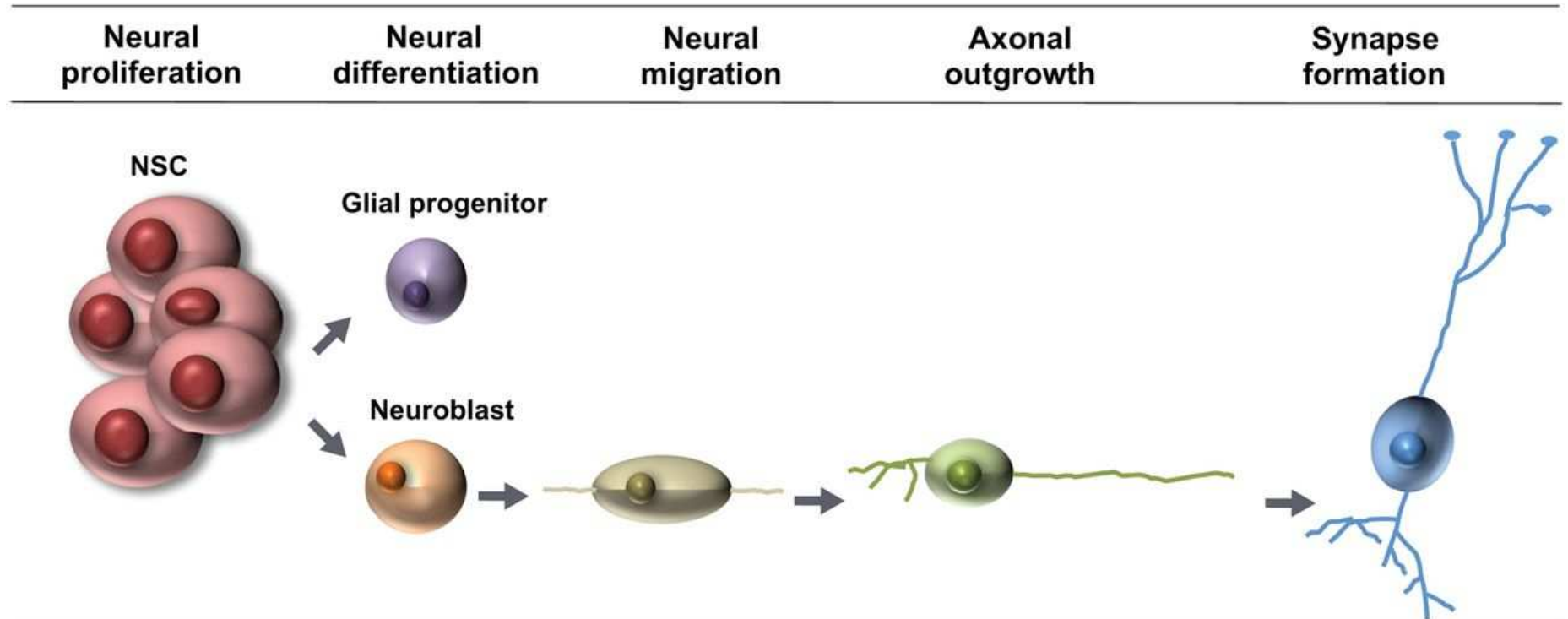
J. F. R. KERR*, A. H. WYLLIE AND A. R. CURRIE†

From the Department of Pathology, University of Aberdeen





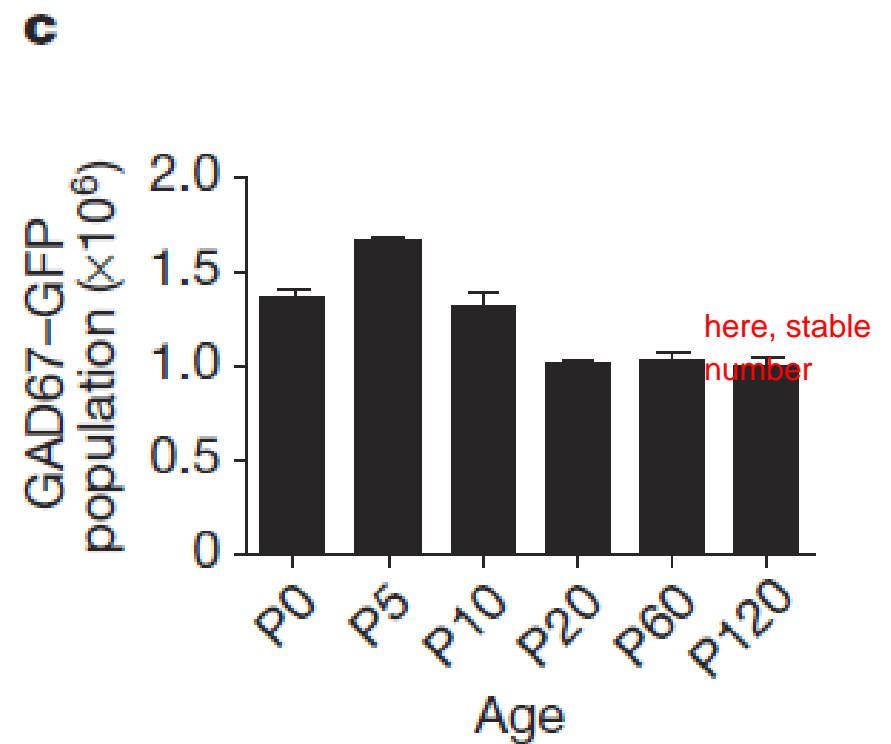
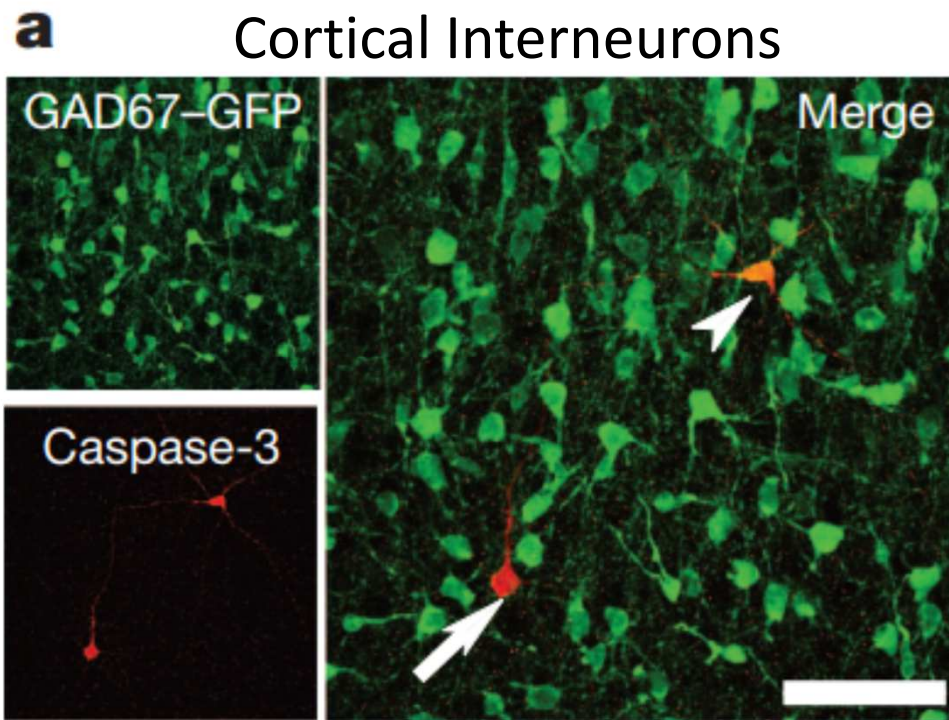
Neural Development



injury induced cell death is not apoptosis



So Many Neurons Die during Development

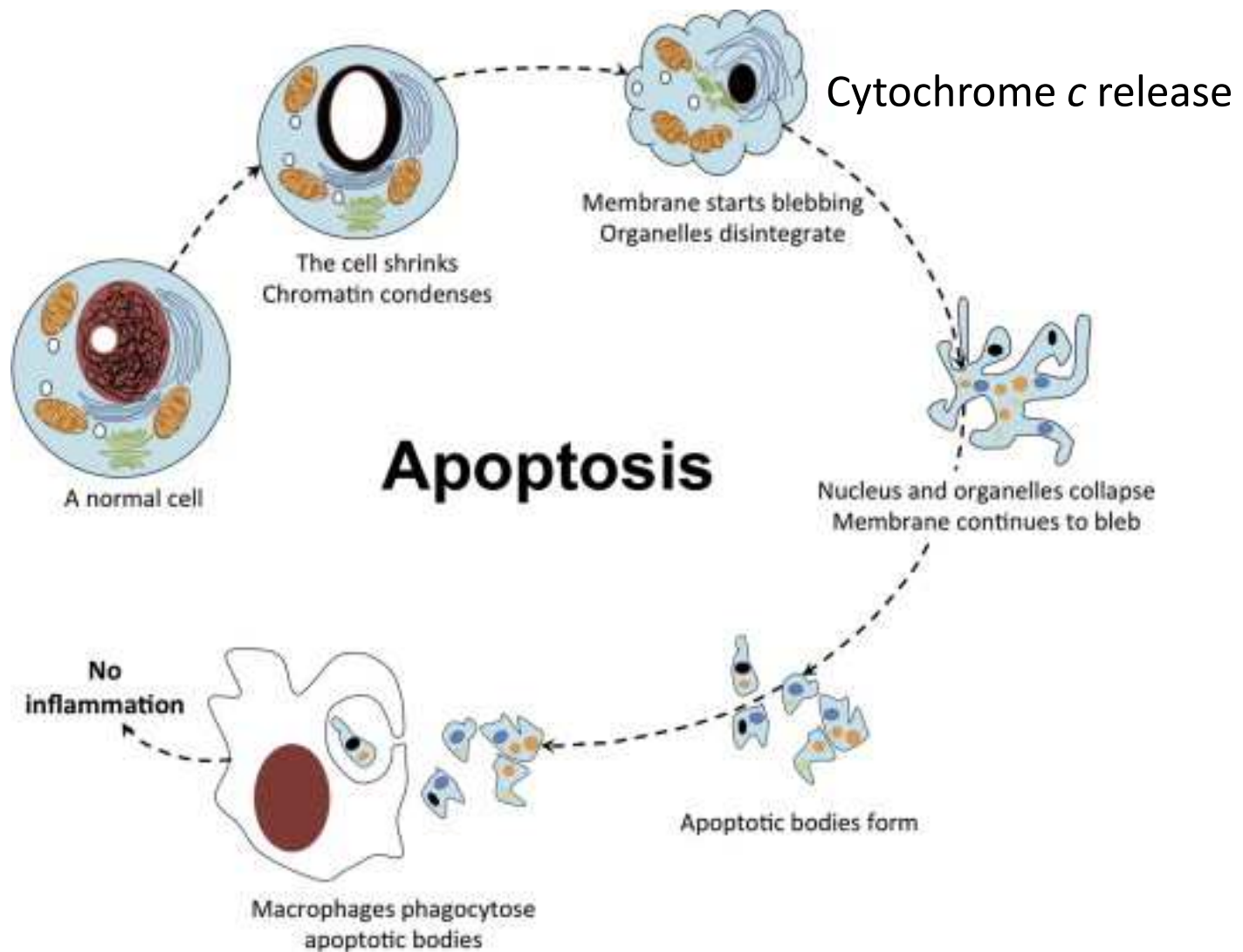


Casp3 is an apoptotic marker (red cells undergo apoptosis)

