# Cellular and Molecular Biology of the Neuron
# Part I
# 神经元细胞分子生物学（一）

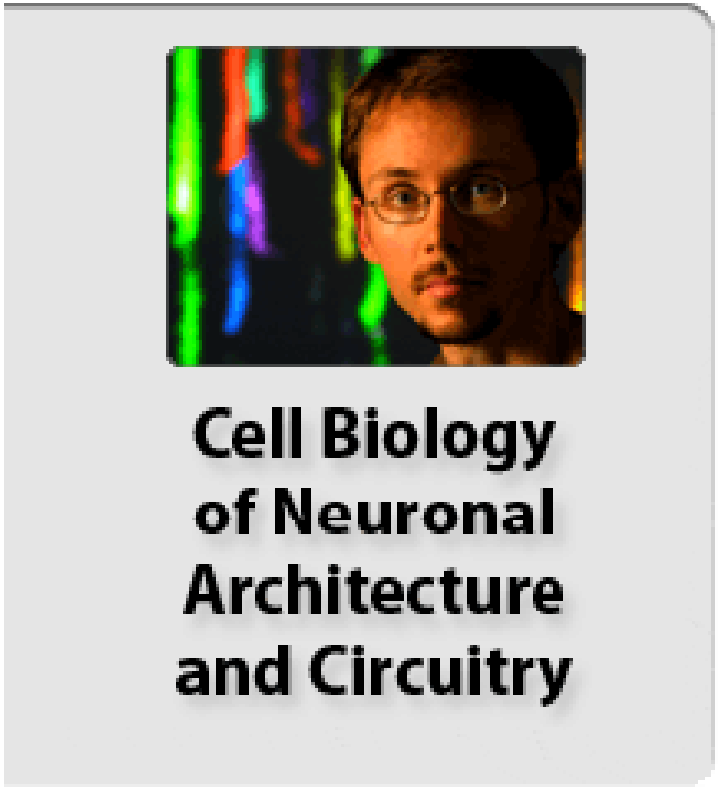
Yan Zhang
张研

# Cellular and Molecular Biology of the Neuron
# 神经元细胞分子生物学（一）

- The Cytology of Neurons 神经元细胞学
- Synthesis and Trafficking of Neuronal Protein
  神经元蛋白的合成和运输

# The cytology of neurons
# 神经元细胞学

- Cell biology research facility can be applied to neuroscience
  细胞生物学研究人员可以投身神经科学




Mike Ehlers

is interested in the cell biological mechanisms underlying neuronal architecture and plasticity.
研究兴趣在于神经架构和可塑性的细胞生物学机制

1.

Neuronal and glial cell biology.

Ehlers MD, Polleux F.

Curr Opin Neurobiol. 2010 Jul 31. [Epub ahead of print] No abstract available. PMID: 20678922 [PubMed - as supplied by publisher]Related citations

2.

Metaplasticity at single glutamatergic synapses.

Lee MC, Yasuda R, Ehlers MD.

Neuron. 2010 Jun 24;66(6):859-70.PMID: 20620872 [PubMed - indexed for MEDLINE]Related citations

3.

Ubiquitination in Postsynaptic Function and Plasticity.

Mabb AM, Ehlers MD.

Annu Rev Cell Dev Biol. 2010 Jul 6. [Epub ahead of print]PMID: 20604708 [PubMed - as supplied by publisher]Related citations

4.

TGF-beta signaling specifies axons during brain development.

Yi JJ, Barnes AP, Hand R, Polleux F, Ehlers MD.

Cell. 2010 Jul 9;142(1):144-57.PMID: 20603020 [PubMed - indexed for MEDLINE]Related citations

5.

Parallel on-axis holographic phase microscopy of biological cells and unicellular microorganism dynamics.

Shaked NT, Newpher TM, Ehlers MD, Wax A.

Appl Opt. 2010 May 20;49(15):2872-8. doi: 10.1364/AO.49.002872.PMID: 20490249 [PubMed - in process]Related citations

6.

Syntaxin-4 defines a domain for activity-dependent exocytosis in dendritic spines.

Kennedy MJ, Davison IG, Robinson CG, Ehlers MD.

Cell. 2010 Apr 30;141(3):524-35.PMID: 20434989 [PubMed - indexed for MEDLINE]Related citations

7.

Molecular genetics and imaging technologies for circuit-based neuroanatomy.

Arenkiel BR, Ehlers MD.

Nature. 2009 Oct 15;461(7266):900-7. Review.PMID: 19829369 [PubMed - indexed for MEDLINE]Free PMC ArticleFree textRelated citations

8.

Signalling mechanisms.

Ehlers MD, Turrigiano G.

Curr Opin Neurobiol. 2009 Jun;19(3):235-6. Epub 2009 Aug 7. No abstract available. PMID: 19665884 [PubMed - indexed for MEDLINE]Free PMC ArticleFree textRelated citations

9.

Endocytic trafficking and recycling maintain a pool of mobile surface AMPA receptors required for synaptic potentiation.

Petrini EM, Lu J, Cognet L, Lounis B, Ehlers MD, Choquet D.

Neuron. 2009 Jul 16;63(1):92-105.PMID: 19607795 [PubMed - indexed for MEDLINE]Free PMC ArticleFree textRelated citations

10.

Ube3a is required for experience-dependent maturation of the neocortex.

Yashiro K, Riday TT, Condon KH, Roberts AC, Bernardo DR, Prakash R, Weinberg RJ, Ehlers MD, Philpot BD.

Nat Neurosci. 2009 Jun;12(6):777-83. Epub 2009 May 10.PMID: 19430469 [PubMed - indexed for MEDLINE]Free PMC ArticleFree textRelated citations

11.

Spine microdomains for postsynaptic signaling and plasticity.

Newpher TM, Ehlers MD.

Trends Cell Biol. 2009 May;19(5):218-27. Epub 2009 Mar 28. Review.PMID: 19328694 [PubMed - indexed for MEDLINE]Related citations

12.

The effects of amyloid precursor protein on postsynaptic composition and activity.

Hoe HS, Fu Z, Makarova A, Lee JY, Lu C, Feng L, Pajoohesh-Ganji A, Matsuoka Y, Hyman BT, Ehlers MD, Vicini S, Pak DT, Rebeck GW.

J Biol Chem. 2009 Mar 27;284(13):8495-506. Epub 2009 Jan 21.PMID: 19164281 [PubMed - indexed for MEDLINE]Free PMC ArticleFree textRelated citations

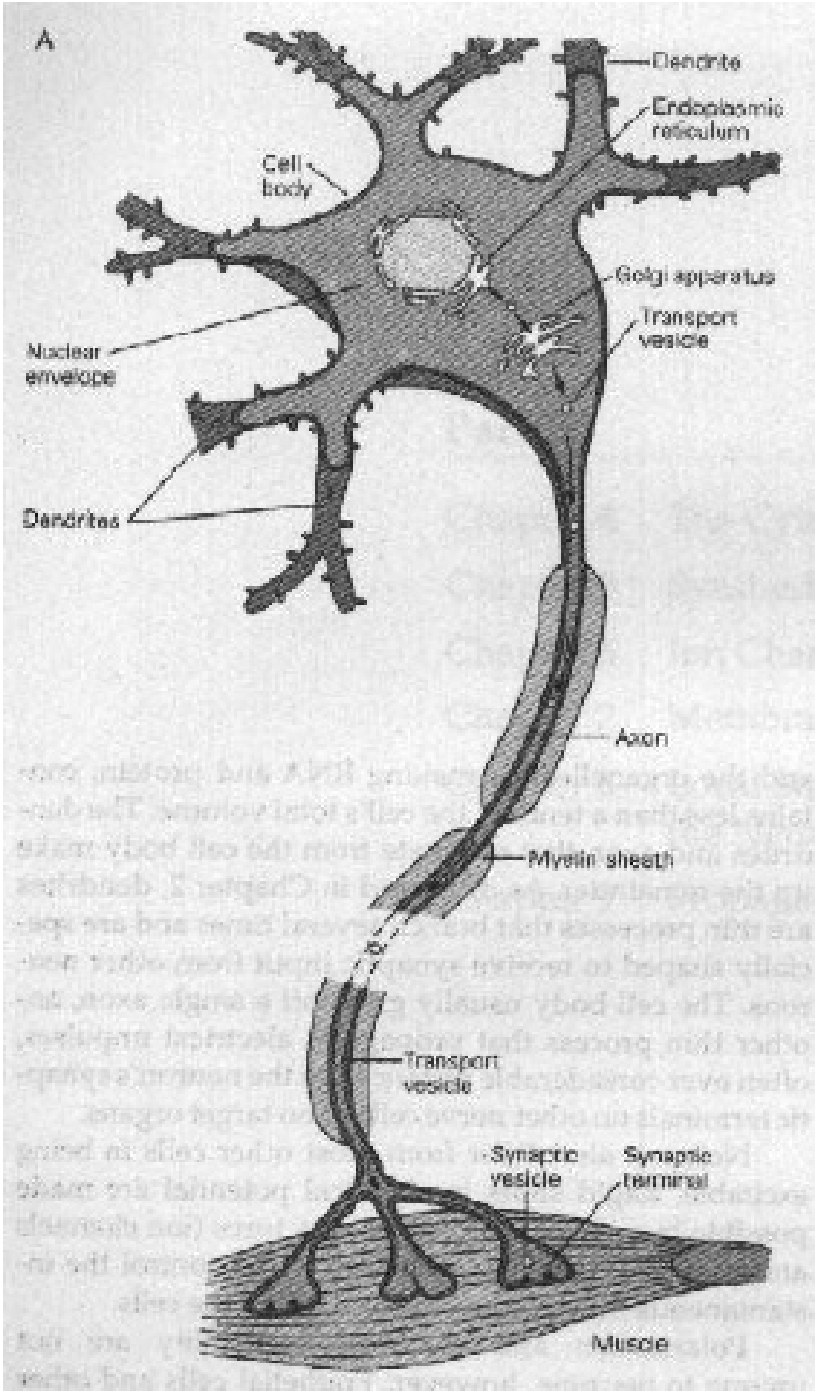
# The structural and functional blueprint of neurons is similar to epithelial cells