Southwell et al 2012

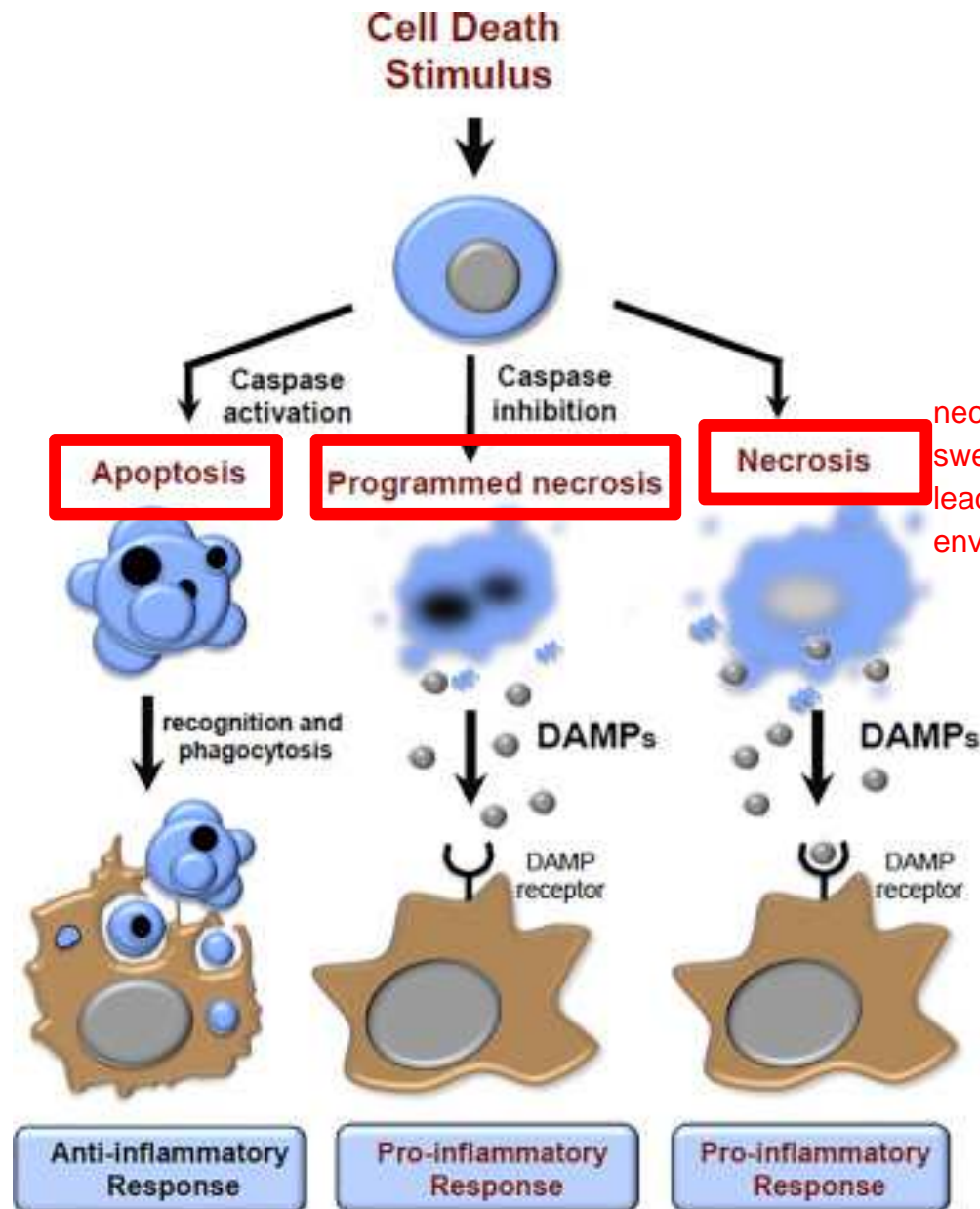


Apoptosis is Associated with Morphological Changes





Apoptosis V.S. Necroptosis V.S. Necrosis



necrosis: induced by cell trauma.
swelling of cell and rupture of membrane
leads to release of contents into
environemnt



Apoptosis in Neurons

Apoptosis

Apoptotic Machinery : Caspases & Bcl-2 family

The Neurotrophin Hypothesis

- The Discovery of Nerve Growth Factor

- The Neurotrophin Family

- Neurotrophin Receptors

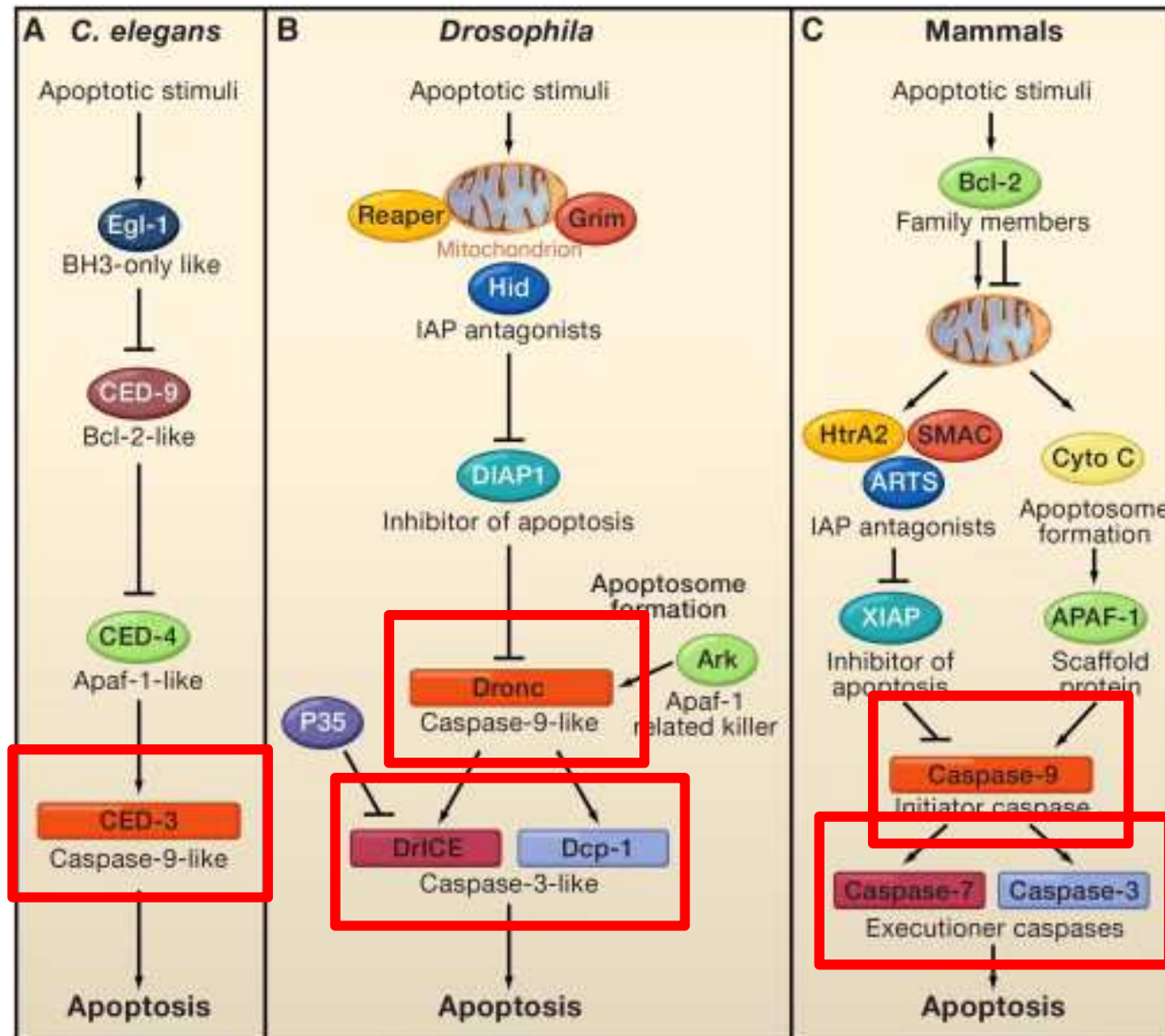
- Developing NGF-dependent Sympathetic Neurons as Model

- Reexamine Neurotrophin Hypothesis in CNS

Why do Neurons Die during Development?



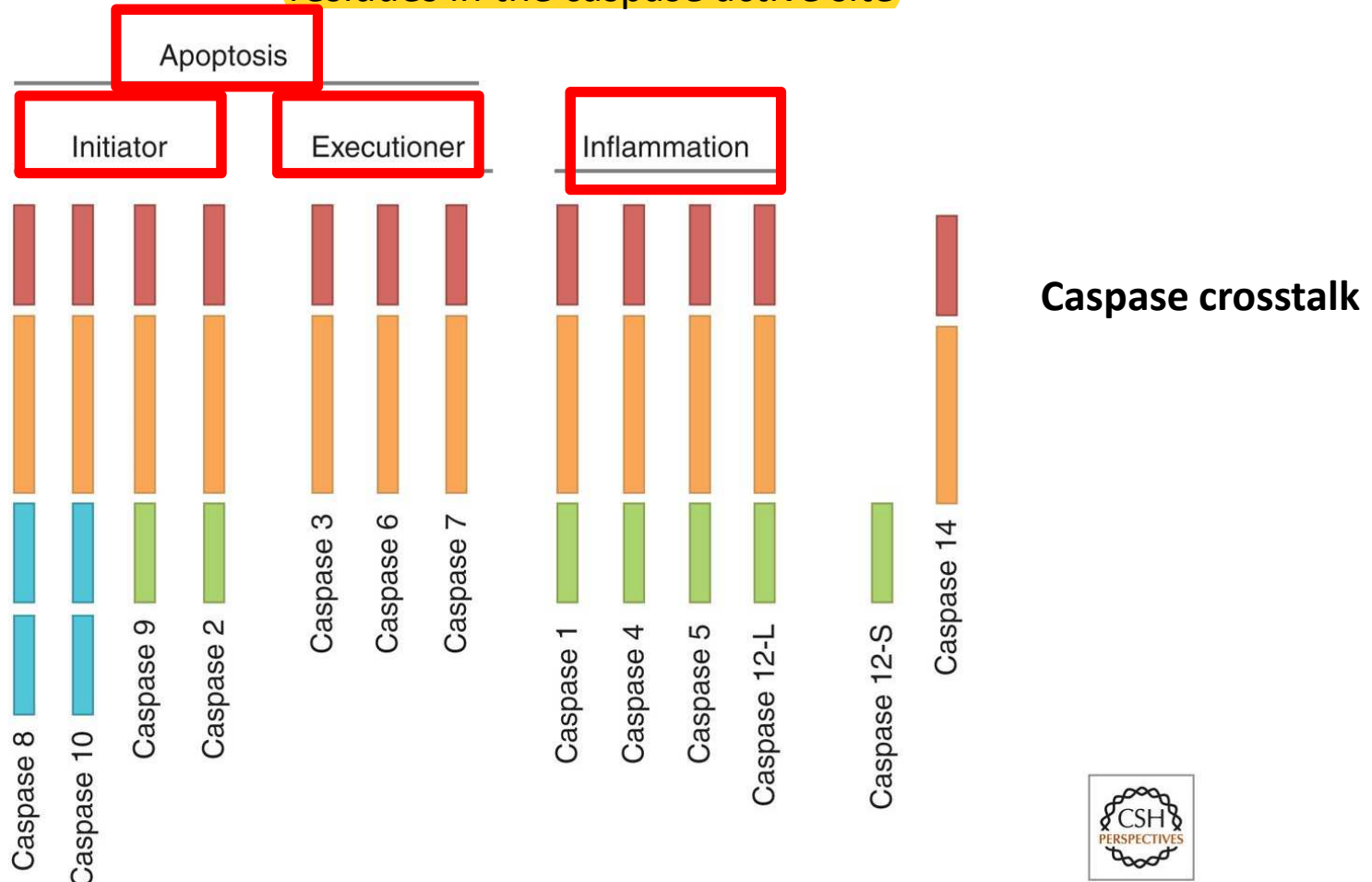
Evolutionary Conservation of the Core Apoptotic Machinery