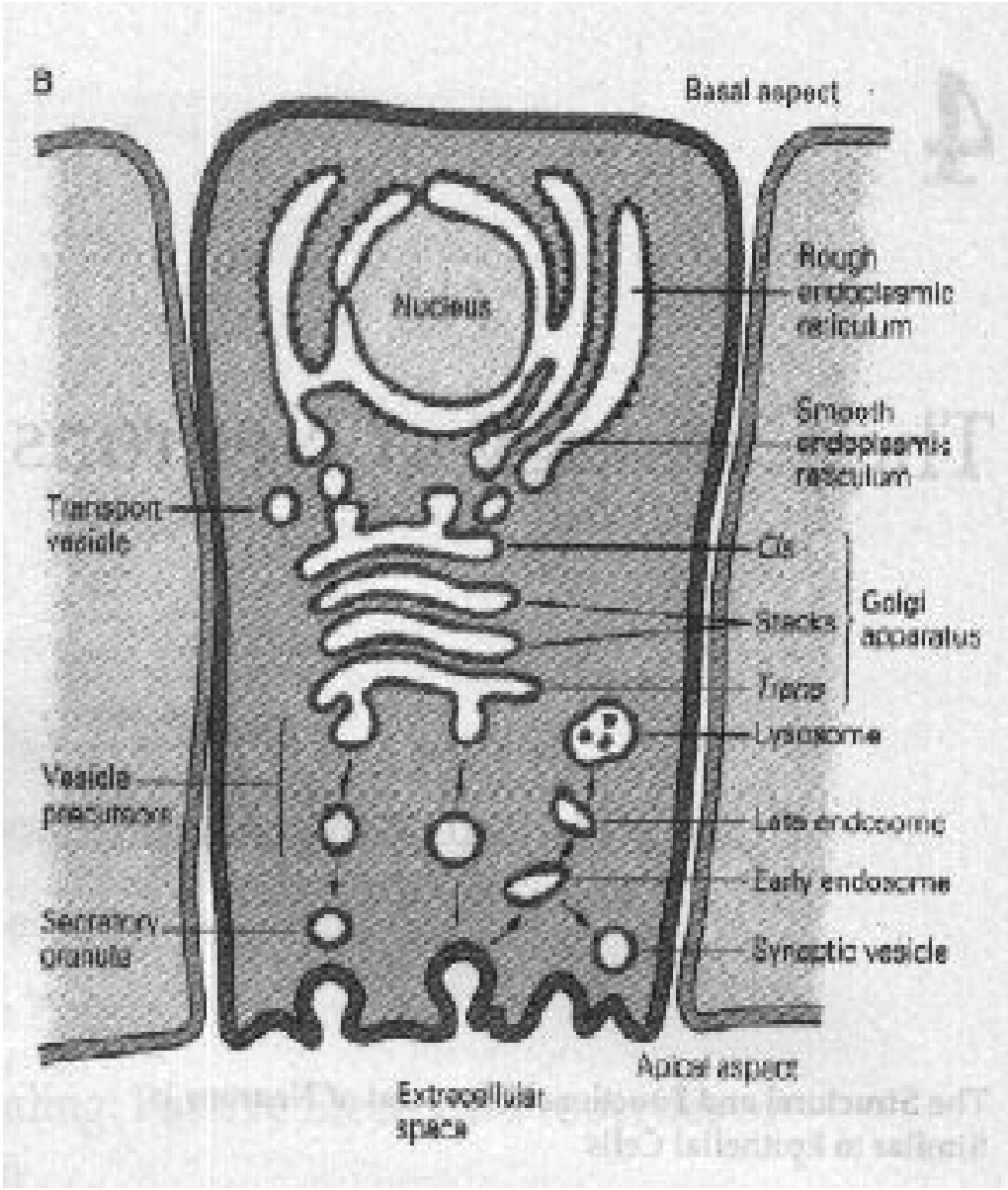
## 神经元结构和功能“蓝图”和上皮细胞相似

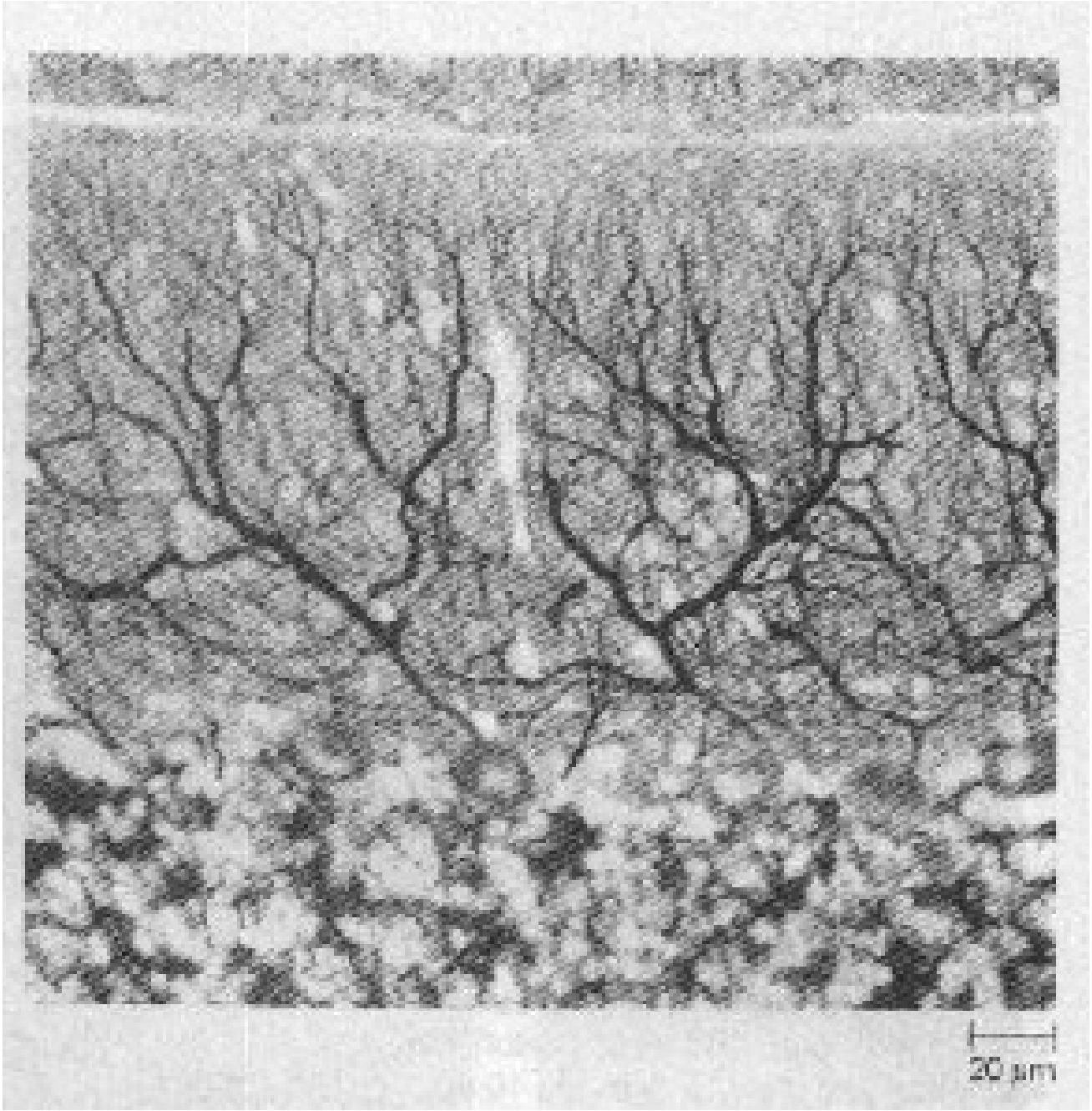
- Neurons develop from epithelial cells and retain fundamental epithelial features.

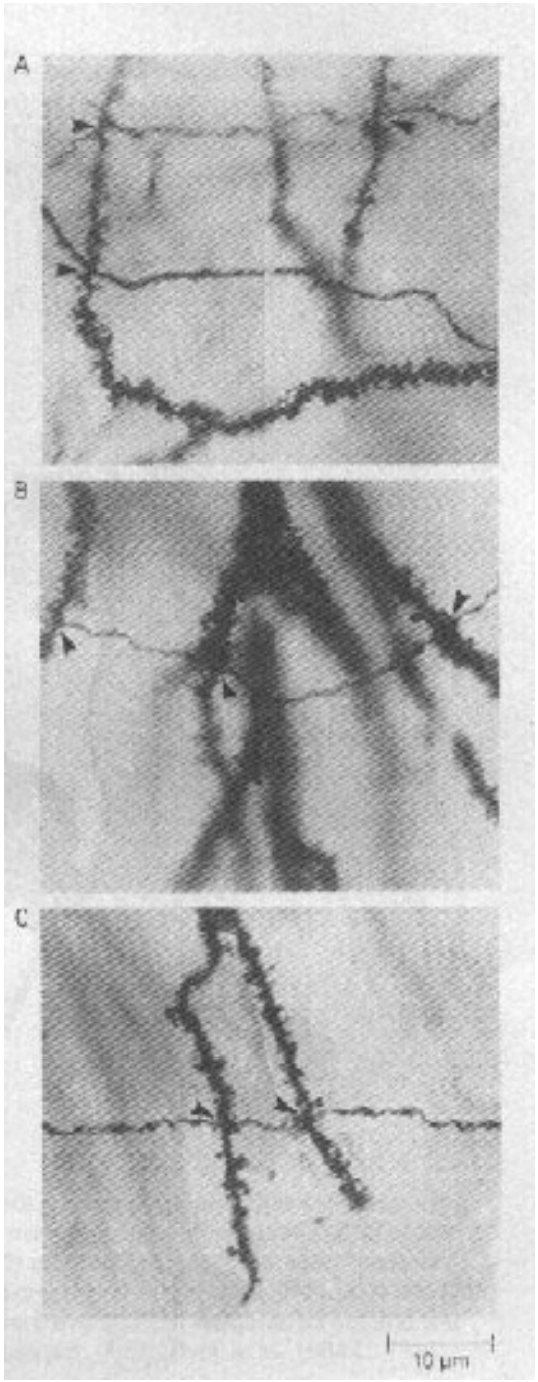
  神经元由上皮细胞发育而来，保持基本的上皮特征

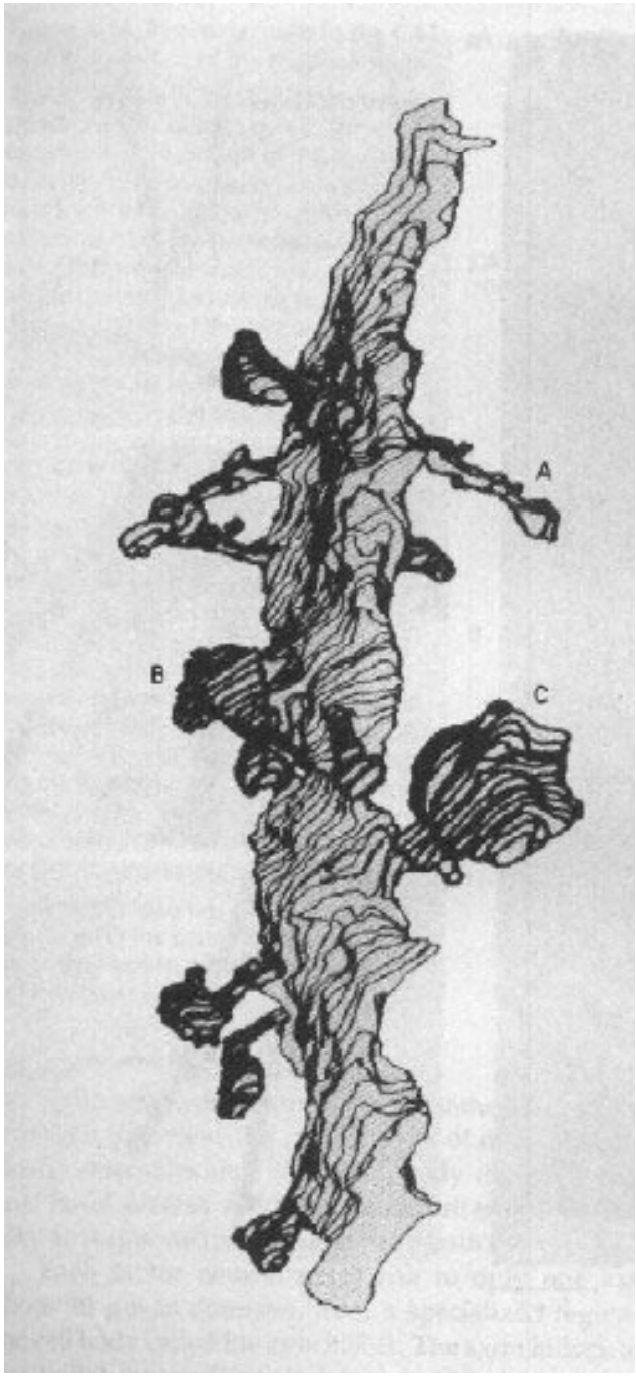
  - Highly polarized 高度极化
    - Cell body 细胞体
    - Dendrites 树突
    - Axons 轴突
  - Cell functions are compartmentalized 细胞功能分区
    - Cell body: less than 1/10 of the cell’s total volume
      细胞体：少于细胞总体积的1/10
    - Dendrites and axon: over 9/10 of the cell’s total volume
      树突和轴突：超过细胞总体积 的9/10
    - Over 50 distinct types of neurons: developmental differentiation
      超过50种不同种类神经元：发育分化


A
Dendrite
Endoplasmic reticulum
Cell body
Golgi apparatus
Transport vesicle
Nuclear envelope
Dendrites
Axon
Myelin sheath
Transport vesicle
Synaptic vesicle
Synaptic terminal
Muscle


B
Basal aspect
Nucleus
Rough endoplasmic reticulum
Smooth endoplasmic reticulum
Transport vesicle
Cis
Stacks
Golgi apparatus
Trans
Lysosome
Vesicle precursors
Late endosome
Early endosome
Secretory granule
Synaptic vesicle
Apical aspect
Extracellular space


20 µm


A
B
C
10 µm


A
B
C

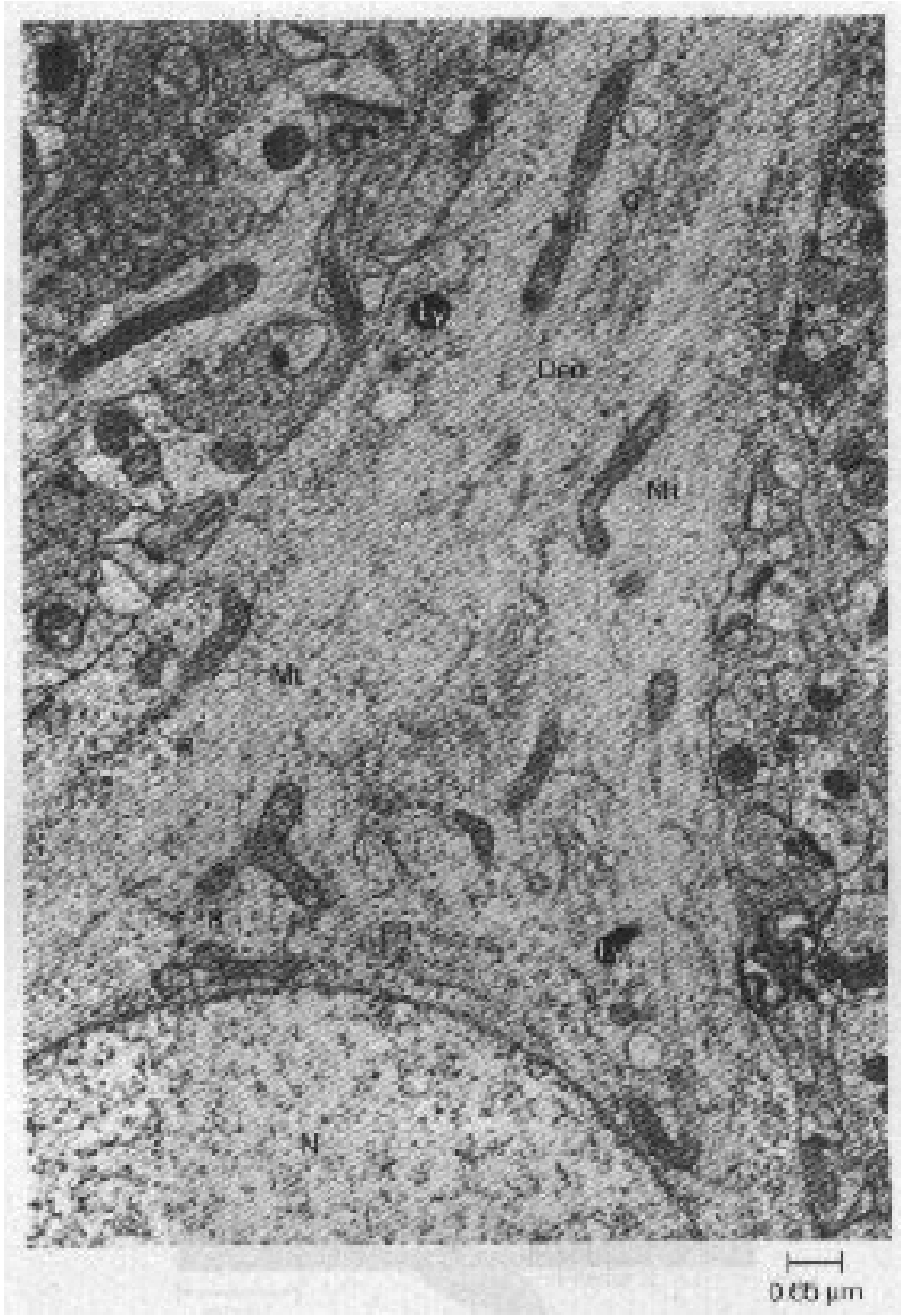
# Major cellular compartments of neurons
# 神经元的主要细胞分区

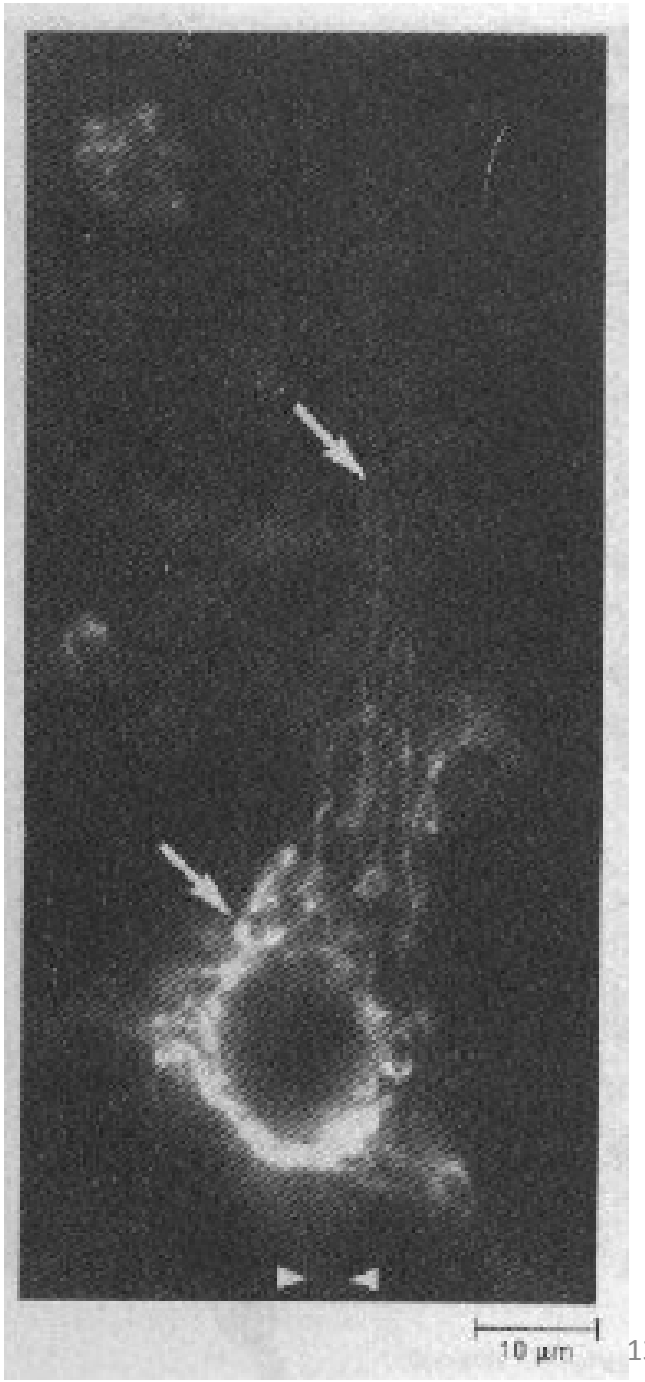
- Cell membrane: a hydrophobic barrier
  细胞膜：疏水屏障
- Cytoplasm 细胞质
  - Cytosol: including the cytoskeletal matrix
    细胞液：包括细胞骨架
    - the aqueous phase of the cytoplasm
      细胞质液相成分
    - only a very few proteins are freely soluble, most proteins are distributed unevenly
      只有很少蛋白是自由溶解的，大多数分布不均衡
  - Membranous organelles
    膜细胞器

# Membranous organelles are selectively distributed throughout the neuron
# 膜细胞器在整个神经元中选择性分布

- Mitochondria 线粒体
- Peroxisomes 过氧化物酶体
- Endoplasmic reticulum内质网
  - Rough ER 粗面内质网
  - Smooth ER 光面内质网
- Golgi complex 高尔基体
- Secretory vesicles 分泌小泡
- Endosomes 内涵体
- Lysosomes 溶酶体
- Transport vesicles 运输小泡

Vacuolar apparatus
空泡状细胞器


Ly
Dem
Mt
Mt
N
0.65 µm


10 µm

# Vacuolar apparatus 空泡状细胞器

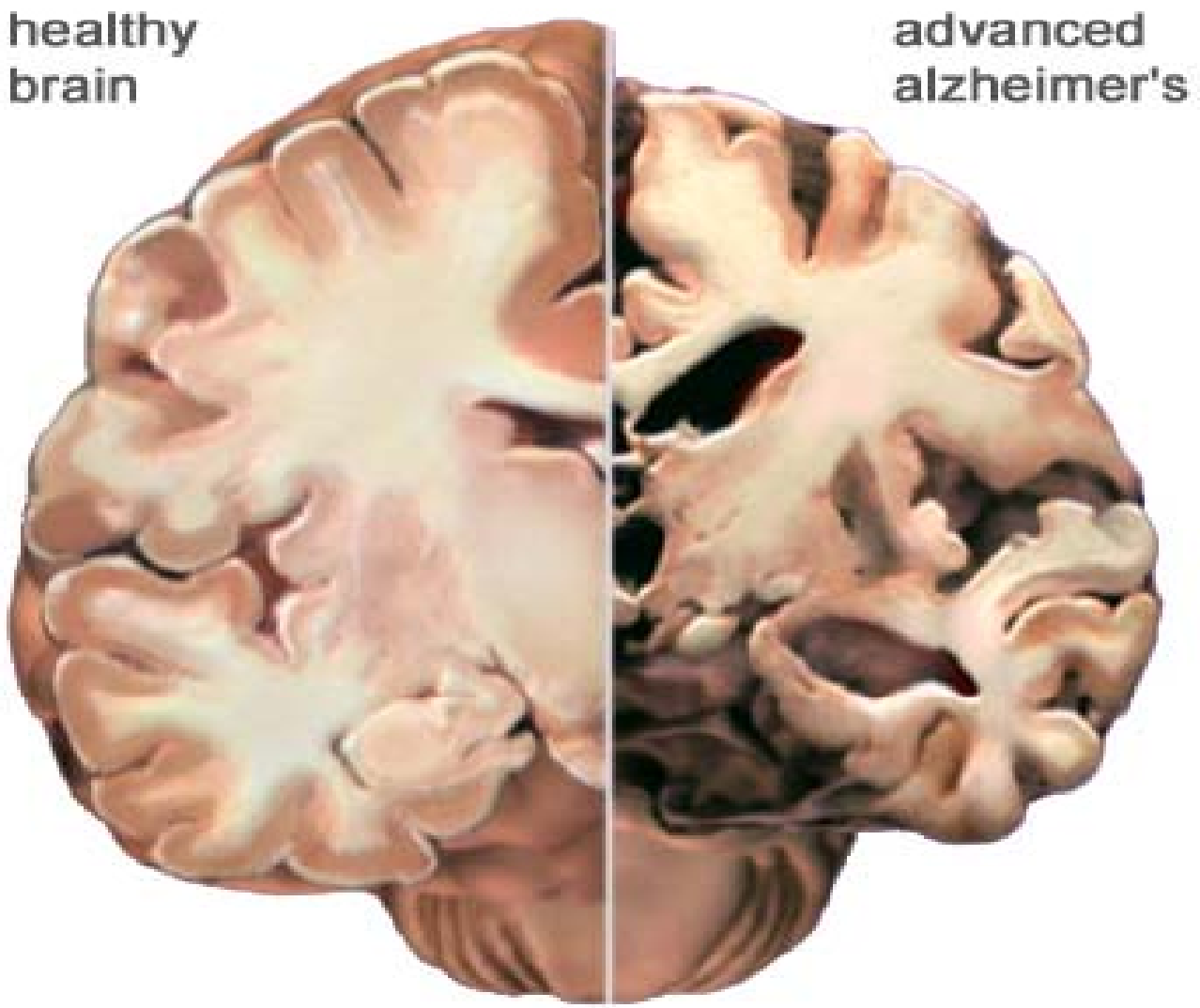
- Derived from deep invaginations of the cell's external membrane
  细胞膜内陷形成
- Lumen: corresponds to the outside of the cell
  腔室：对应于细胞外区间
- Inner leaflet: corresponds to the outer leaflet of the plasmalemma
  内膜：对应于原生质膜外膜
- Membranous and lumenal material are moved from one compartment to another by transport vesicles
  膜、腔物质通过运输小泡由一个区域运输到另一个区域

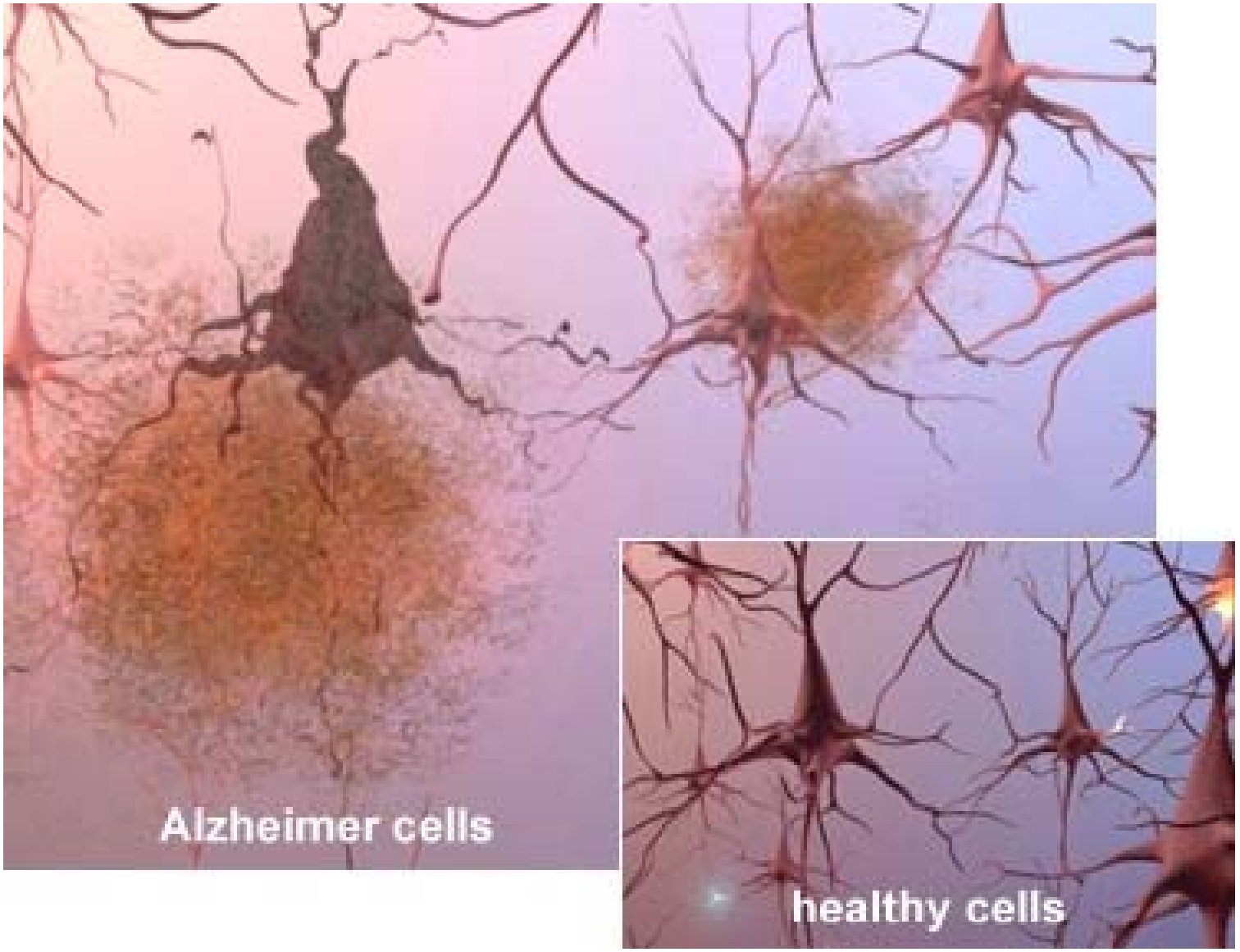
# Real life situation: how does amyloid β get into the cytosol