Domain Structure of Human Caspases

Proteases that hydrolyze peptide bonds in a reaction that depends on cysteine residues in the caspase active site

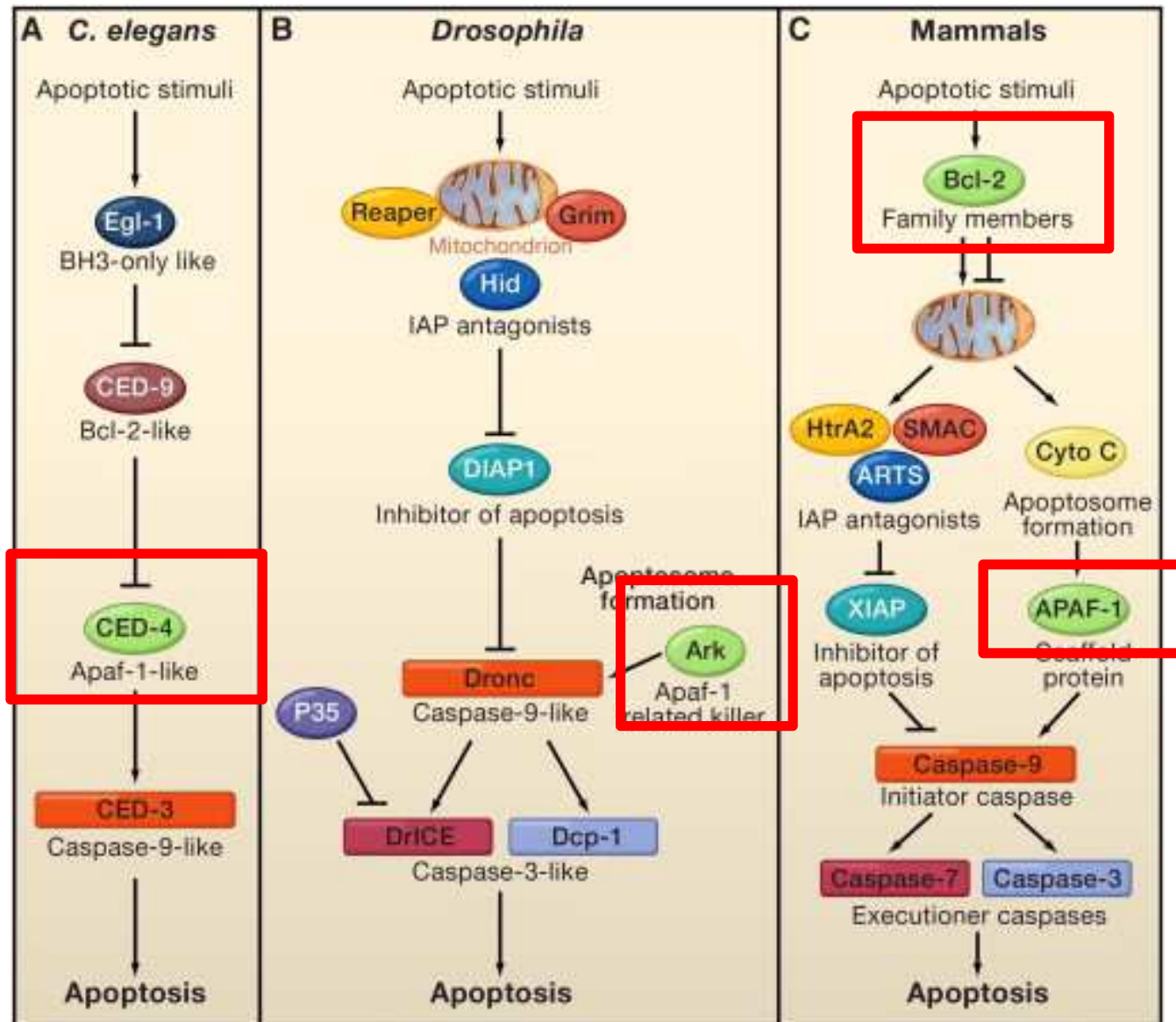


David R. McIlwain et al. Cold Spring Harb Perspect Biol
2013;5:a008656



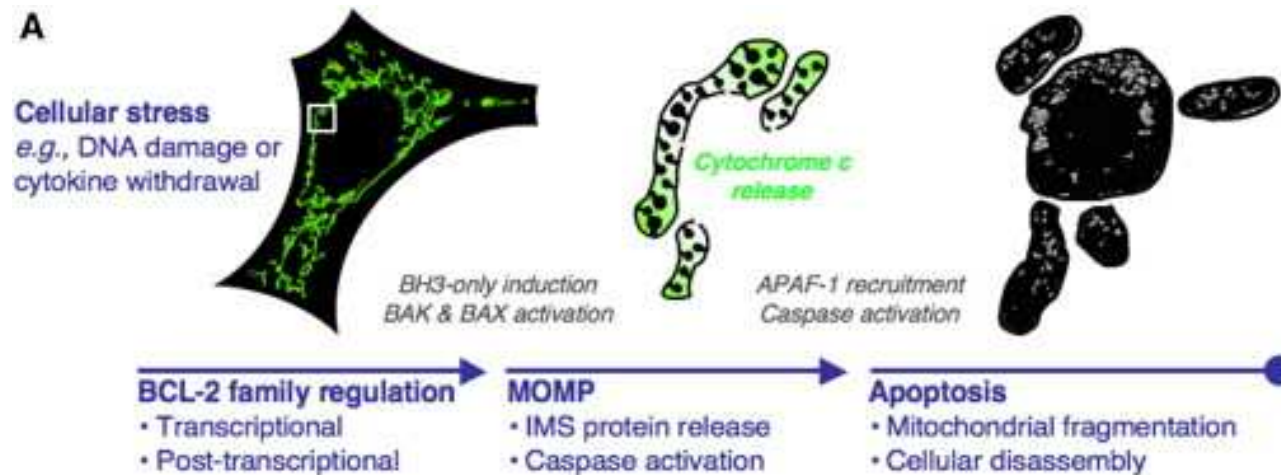


Evolutionary Conservation of the Core Apoptotic Machinery





Release of Cytochrome c is Regulated by the Bcl-2 Family



B

Anti-apoptotic BCL-2 family proteins

- A1, BCL-2, BCL-w, BCL-xL and MCL-1

BCL-2 family effector proteins

- BAK and BAX

Direct activator BH3-only proteins

- Direct activators: BID and BIM

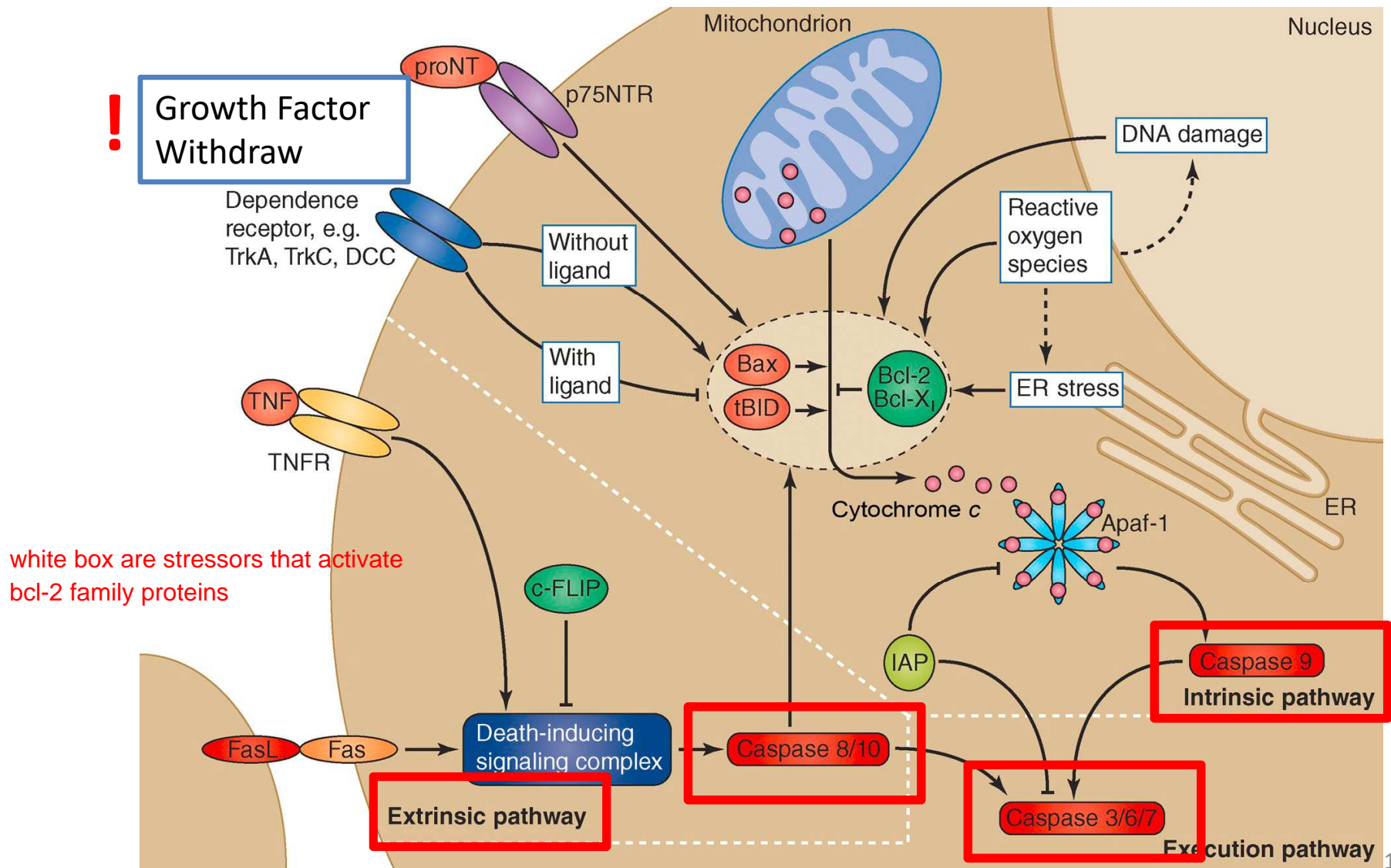
Sensitizers/de-repressors BH3-only proteins

- BAD, BIK, BMF, HRK, Noxa and PUMA

Pro-apoptotic



Mammalian Apoptotic Machinery



white box are stressors that activate bcl-2 family proteins



Apoptosis in Neurons

Apoptosis

Apoptotic Machinery : Caspases & Bcl-2 family

The Neurotrophin Hypothesis

The Discovery of Nerve Growth Factor

The Neurotrophin Family

Neurotrophin Receptors

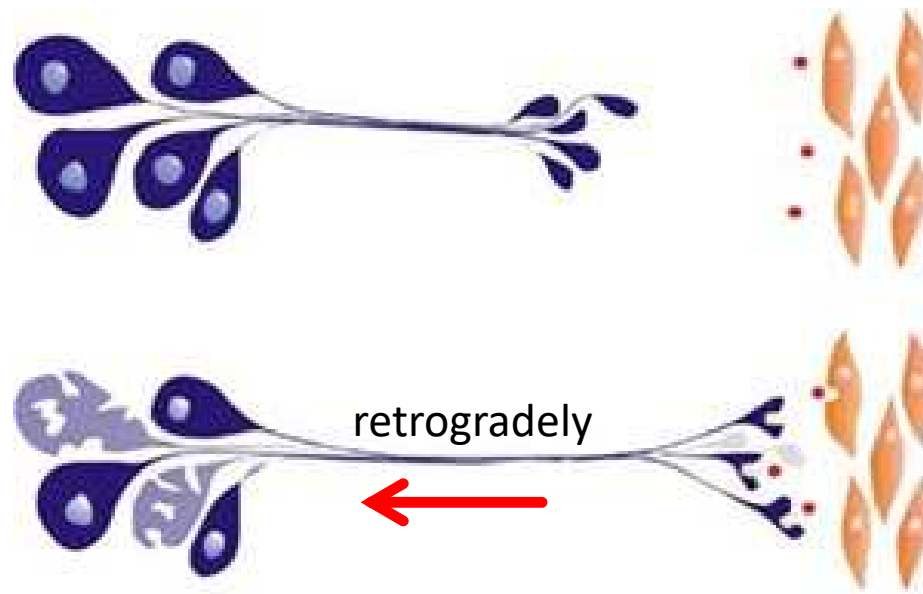
Developing NGF-dependent Sympathetic Neurons as Model

Reexamine Neurotrophin Hypothesis in CNS

Why do Neurons Die during Development?



The Neurotrophic Hypothesis





The Discovery of Nerve Growth Factor

The Prototype Target-Derived Neuronal Survival Factor

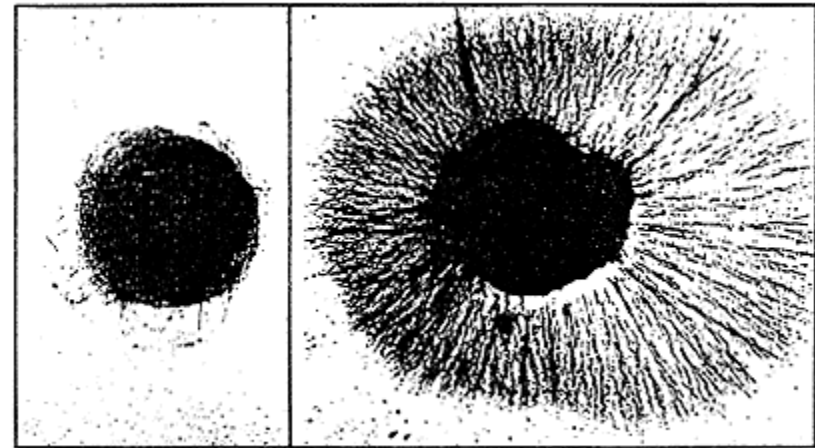
The Nobel Prize in Physiology or Medicine 1986



Stanley Cohen
Prize share: 1/2



Rita Levi-Montalcini
Prize share: 1/2



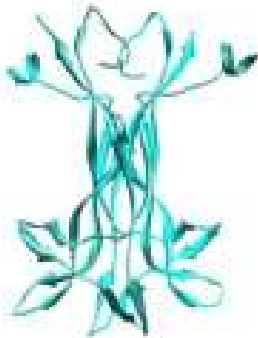
The Nobel Prize in Physiology or Medicine 1986 was awarded jointly to Stanley Cohen and Rita Levi-Montalcini *"for their discoveries of growth factors"*