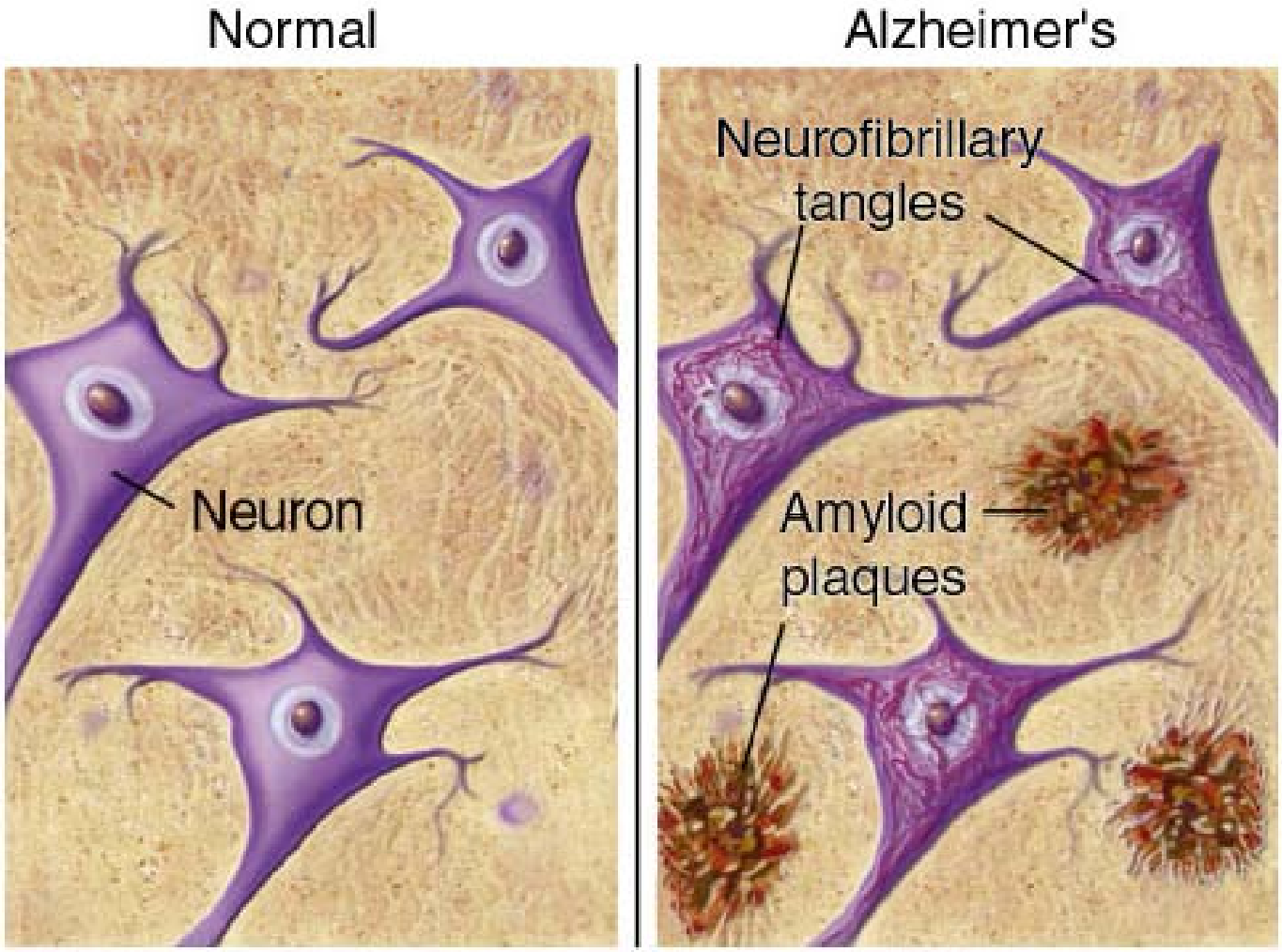
# 真实的生活情况：Aβ如何进入细胞液

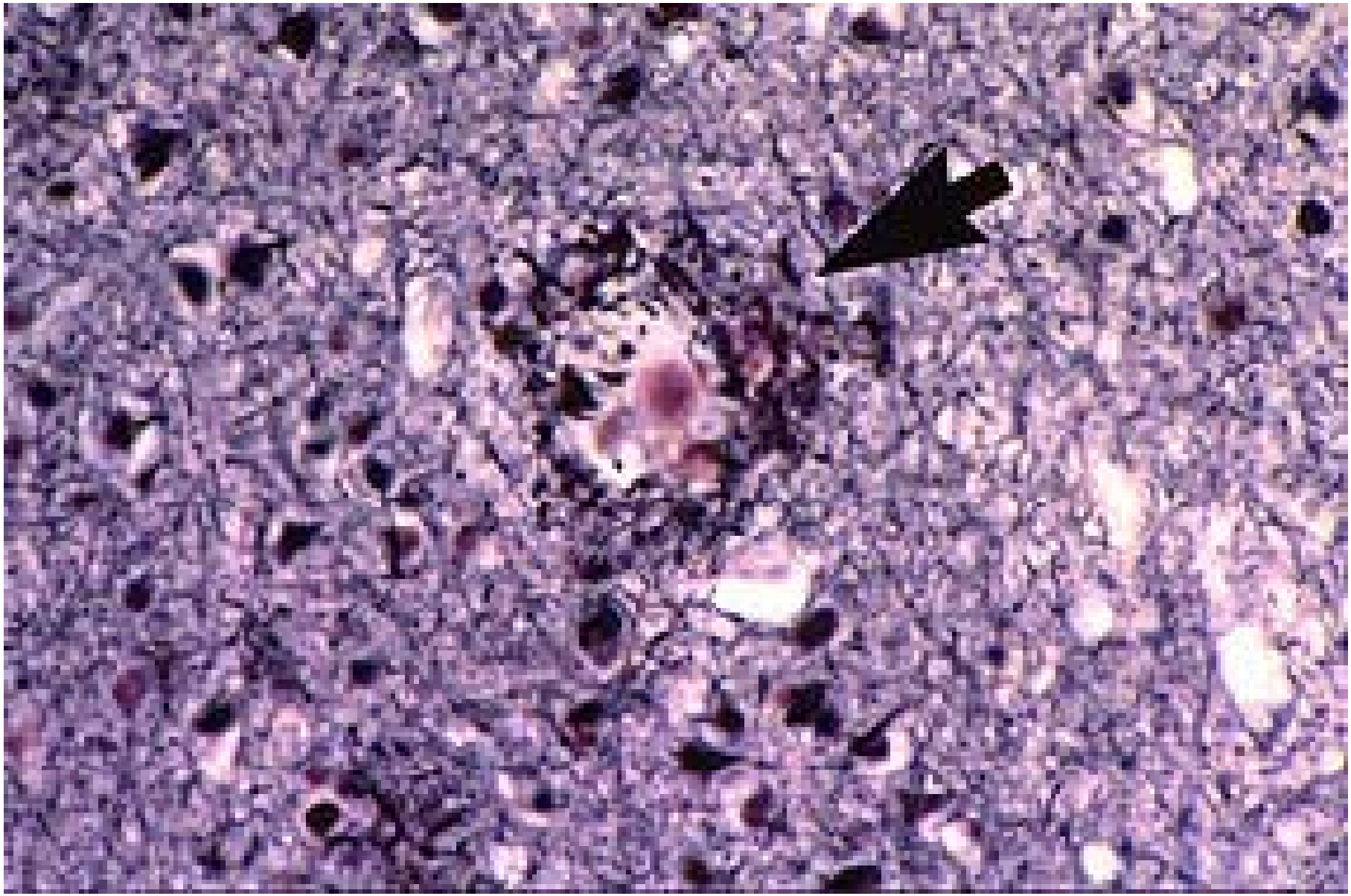
- Alzheimer's disease is a progressive brain disorder that gradually destroys a person's memory and ability to learn, reason, make judgments, communicate and carry out daily activities. As Alzheimer's progresses, individuals may also experience changes in personality and behavior, such as anxiety, suspiciousness or agitation, as well as delusions or hallucinations.

阿尔兹海默氏症是一种进行性脑部疾病，逐渐损害记忆和学习、推理、判断、交流和日常活动的能力。随着病程进展，病人可能也会发生性格和行为改变，比如焦虑、疑心、易激动、妄想甚至幻觉。


healthy
brain
advanced
alzheimer's


Alzheimer cells
healthy cells


Normal
Alzheimer's
Neuron
Neurofibrillary tangles
Amyloid plaques

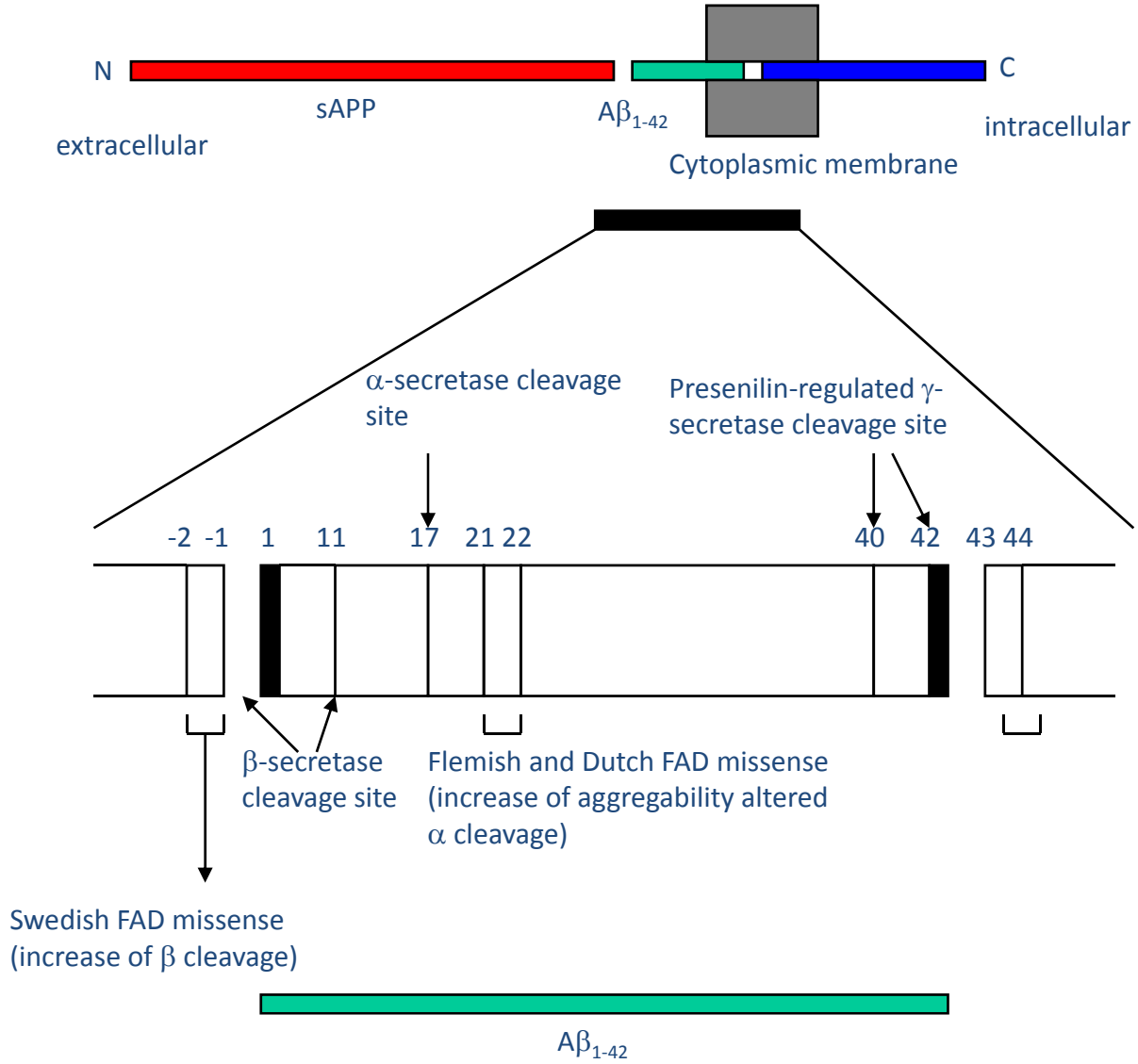


Amyloid precursor protein (APP), cloned in 1987 (Kang et al., 1987), is a type-I transmembrane glycoprotein with ten isoforms generated by alternative mRNA splicing. APP is encoded by a single gene at human chromosome 21 containing 18 exons (Kang et al., 1987; Goate et al., 1991). APP has a signal peptide, a large extracellular N terminal domain and a small intracellular C terminal domain, a single transmembrane domain and an endocytosis signal at the C terminal.

淀粉样前体蛋白（APP）于1987年被克隆（ Kang等., 1987），是I型跨膜糖蛋白，有因mRNA可变剪接产生的10个亚型。APP由人21号染色体单基因编码，该基因含有18个外显子（ Kang等, 1987; Goate等, 1991）。APP含一个信号肽，一个较大的胞外N端和一个较小的胞内C端，一个单次跨膜区和一个C端内吞信号。

Among ten isoforms of APP ranging from 563 to 770 amino acids, the major ones are APP770, APP751 and APP695. Isoform APP695 is expressed at high levels in the brain.

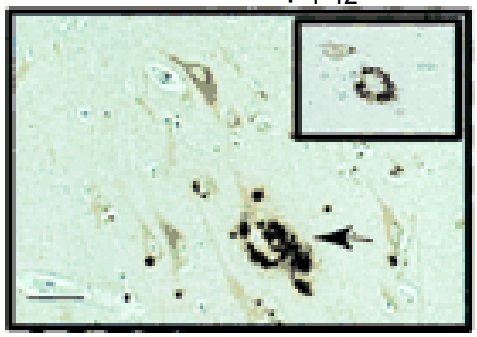
在APP10个亚型（大小从563到770个氨基酸不等）中，主要的是APP770、APP751和APP695。APP695在脑中高表达。


N
C
sAPP
Aβ1-42
extracellular
intracellular
Cytoplasmic membrane
α-secretase cleavage site
Presenilin-regulated γ-secretase cleavage site
-2 -1 1 11 17 21 22 40 42 43 44
β-secretase cleavage site
Flemish and Dutch FAD missense (increase of aggregability altered α cleavage)
Swedish FAD missense (increase of β cleavage)
Aβ1-42

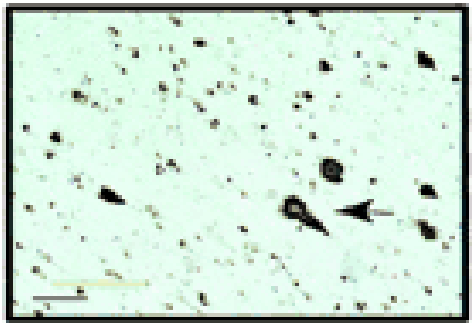
# Intracellular Aβ is an early event in AD development
# 胞内Aβ是AD进程的早期事件

★ Intracellular Aβ is observed in AD and mild cognitive impairment patient brains. 胞内Aβ在AD和轻度认知功能障碍病人中被观察到。
(Chui et al., 1999; Gouras et al., 2000; D'Andrea et al., 2001, 2002; Nagele et al., 2002; Tabira et al., 2002; Wang et al., 2002).