The Neurotrophin Family

a

NGF



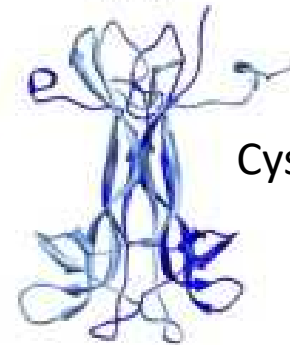
BDNF



NT3



NT4

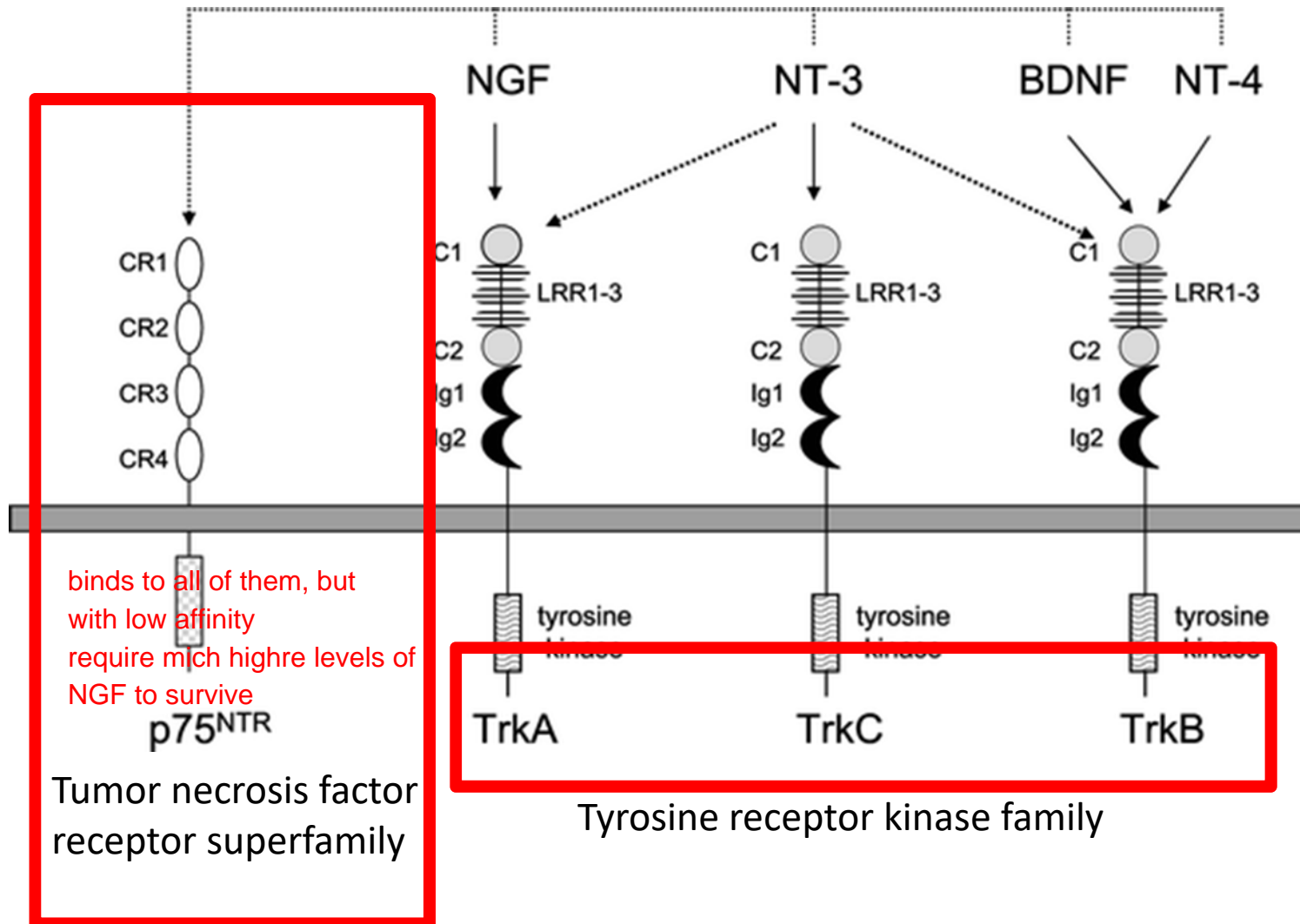


Cysteine knot



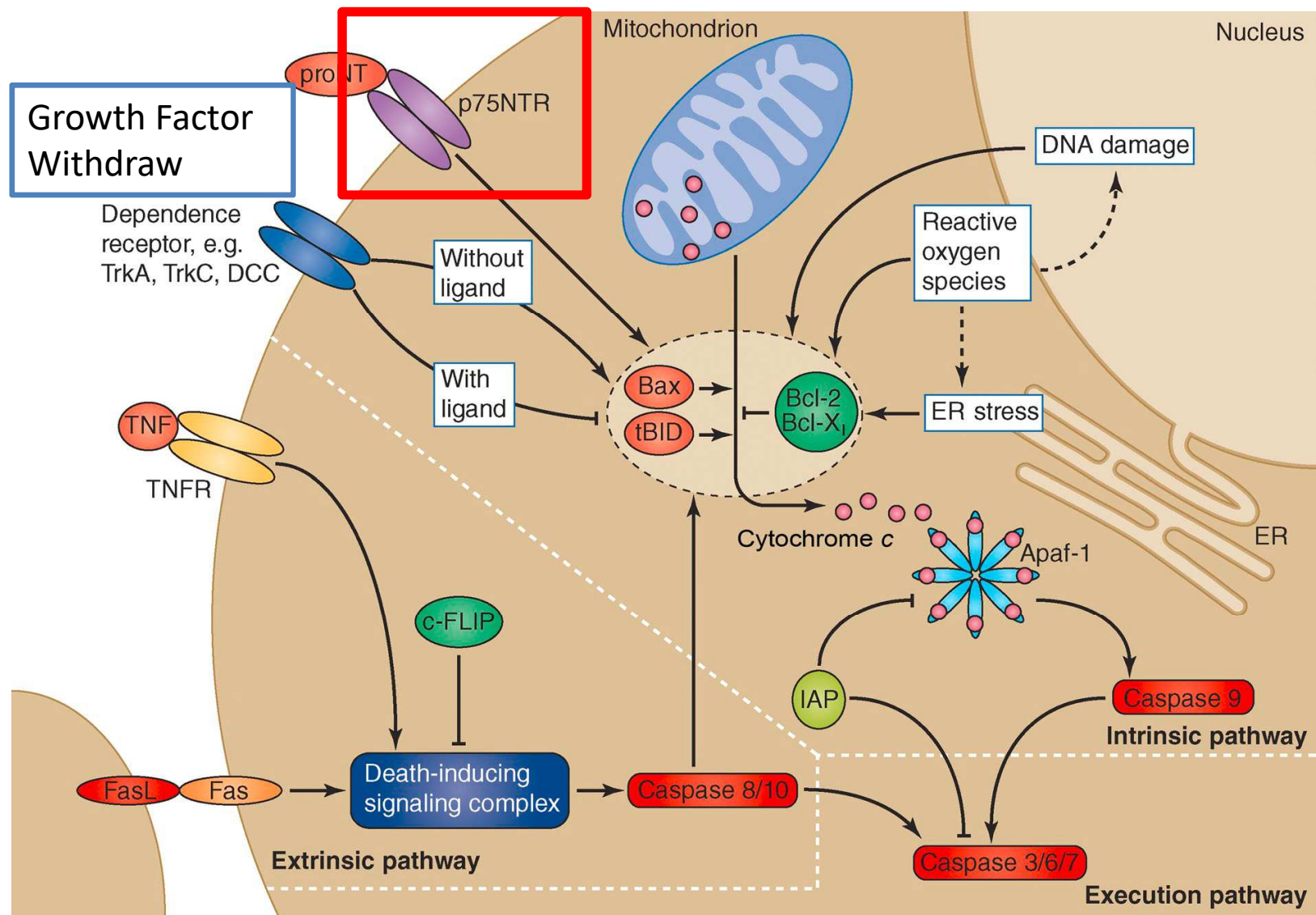
Neurotrophin Receptors

Anti-apoptosis





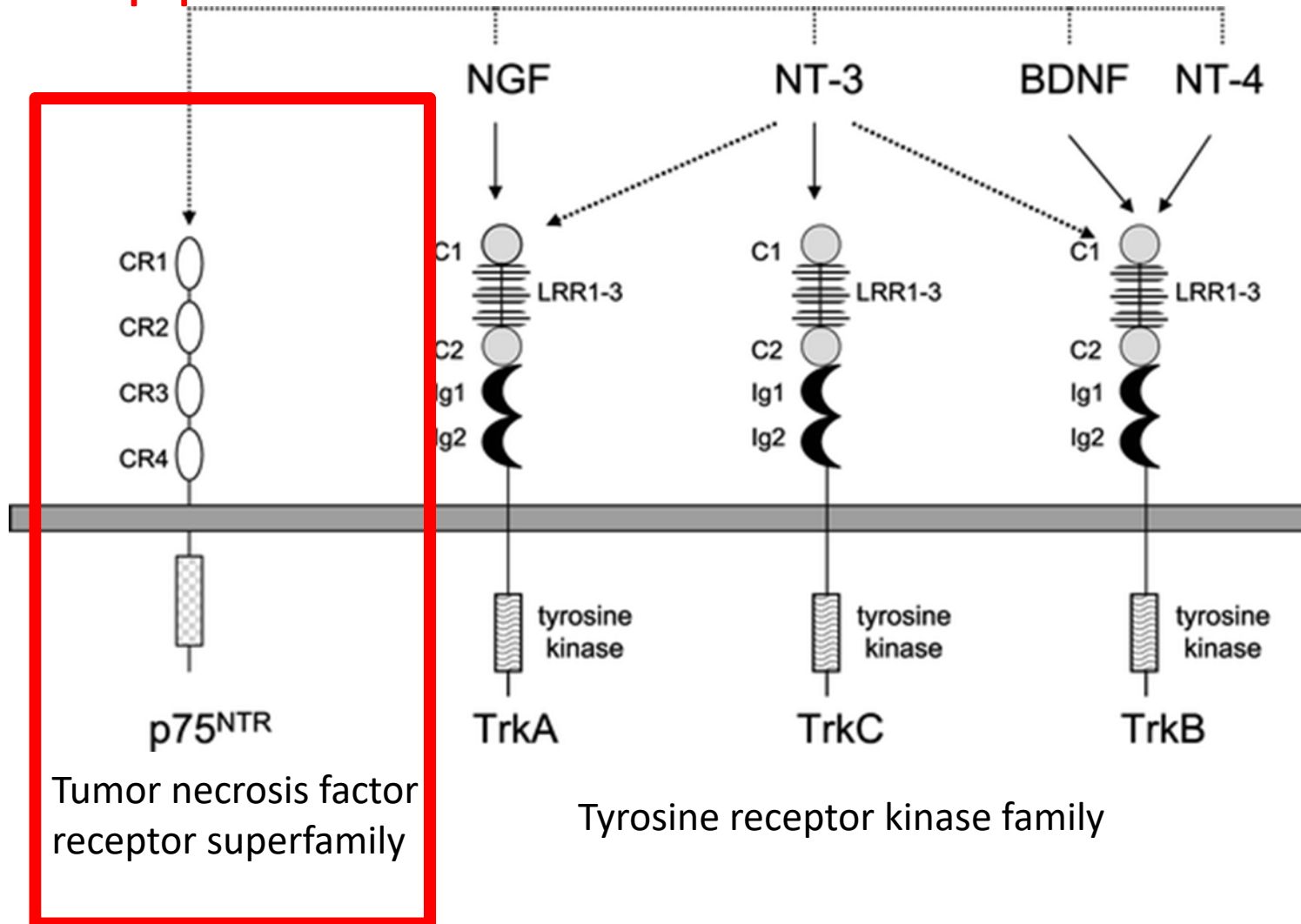
Mammalian Apoptotic Machinery





Neurotrophin Receptors

Anti-apoptosis
Pro-apoptosis





Apoptosis in Neurons

Apoptosis

Apoptotic Machinery : Caspases & Bcl-2 family

The Neurotrophin Hypothesis

The Discovery of Nerve Growth Factor

The Neurotrophin Family

Neurotrophin Receptors

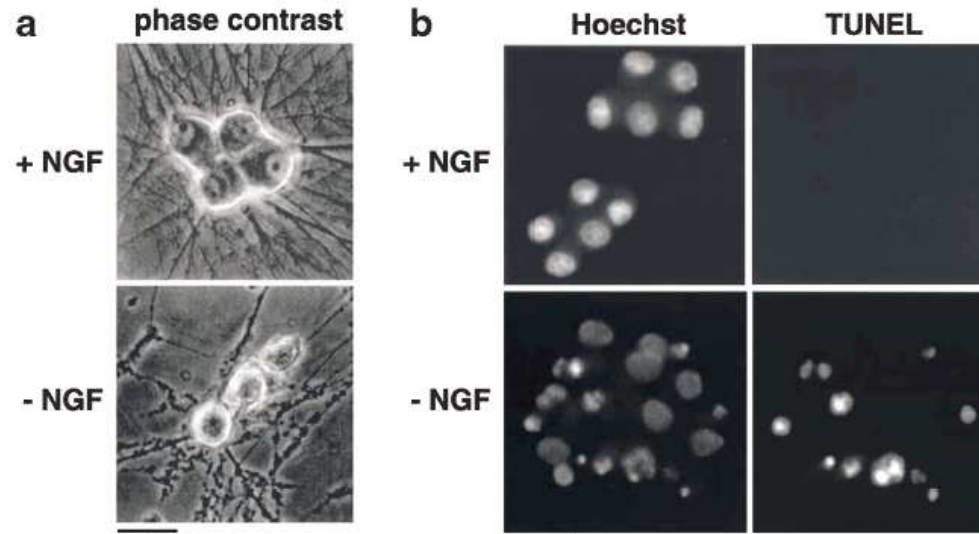
Developing NGF-dependent Sympathetic Neurons as Model

Reexamine Neurotrophin Hypothesis in CNS

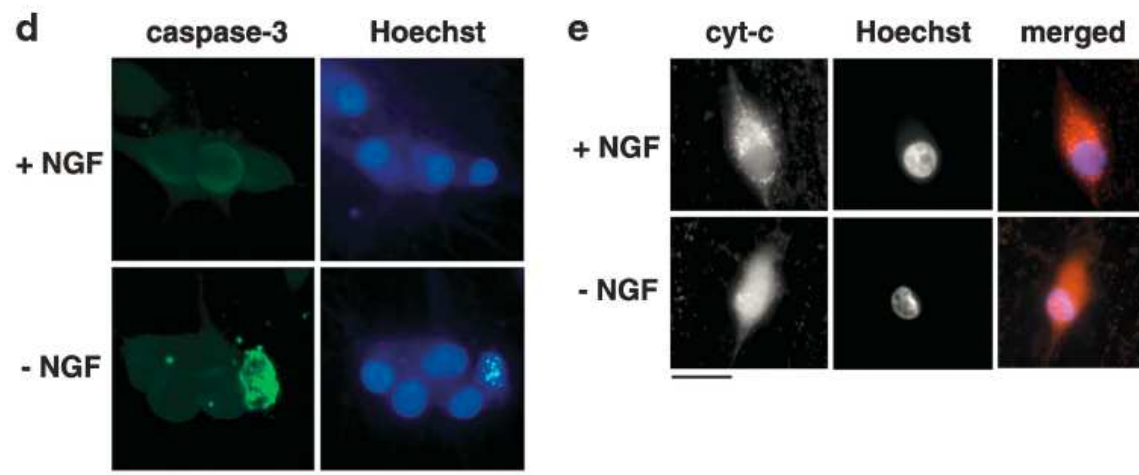
Why do Neurons Die during Development?



Morphological and Biochemical Changes Following NGF Withdrawal

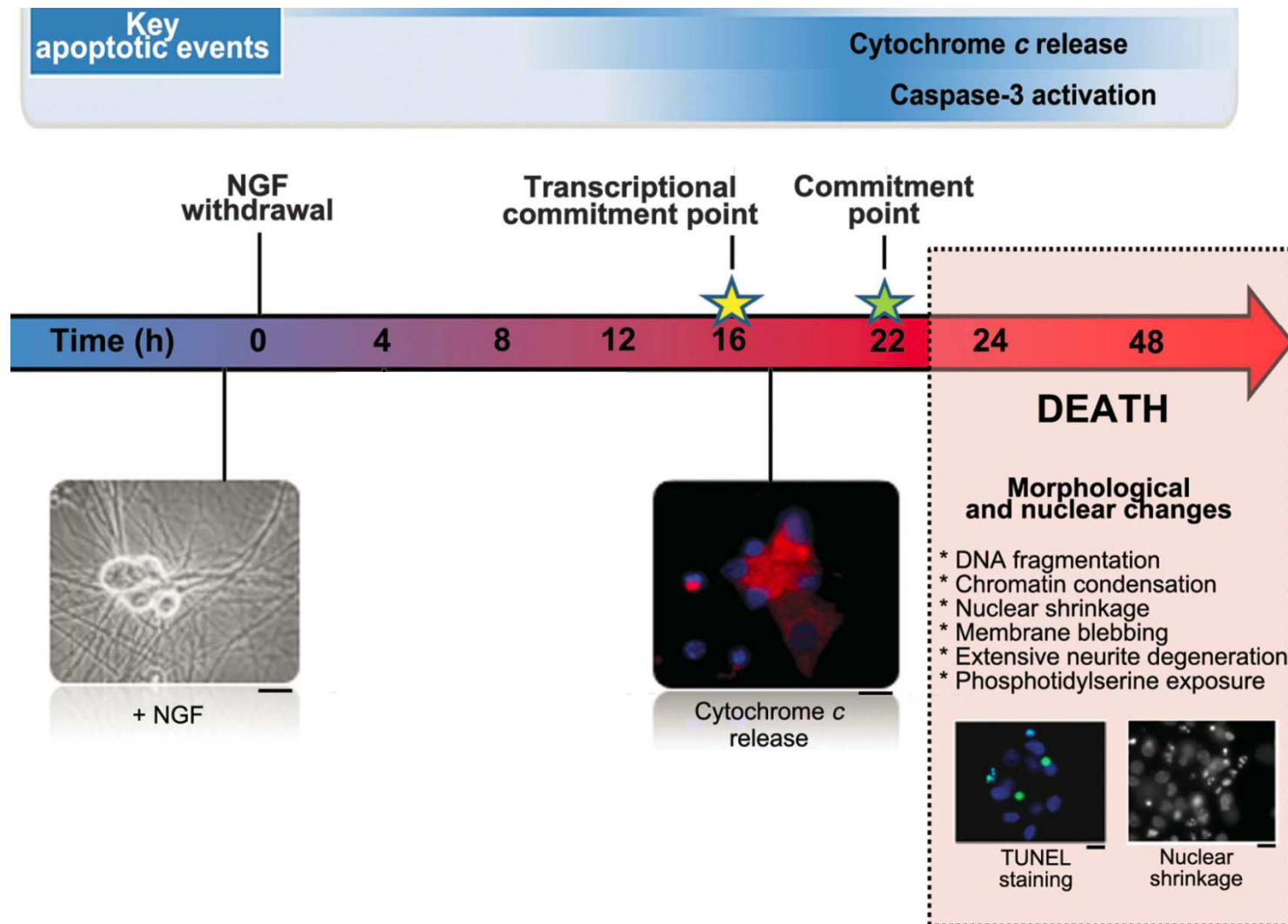


hoechst: marker to stain DNA
in dying neuron, the staining different
TUNEL stains DNA fragmentation
specifically, no stain in normals, but
staining in dying cells. important apoptotic
markers