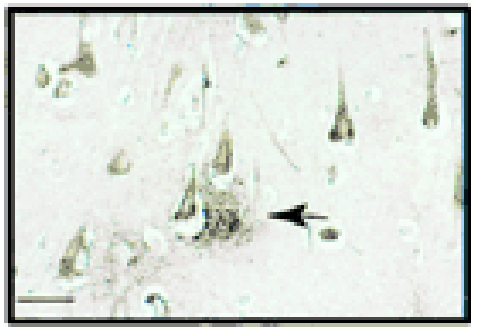
Hippocampal Neuronal staining for $A\beta_{1-42}$ (RU antibody) (Gouras et al., 2000)
海马神经元$A\beta_{1-42}$染色



Cognitively impaired, developing intracellular $A\beta_{1-42}$
认知损伤，发展的胞内Aβ



Advanced AD, intensive intracellular $A\beta_{1-42}$
AD进展中，集中的胞内Aβ

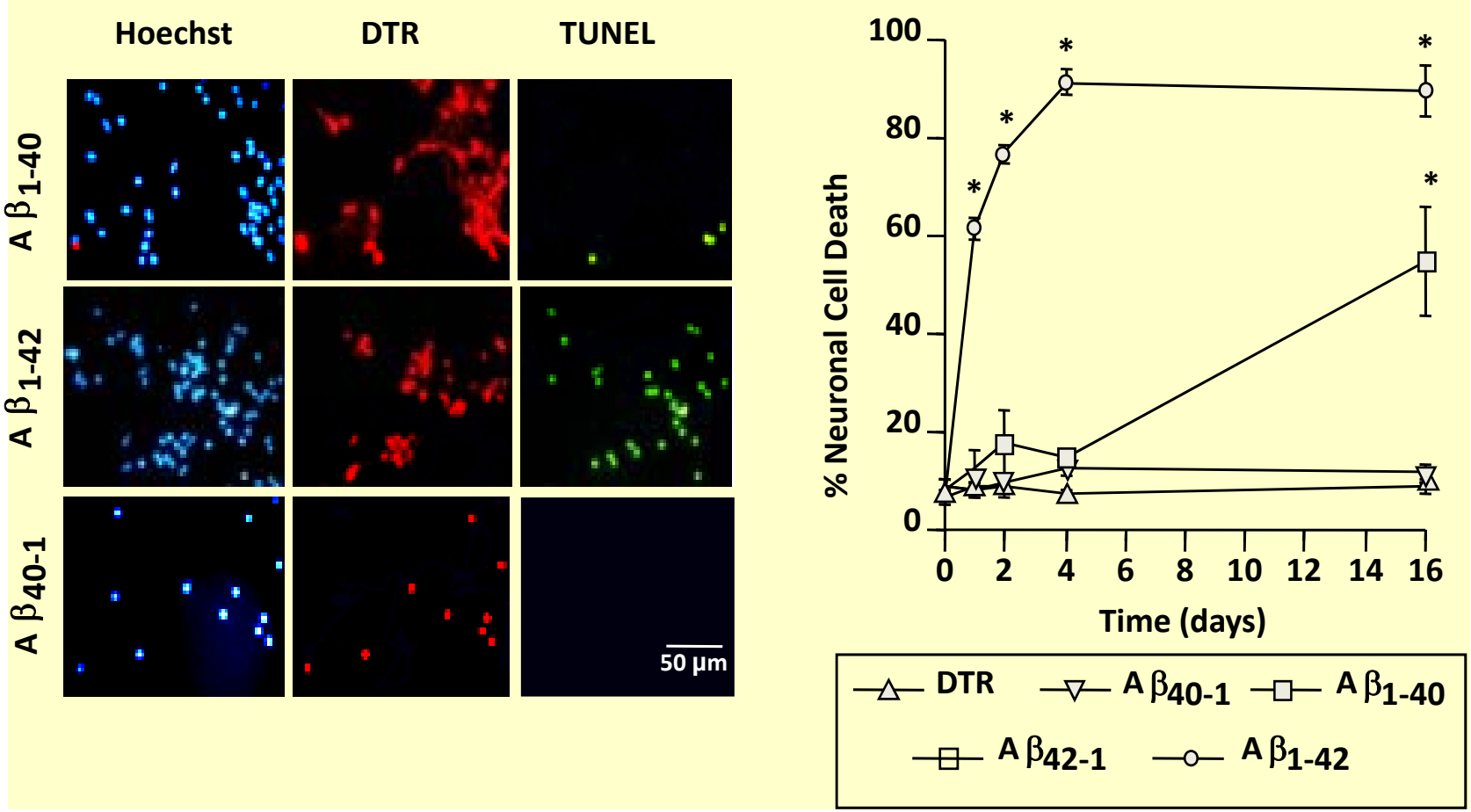


Cognitively impaired, with both intracellular $A\beta_{1-42}$ and extracellular defused SP-like $A\beta_{1-42}$
认知损伤，胞内外$A\beta_{1-42}$去除SP样$A\beta_{1-42}$危险性

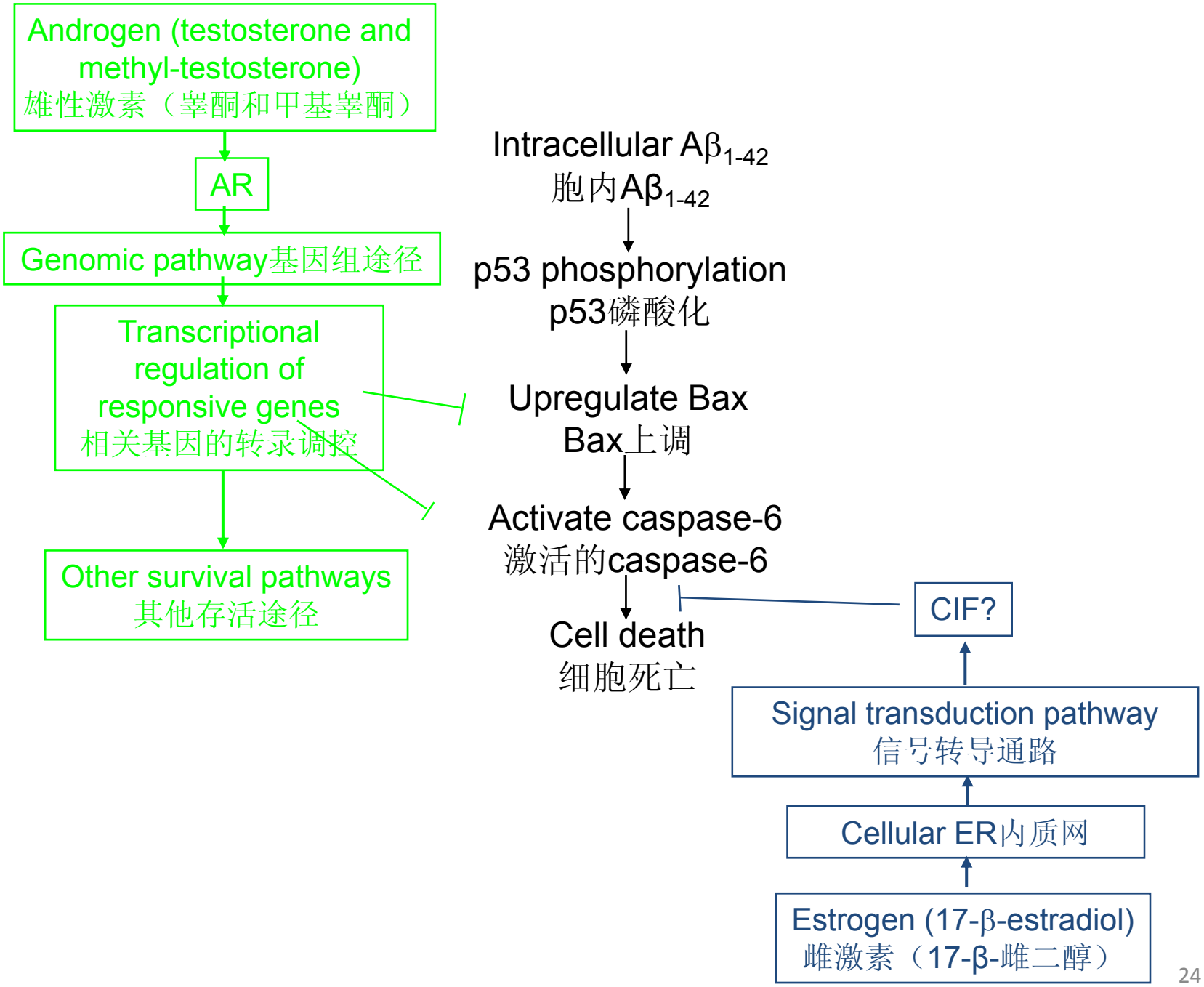
★ Accumulation of intracellular $A\beta_{1-42}$ is observed also in other two amyloid-related diseases, Down's syndrome (Busciglio et al., 2002) and inclusion body myositis pathology (Askanas et al., 1992; Sugarman et al., 2002).
胞内Aβ聚集也在另两种淀粉样蛋白相关疾病中被发现：唐氏综合症和包涵体肌炎病理

★ The only AD animal model showing neuronal loss has significant intracellular Aβ deposition (LaFerla et al., 1995, 1996).AD仅有的表现出神经元死亡动物模型有明显胞内Aβ沉积

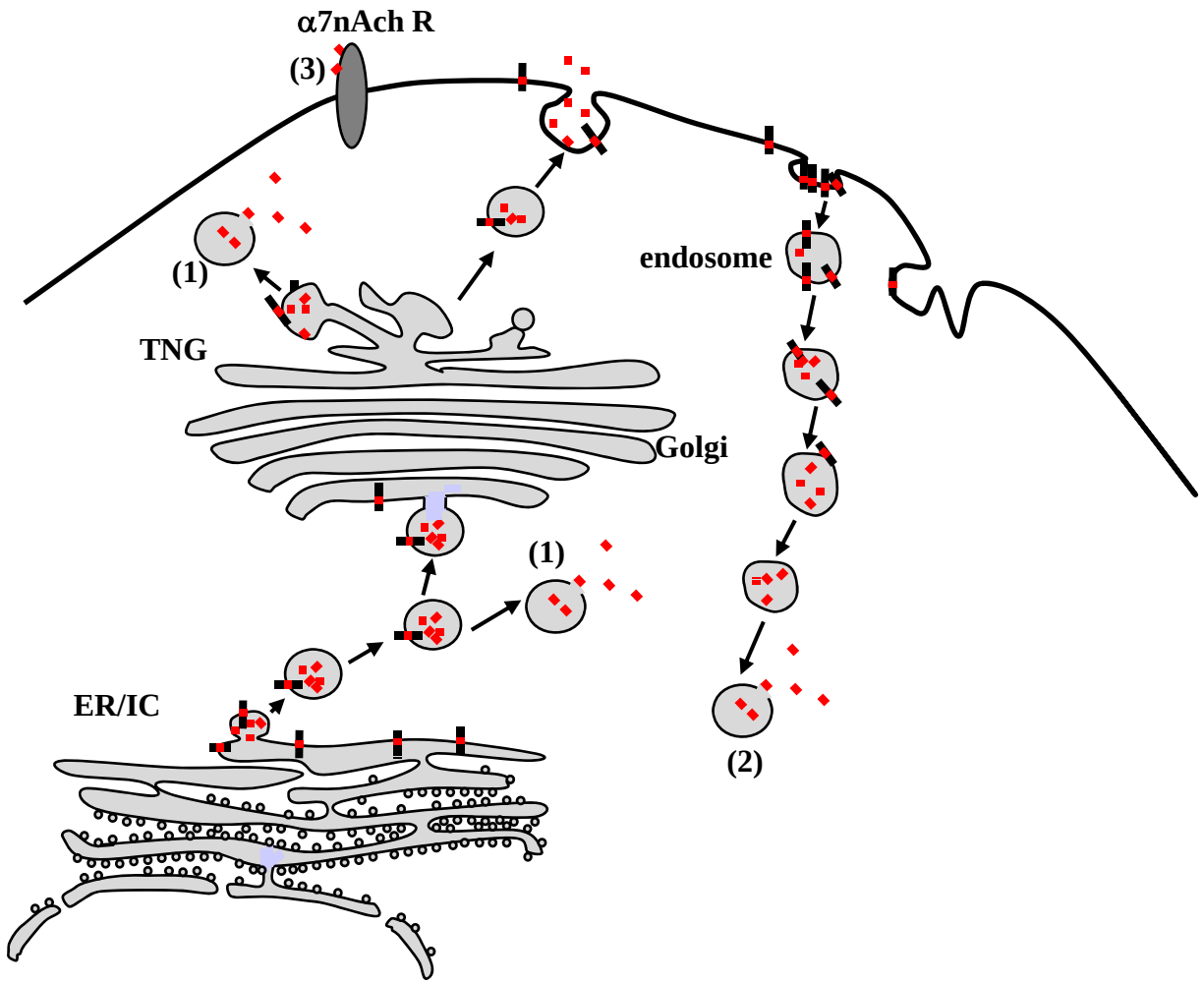
# Intracellular $A\beta_{1-42}$ is toxic to human neurons
# 胞内$A\beta_{1-42}$的神经元毒性




The Aβ peptides were prepared by Neurochem Inc. (Ville St-Laurent, Quebec)


Androgen (testosterone and methyl-testosterone)
雄性激素（睾酮和甲基睾酮）
AR
Genomic pathway基因组途径
Transcriptional regulation of responsive genes
相关基因的转录调控
Other survival pathways
其他存活途径
Intracellular Aβ1-42
胞内Aβ1-42
p53 phosphorylation
p53磷酸化
Upregulate Bax
Bax上调
Activate caspase-6
激活的caspase-6
Cell death
细胞死亡
CIF?
Signal transduction pathway
信号转导通路
Cellular ER内质网
Estrogen (17-β-estradiol)
雌激素（17-β-雌二醇）

# How does Aβ get into the cytosol
# Aβ如何进入细胞液



# Mitochondria and peroxisomes
# 线粒体和过氧化物酶体

- Make use of molecular oxygen

  利用分子氧
- Mitochondria generate ATP

  线粒体产生ATP
- Peroxisomes engage in detoxification through peroxidation reactions and prevent the accumulation of the strong oxidizing agent hydrogen peroxide

  过氧化物酶体通过过氧化反应参与解毒作用，阻止强氧化剂过氧化氢聚集
- Derived from symbiotic organisms that invaded eukaryotic cells early in evolution

  从进化早期入侵真核生物的共生生物起源

# Positions of cellular compartments
# 细胞分区的位置

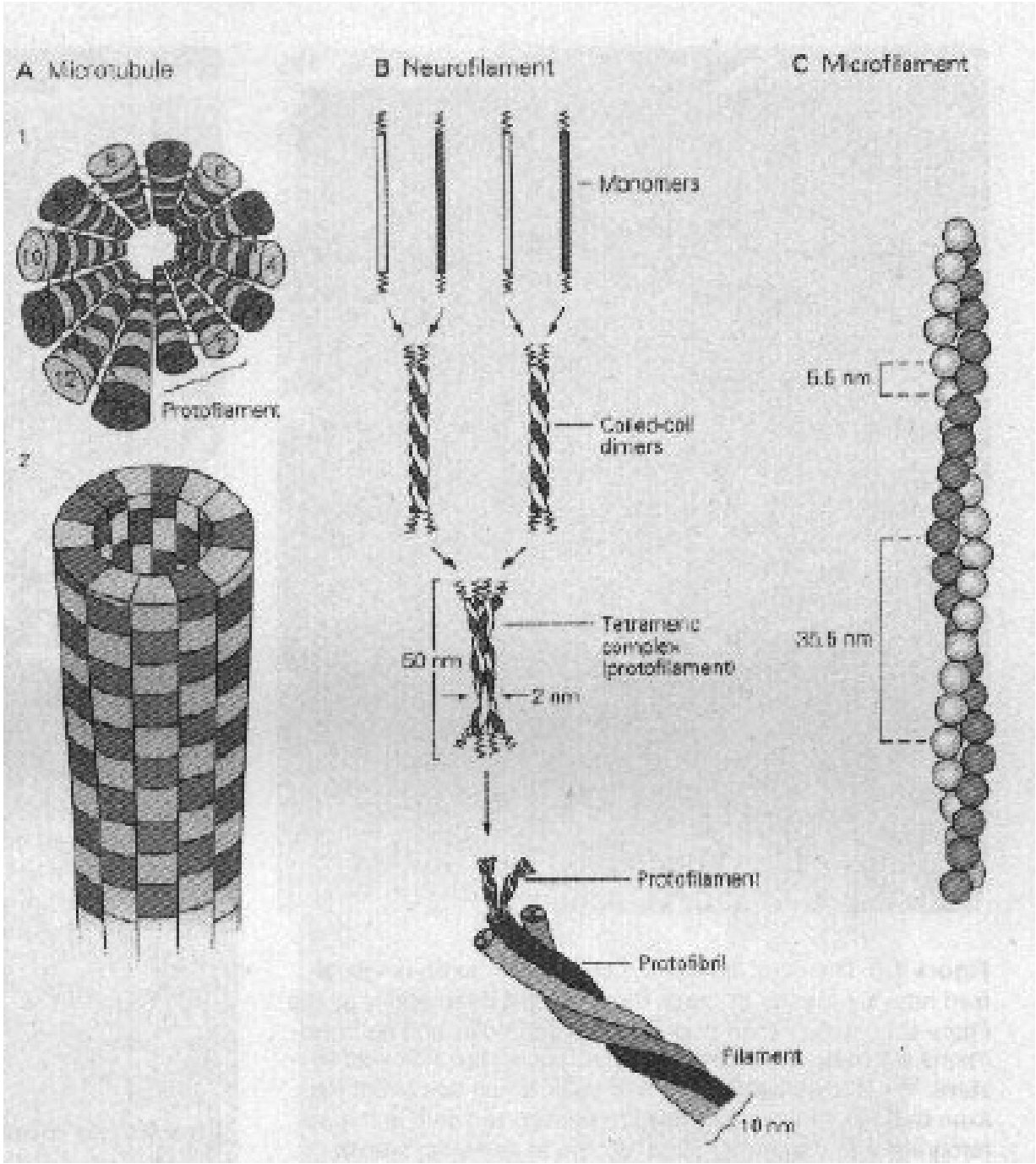
- Not in the axon: ribosomes, rough ER, Golgi complex, lysosomes

  不在轴突中的：核糖体、粗面内质网、高尔基体、溶酶体
- In all compartments: mitochondria, smooth ER

  在所有分区中：线粒体，光面内质网

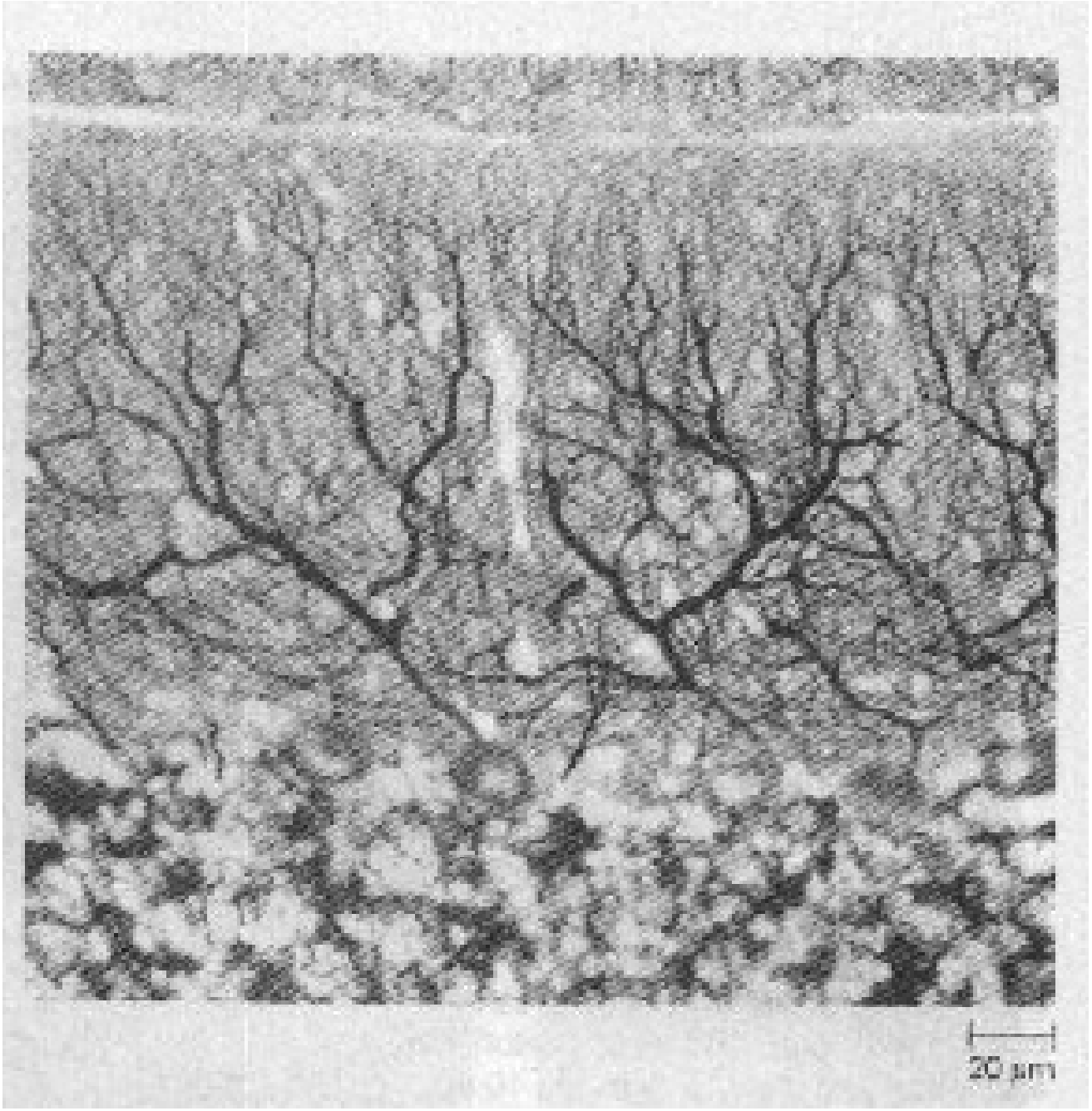
# The cytoskeleton 细胞骨架

- Determine the shape of a neuron 决定神经元形状
- Serve as scaffold 作为脚手架
- Material transportation 物质运输
- Account for about ¼ of the total protein of the neuron 占神经元总蛋白的¼
- Three main structures: microtubules, neurofilaments, actin microfilaments
  三个主要结构：微管、神经丝、肌动蛋白微丝


A Microtubule
1
Protofilament
2
B Neurofilament
Monomers
Coiled-coil dimers
Tetrameric complex (protofilament)
60 nm
2 nm
C Microfilament
5.5 nm
35.5 nm
Protofilament
Protofibril
Filament
10 nm

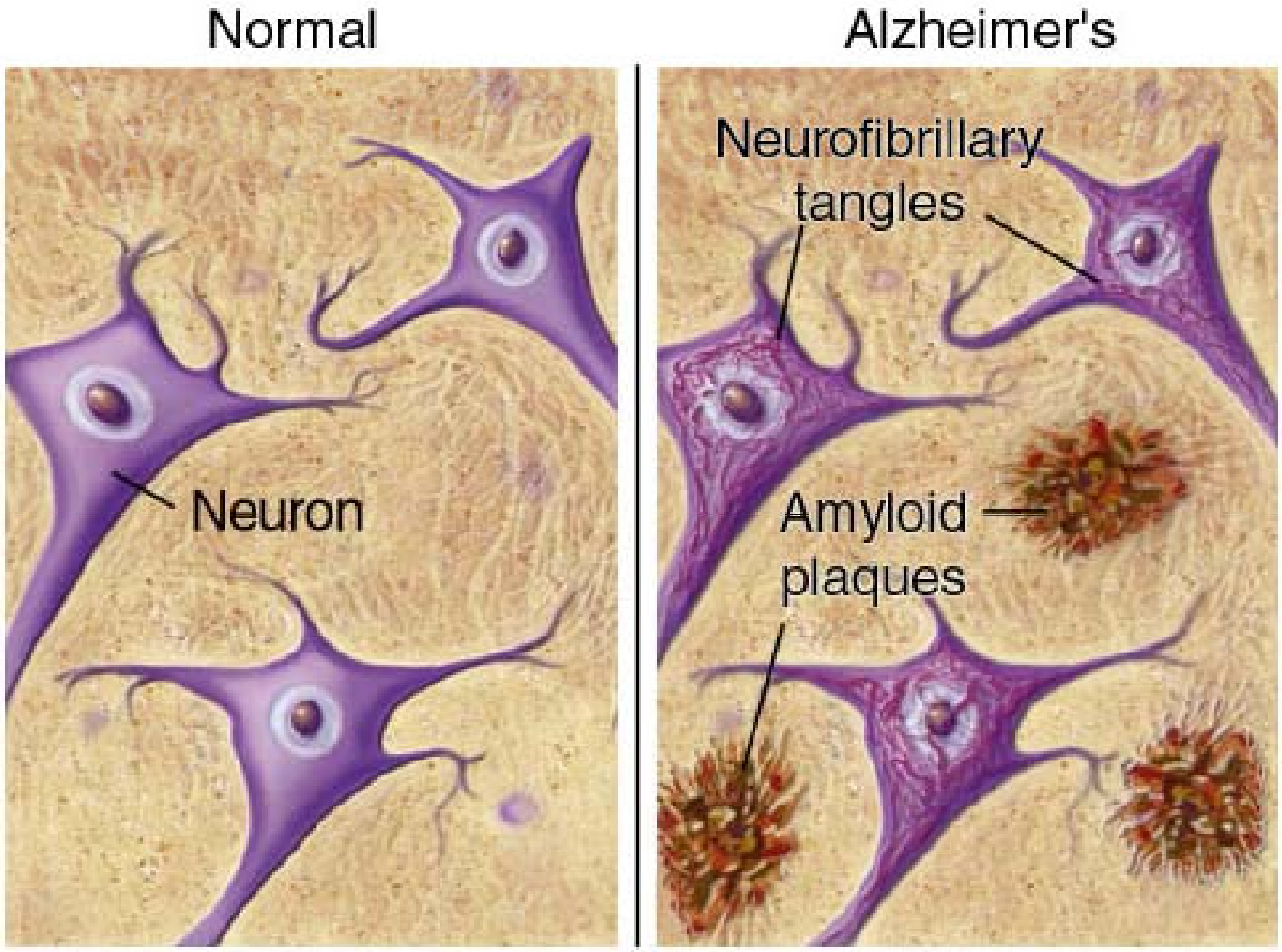
# Microtubules 微管

- Each protofilament consists of α- and β-tubulin
  每条原丝由α-微管蛋白和β-微管蛋白组成
- Microtubules undergo rapid cycles of polymerization and depolymerization
  微管经历快速的聚合和解聚循环
- The stability is due to microtubule-associated proteins (MAPs).
  稳定性由微管相关蛋白（MAP）维持
- MAP2 is only present in dendrites
  MAP2只在树突中存在
- MAP3 and tau are only in axons
  MAP3和tau只在轴突中存在


20 µm

# Neurofilaments 神经丝

- Very stable and almost totally polymerized
  非常稳定，几乎全部聚合
- The most abundant fibrillar components of the axon: 3-10 times more neurofilaments than microtubules in an axon
  轴突中丰度最高的纤维成分，是轴突中微管的3-10倍
- AD: Neurofibrillary tangle, hyperphosphorylated tau
  AD：神经原纤维缠结，过度磷酸化的tau


Normal
Alzheimer's
Neuron
Neurofibrillary tangles
Amyloid plaques

# Microfilaments 微丝

- Consist with actin

  由肌动蛋白组成
- Actin perhaps is the most abundant animal protein in nature

  肌动蛋白可能是自然界中含量最多的动物蛋白
- Highly conserved from humans to protozoa

  从原生动物到人高度保守
- Actin filaments form short polymers

  肌动蛋白丝形成短多聚体
- Concentrated at the cell's periphery lying just underneath the plasmalemma

  聚集在细胞周围，紧挨原生质膜
- Function indication: motility of growth cones; generation of specialized microdomains; the formation of pre- and postsynaptic specializations