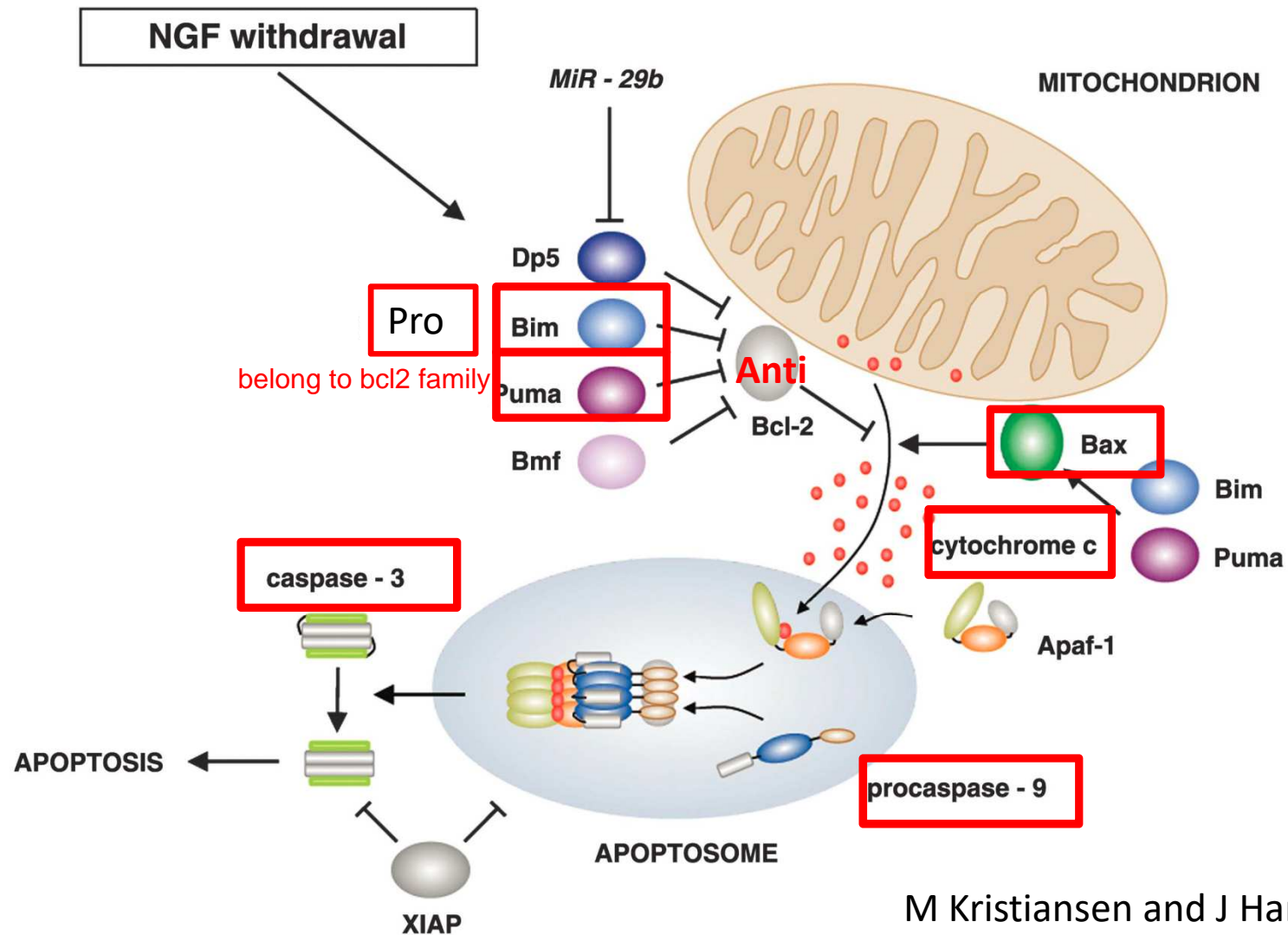


Key Events Following NGF Withdrawal



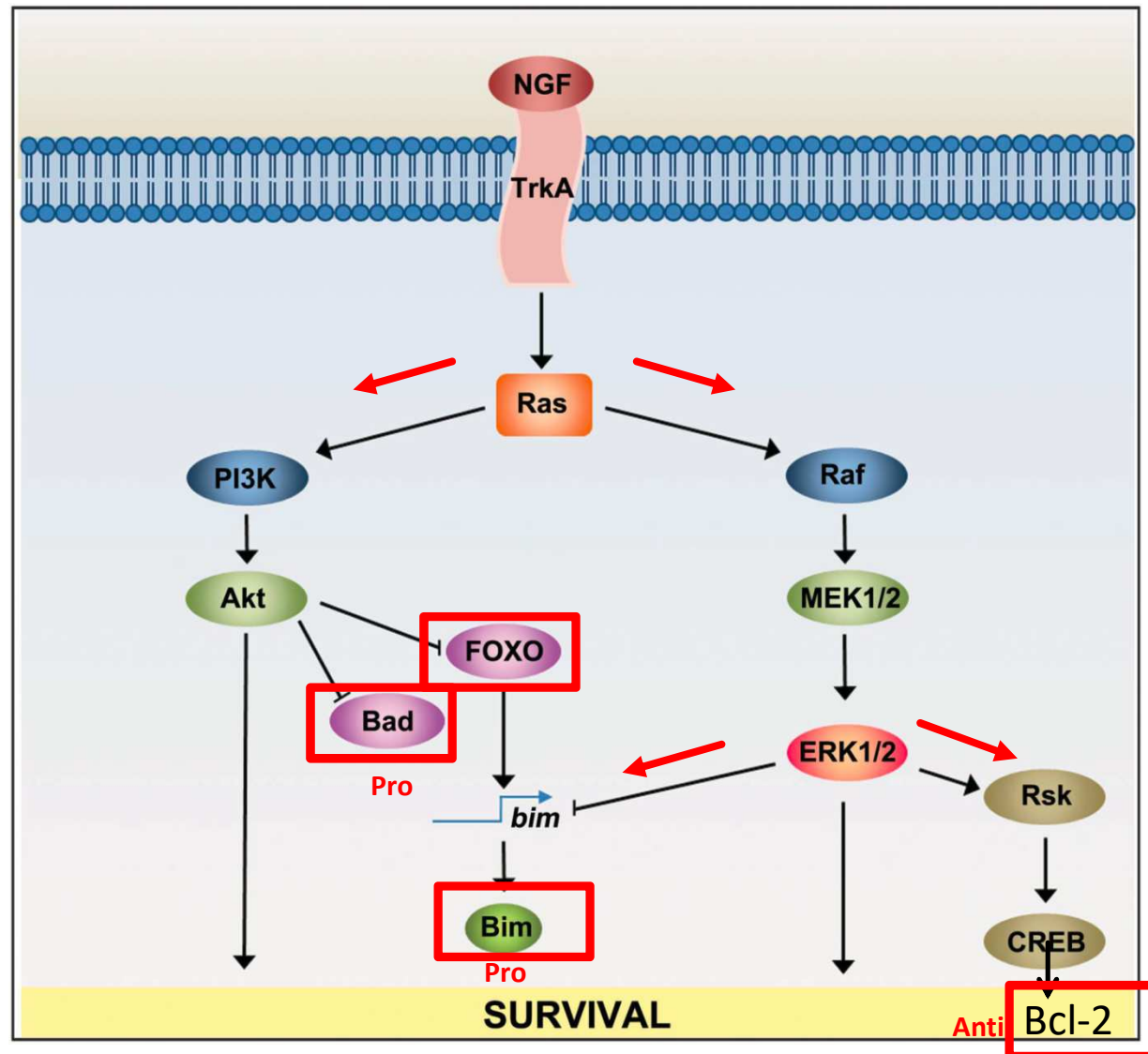


NGF Withdrawal Activates the Intrinsic Pathway of Apoptosis





Survival Pathways Activated by the Binding of NGF to TrkA





Apoptosis in Neurons

Apoptosis

Apoptotic Machinery : Caspases & Bcl-2 family

The Neurotrophin Hypothesis

The Discovery of Nerve Growth Factor

The Neurotrophin Family

Neurotrophin Receptors

Developing NGF-dependent Sympathetic Neurons as Model

Reexamine Neurotrophin Hypothesis in CNS

Why do Neurons Die during Development?



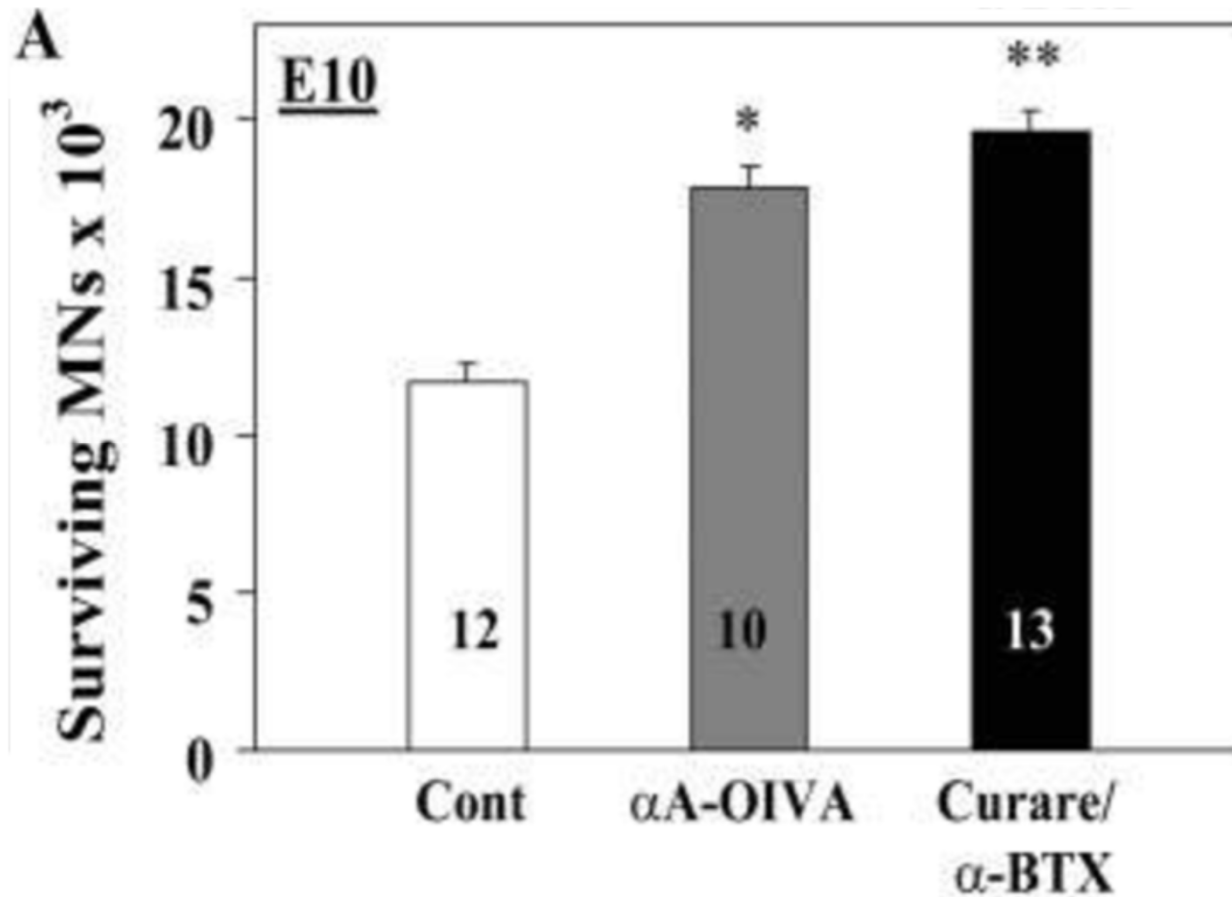
Apoptosis in CNS

- Neuronal Activity and Neurotransmitter Input
- Intrinsic Mechanisms vs. Neurotrophic Hypothesis



Synaptic Transmission: Pro-Apoptosis

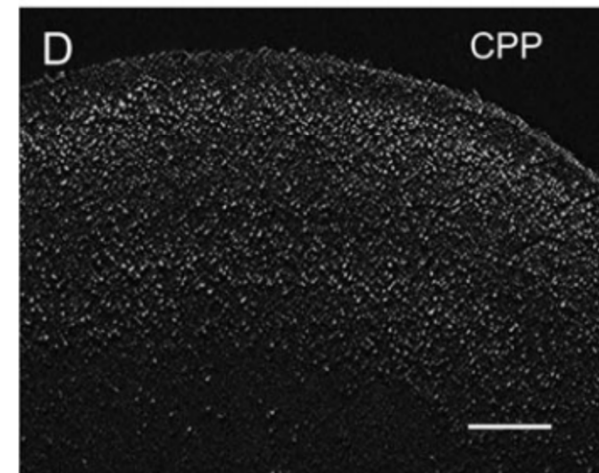
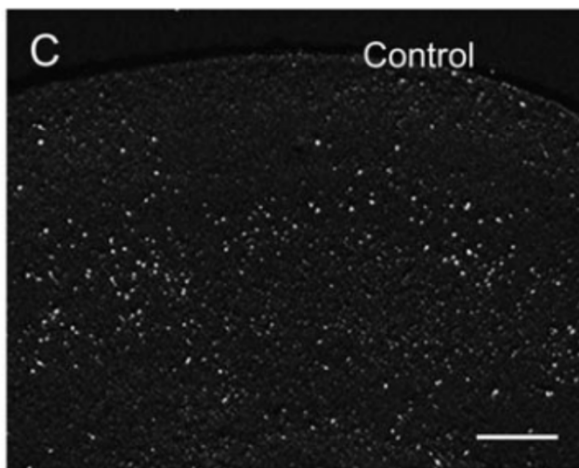
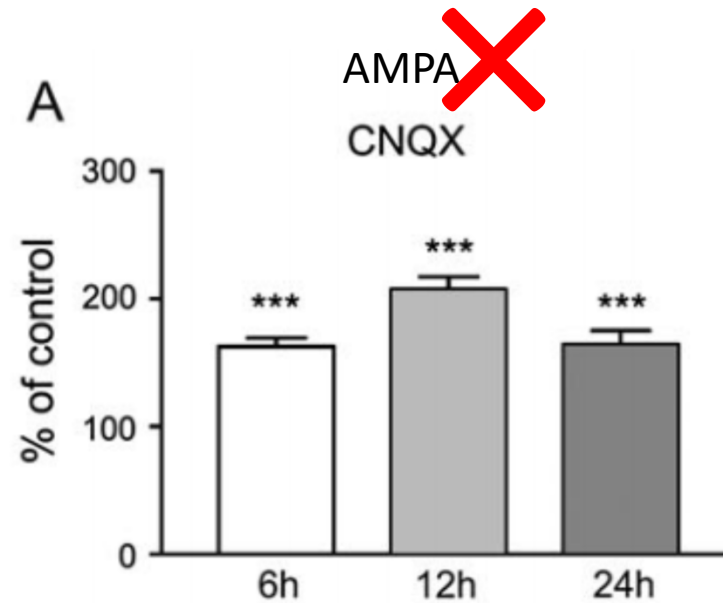
Spinal Cord Motoneurons



Oppenheim et al 2008



Synaptic Transmission: Pro-Survival

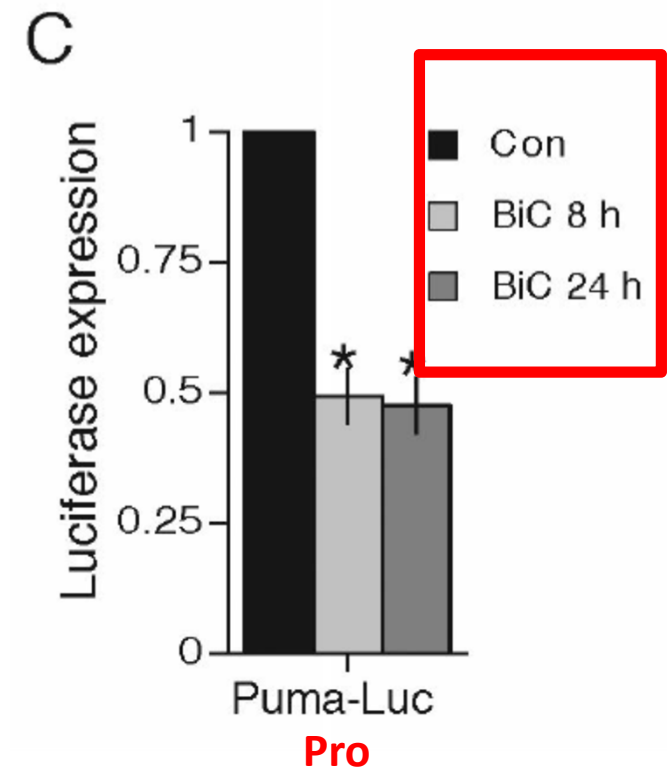
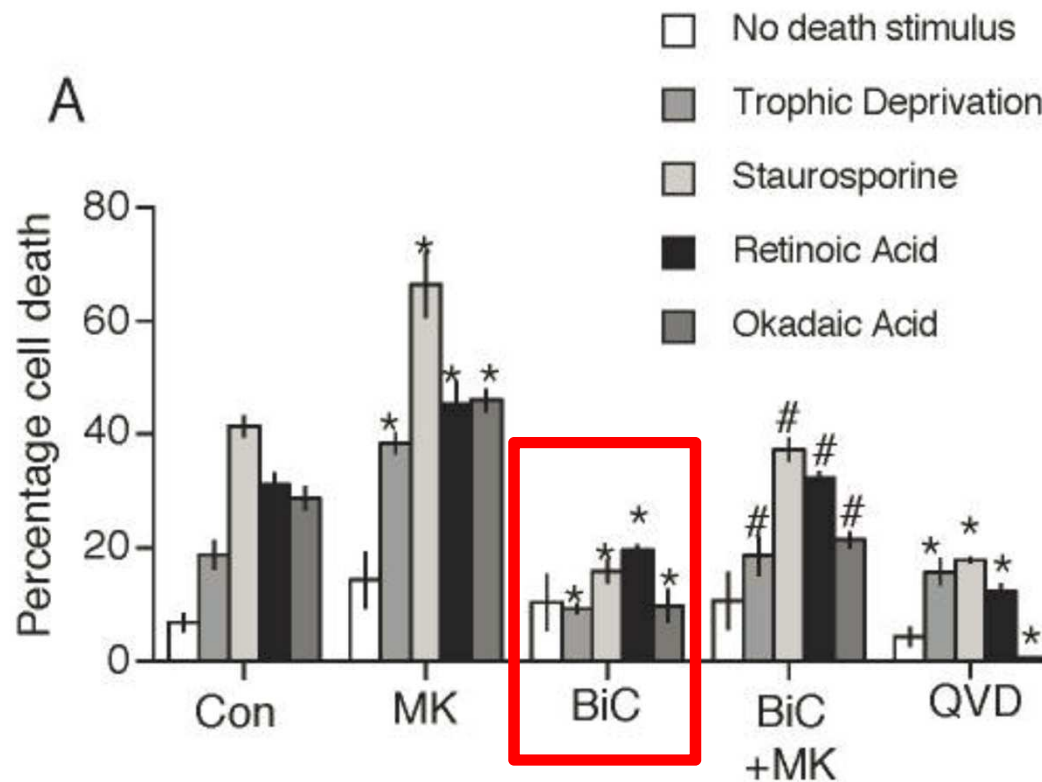


NMDA ~~X~~

Heck et al 2007



Increased Neuronal Activity : Pro-Survival





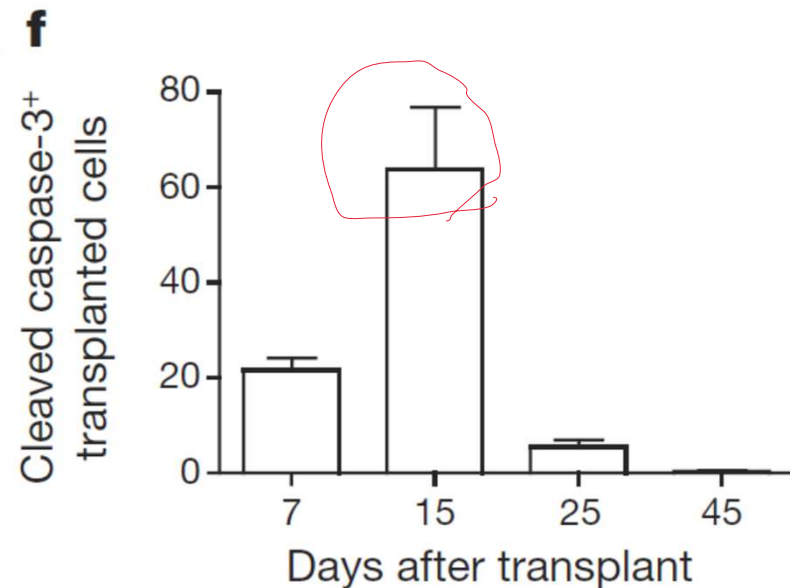
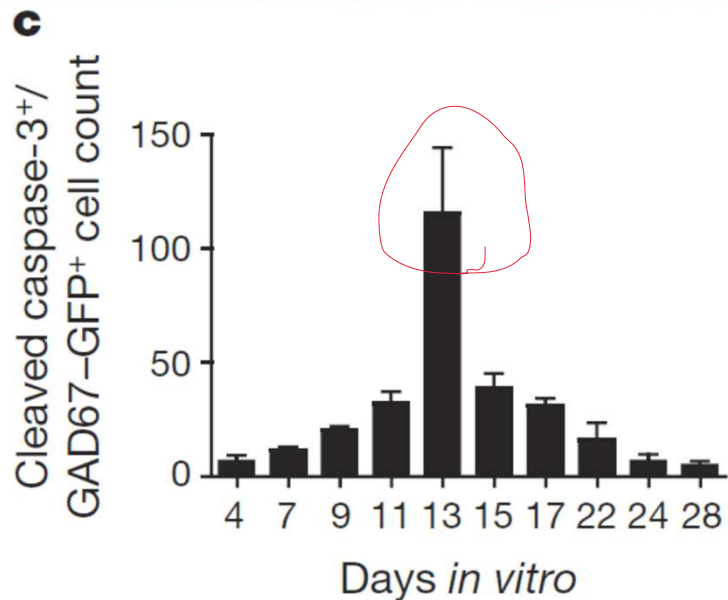
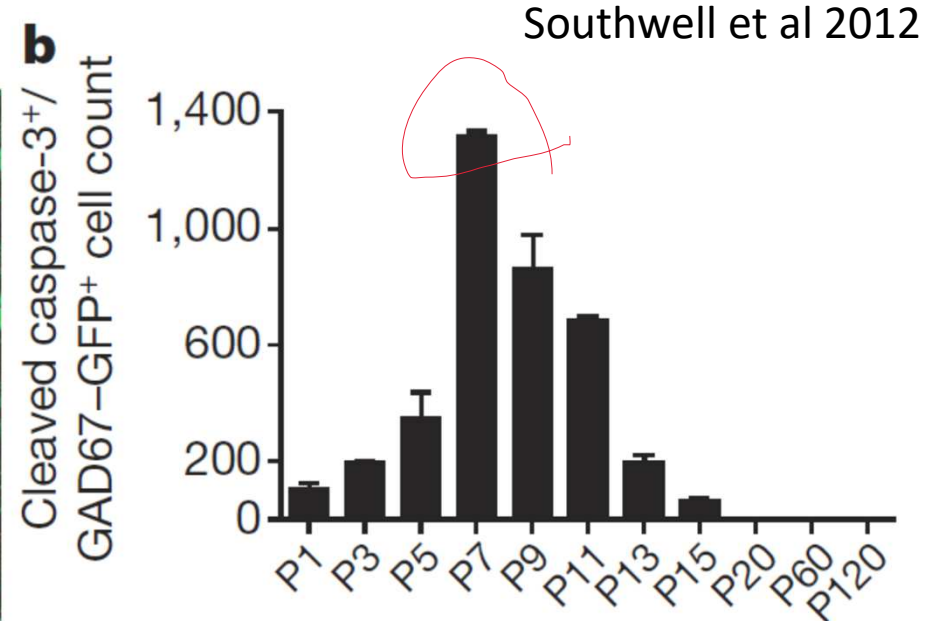
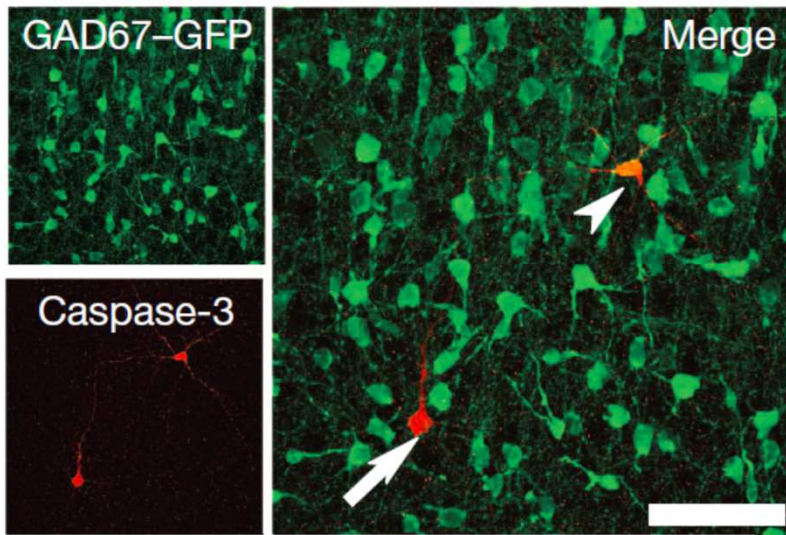
Apoptosis in CNS