  功能：生长锥的运动、特化微区的产生、突触前后特化区域的形成

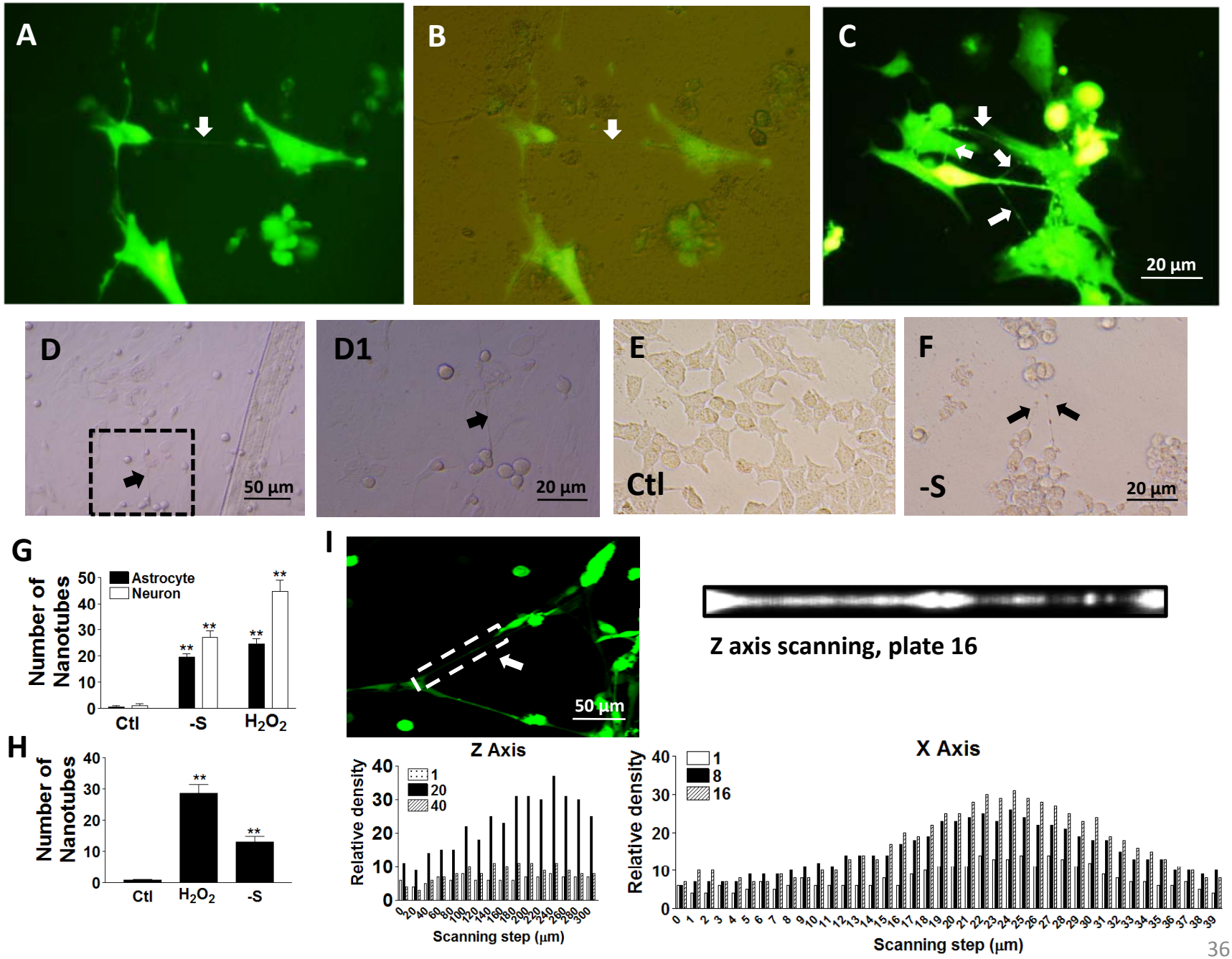
# Real research project: induction of tunneling nanotube
# 真实的研究项目：tunneling nanotube的诱导

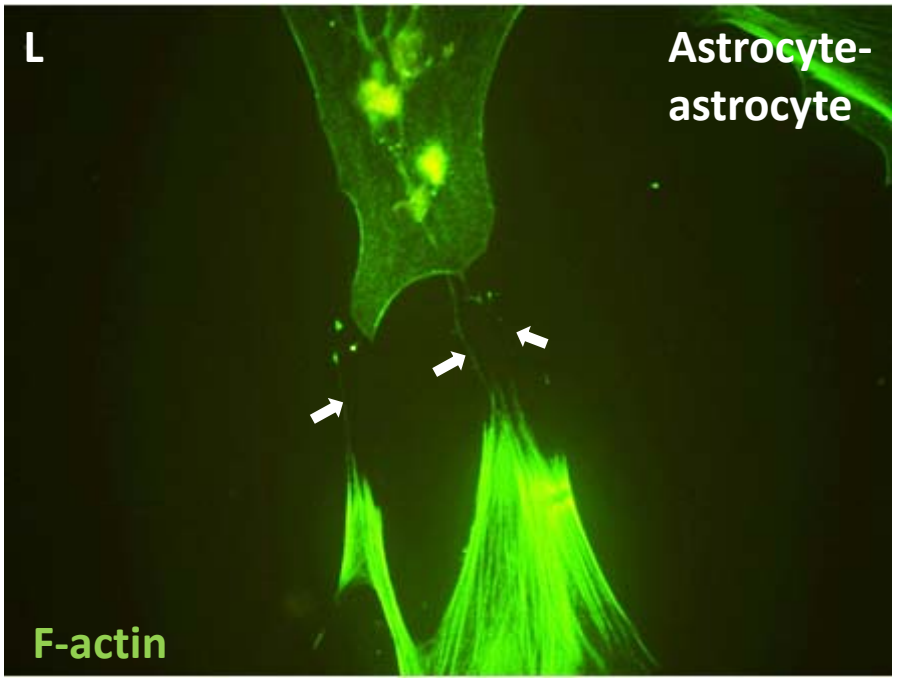
- Tunneling-nanotubes (TNTs) were first described in 2004 as a thin membranous, hovering freely channels between cells with diameter of 50-200 nm mediating communication between cells.

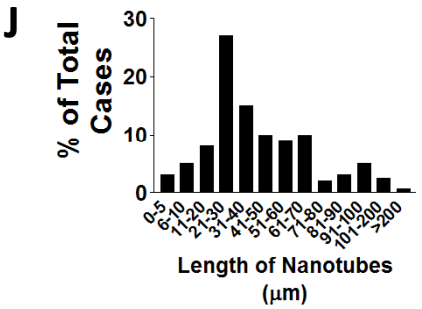
  Tunneling-nanotubes (TNTs)最早于2004年被描述：薄膜、细胞间悬在空中的通道，直径50-200 nm，是细胞间的交流媒介

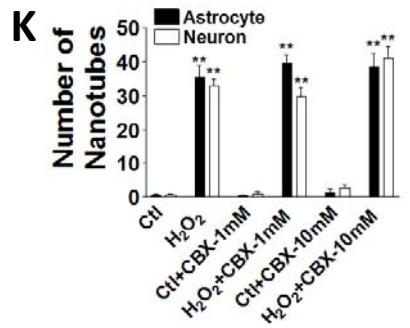
- TNTs are found in rat pheochromocytoma PC12 cells, HEK293 cells, EBV-transformed human B cell line, murine macrophage J774 cells, DU 145 human prostate cancer cells, THP-1 monocytes, hepatic HepG2 cells, TRVb-1 cells, bovine mammary gland epithelial cells, human monocyte-derived macrophages, primary cultures of rat astrocytes, myeloid-lineage dendritic cells and hematopoietic stem and progenitor cells.

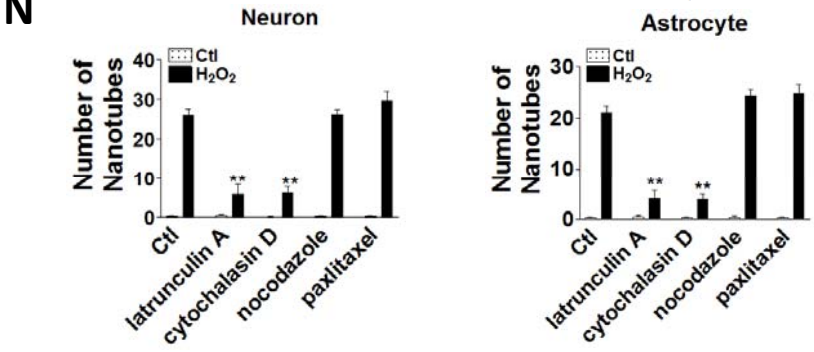
  TNT存在于大鼠嗜铬细胞瘤PC12细胞、HEK293细胞、EBV转化的人B细胞系、鼠巨噬细胞J774细胞、DU 145人前列腺癌细胞、THP-1单核细胞、肝HepG2细胞、TRVb-1细胞、牛乳腺上皮细胞、人单核细胞源巨噬细胞、鼠星形胶质细胞原代培养、骨髓系树突状细胞、造血干细胞和造血祖细胞。

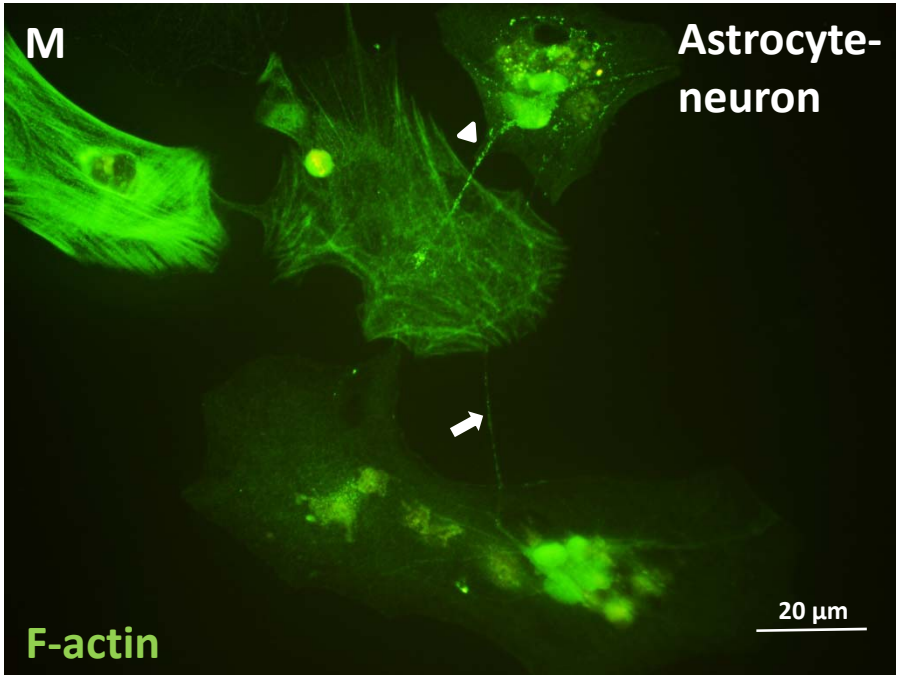

A
B
C
20 µm
D
50 µm
D1
20 µm
E
Ctl
F
-S
20 µm
G
Number of Nanotubes
Astrocyte
Neuron
Ctl
-S
H2O2
H
Number of Nanotubes
Ctl
H2O2
-S
I
50 µm
Z axis scanning, plate 16
Z Axis
Relative density
Scanning step (µm)
X Axis
Relative density
Scanning step (µm)

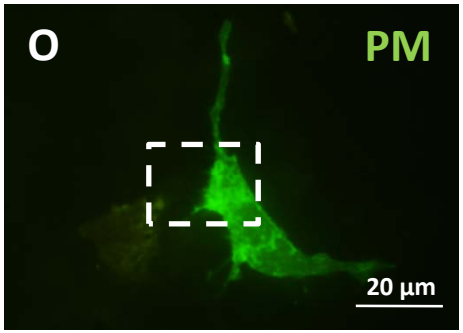

L
Astrocyte-astrocyte
F-actin

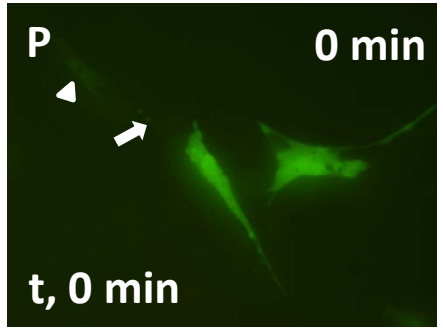

J
% of Total Cases
Length of Nanotubes (μm)
0-5
6-10
11-20
21-30
31-40
41-50
51-60
61-70
71-80
81-90
91-100
101-200
>200

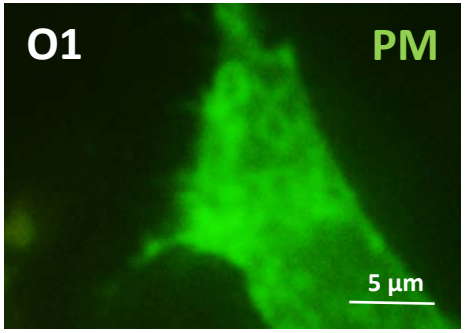

K
Astrocyte
Neuron
Number of Nanotubes
Ctl
H2O2
Ctl+CBX-1mM
H2O2+CBX-1mM
Ctl+CBX-10mM
H2O2+CBX-10mM

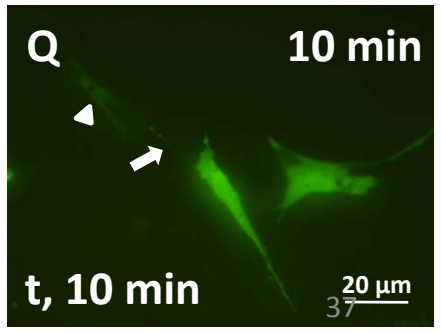

N
Neuron
Astrocyte
Number of Nanotubes
Ctl
H2O2
latrunculin A
cytochalasin D
nocodazole
paxlitaxel