- Neuronal Activity and Neurotransmitter Input
- **Intrinsic Mechanisms** vs. Neurotrophic Hypothesis



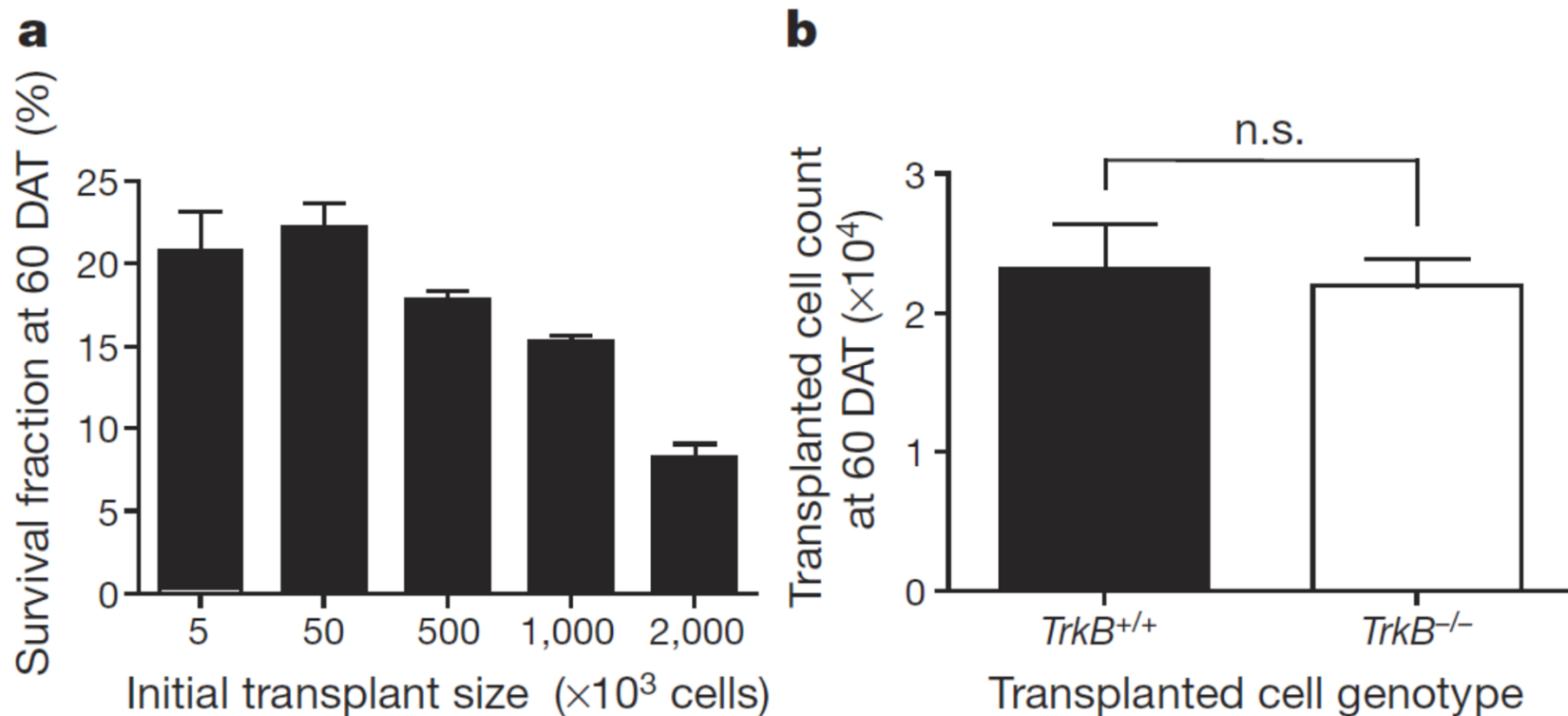
Intrinsic Mechanisms in CNS

a Cortical Interneurons





Intrinsic Mechanisms in CNS



a certain per centages of these cells survives still
the last bar is the absolute number that the cortex can accomodate
so there is no need for competition for neurotrophins

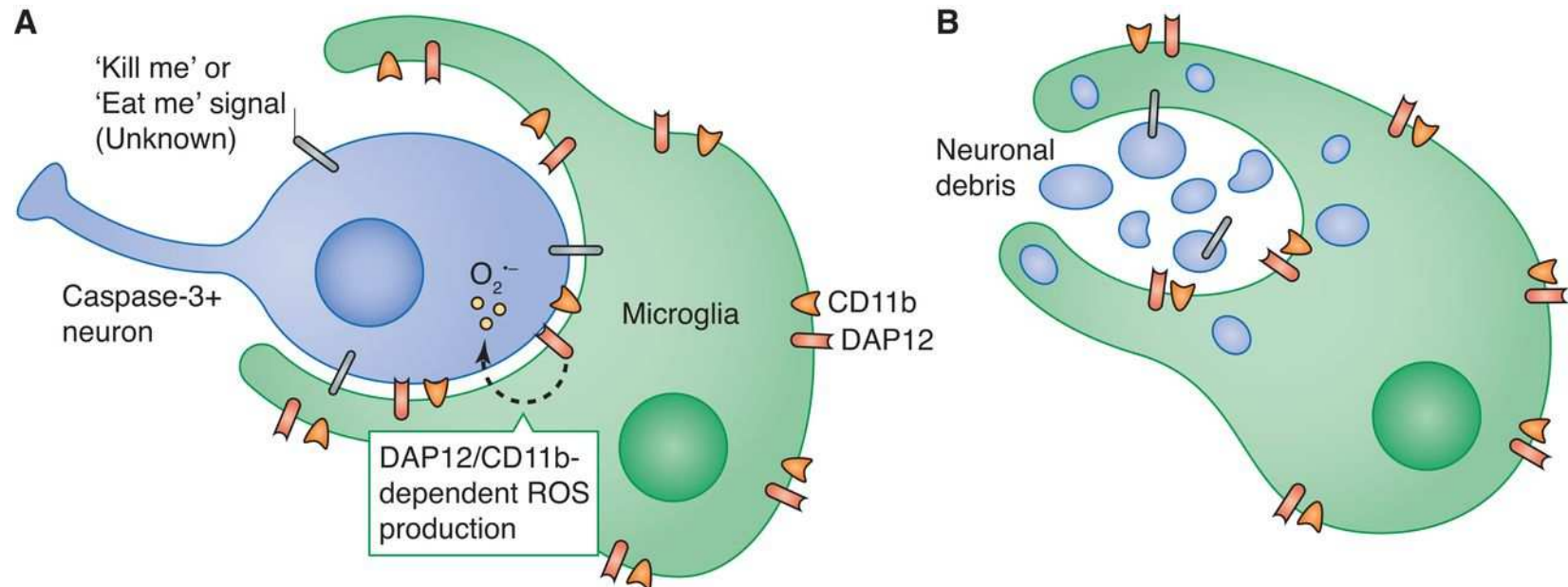


Apoptosis in CNS

- Neuronal Activity and Neurotransmitter Input
- **Intrinsic Mechanisms** vs. Neurotrophic Hypothesis



Microglia promote cell death and clearance of neuronal debris in the developing brain



Megan M. Corty, and Marc R. Freeman J Cell Biol
2013;203:395-405



Apoptosis in Neurons

Apoptosis

Apoptotic Machinery : Caspases & Bcl-2 family

The Neurotrophin Hypothesis

The Discovery of Nerve Growth Factor

The Neurotrophin Family

Neurotrophin Receptors

Developing NGF-dependent Sympathetic Neurons as Model

Reexamine Neurotrophin Hypothesis in CNS

Why do Neurons Die during Development?



Why do so many Neurons Die during Development?

- In various tissues other than the nervous system, apoptosis used to eliminate cells that are no longer needed, defective, or harmful to the function of the organism.
- Apoptotic removal of the surplus neurons generated during development mainly serves the purpose to optimize the size of the nervous system to be minimal, but sufficient.



Apoptosis in Neurons

Apoptosis

Apoptotic Machinery : Caspases & Bcl-2 family

The Neurotrophin Hypothesis

The Discovery of Nerve Growth Factor

The Neurotrophin Family

Neurotrophin Receptors

Developing NGF-dependent Sympathetic Neurons as Model

Reexamine Neurotrophin Hypothesis in CNS

Why do Neurons Die during Development?

1 WHY SHE DIED

Poor Lady. Sansa Stark's direwolf was put down in place of Nymeria, Arya's direwolf who attacked King Joffrey but could not be found.



Lady

Robert Baratheon

WHY HE DIED

It all started with the honorable Ned Stark, beheaded on the order of King Joffrey for challenging his birthright to the throne.

1

WHY THEY DIED

Catelyn, Robb Stark and his pregnant wife Talisa were all brutally murdered at the Red Wedding for breaking the vow Robb made to marry one of Walder Frey's daughters.

3

GAME OF THRONES

WHY DID THEY HAVE TO DIE?

The HBO TV series *Game of Thrones* has no mercy when it comes to killing off your favorite characters, and season four has been the most brutal season yet...

WHY HE DIED

Shae strangled her prostitute and took his life for hooking up with his dad, basically acting as a whore.



Shae

He was fighting dirty and underestimating Arya's skills. Her captor and lethal wounds pushed over a Brieenne of Tarth. He did not mercy kill him.



The Hound

WHY HE DIED

Stark's protector was killed by an ambush of the Lannisters at the end of his quest to bring Bran to the 3-eyed crow. Mercy killed by his own powers, his prophetic powers told him of his death beforehand.



Jojen

She might have been the best Wildling with a bow and arrow, but she let her guard down for Jon Snow and got shot down by a child in the Battle at Castle Black.



Ygritte

4

WHY SHE DIED

Catelyn Stark's eccentric sister fell in love with the wrong man, Littlefinger, who pushed her out of the Moon Door in hopes of taking control of the Vale.



Lyanna Arryn

4



Ser Rodrik Cassel

Spit in the Greyjoy of Winter, him only his alrea respect



Xaro Xhoan Daxos



Ros



Kraznys



Jeor Mormont

The Old Man his own r Mutiny at trying to appease



Locke

Sent by Bolton to kill Bran remaining Stark boys, he (under Bran's warg control) encounters them.

WHY HE DIED

After killing Mormont and Craster, the mutinous Night's Watchman almost killed Jon Snow brought down by one of Craster's wives, the frequent victims of rape and abuse.



Karl Tanner