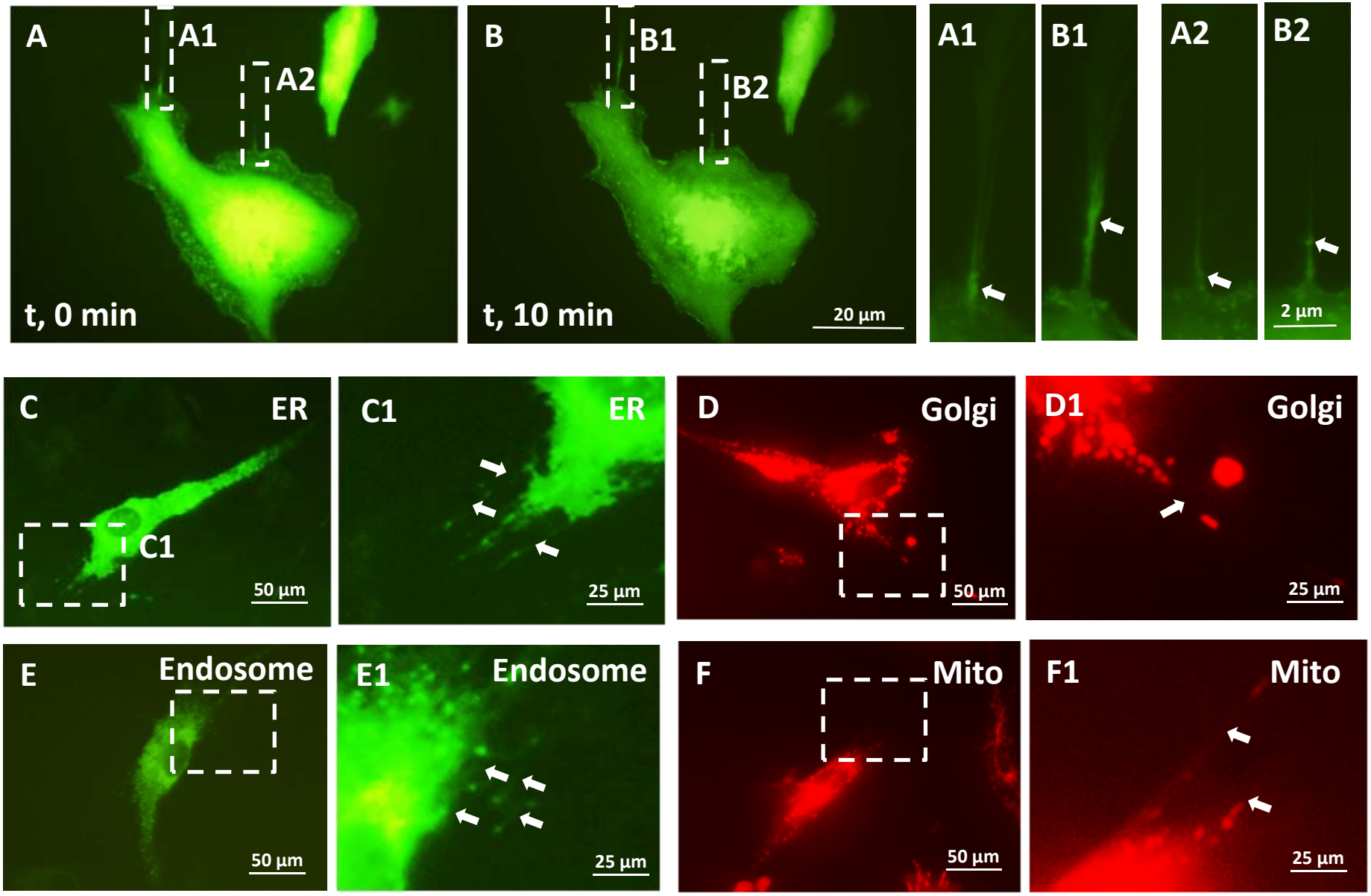

M
Astrocyte-neuron
F-actin
20 μm

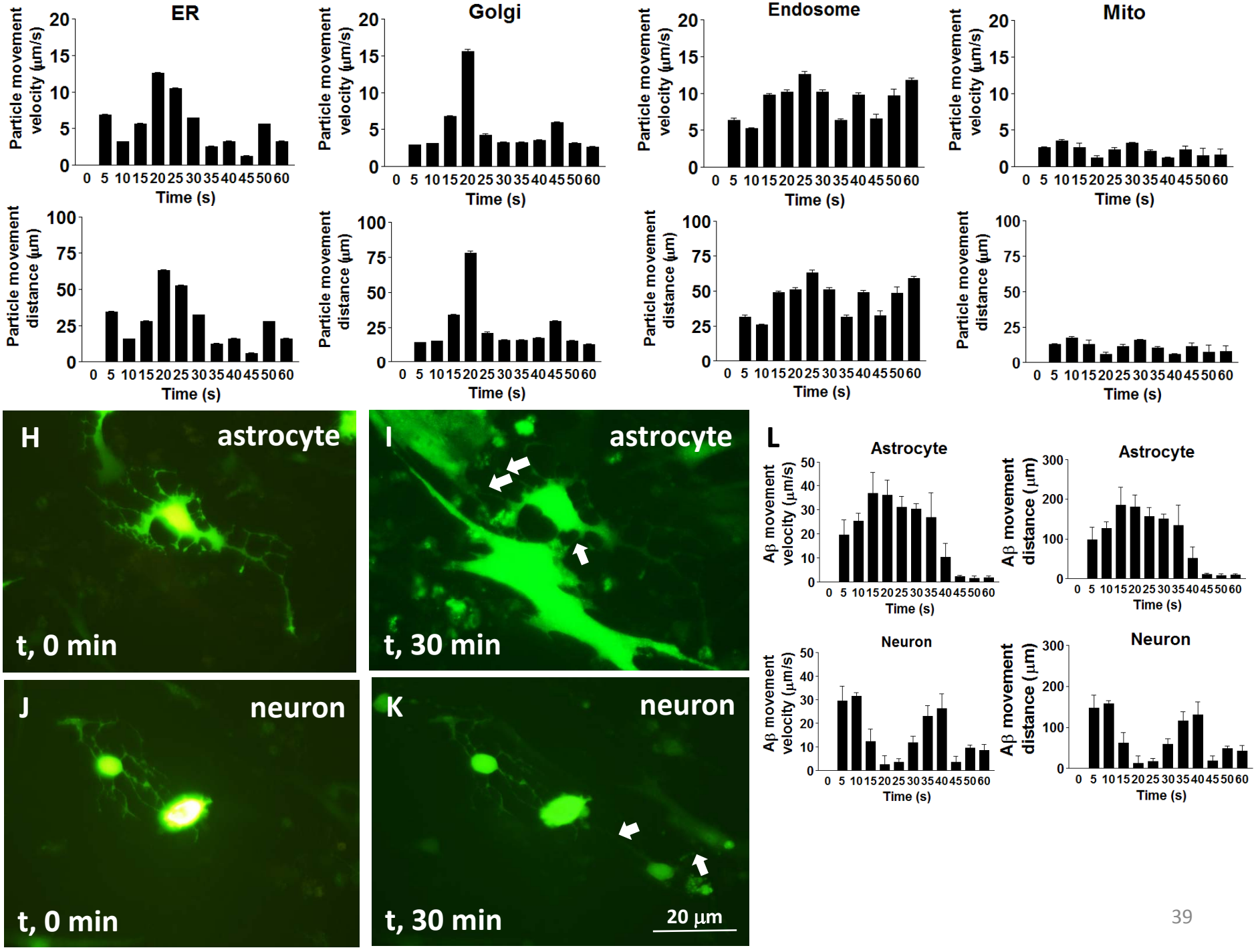

O
PM
20 μm

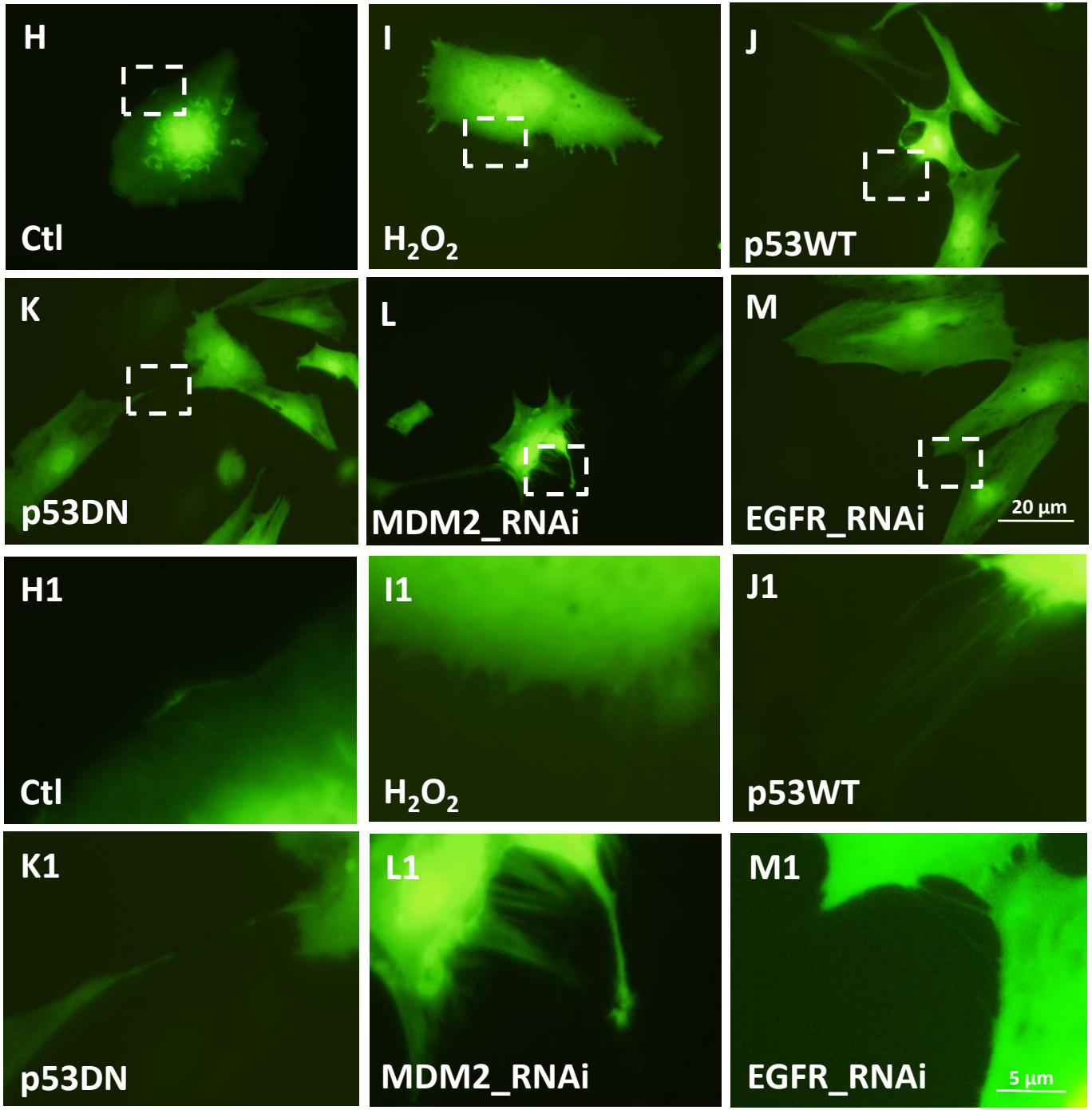

P
0 min
t, 0 min

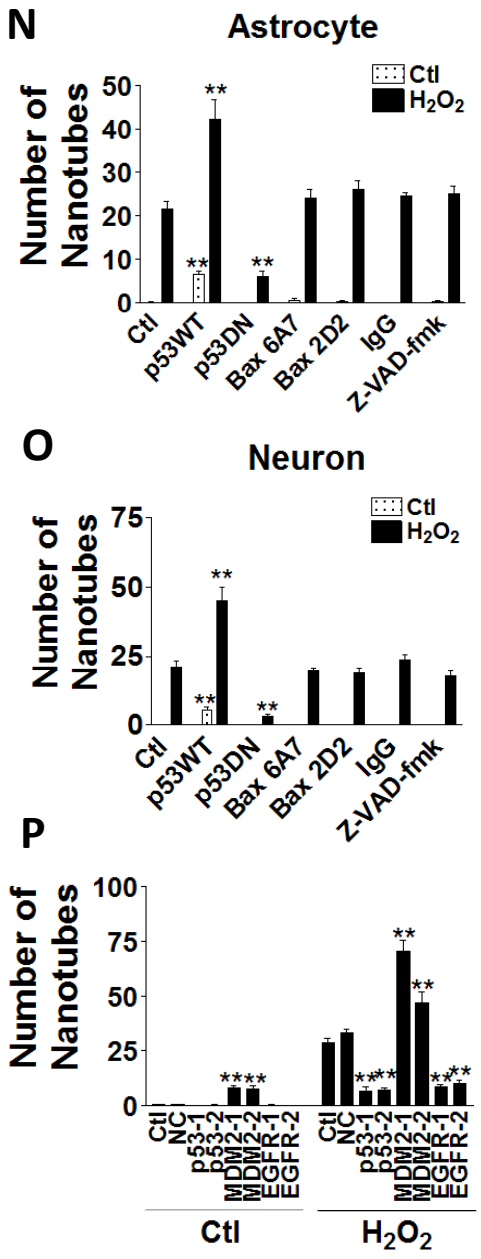

O1
PM
5 μm

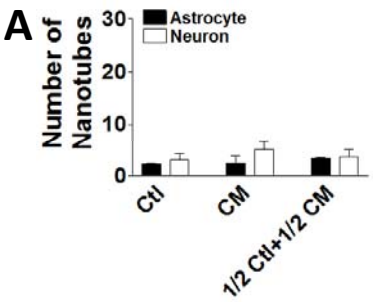

Q
10 min
t, 10 min
20 μm


A
A1
A2
t, 0 min
B
B1
B2
t, 10 min
20 µm
A1
B1
A2
B2
2 µm
C
ER
C1
50 µm
C1
ER
25 µm
D
Golgi
50 µm
D1
Golgi
25 µm
E
Endosome
50 µm
E1
Endosome
25 µm
F
Mito
50 µm
F1
Mito
25 µm
G

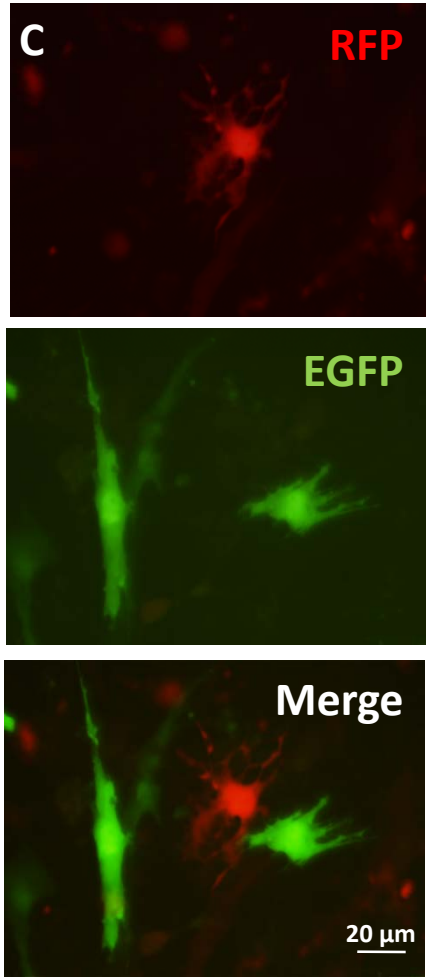

ER
Golgi
Endosome
Mito
Particle movement velocity (μm/s)
Particle movement distance (μm)
Time (s)
H
astrocyte
t, 0 min
I
astrocyte
t, 30 min
J
neuron
t, 0 min
K
neuron
t, 30 min
20 μm
L
Astrocyte
Neuron
Aβ movement velocity (μm/s)
Aβ movement distance (μm)
Time (s)

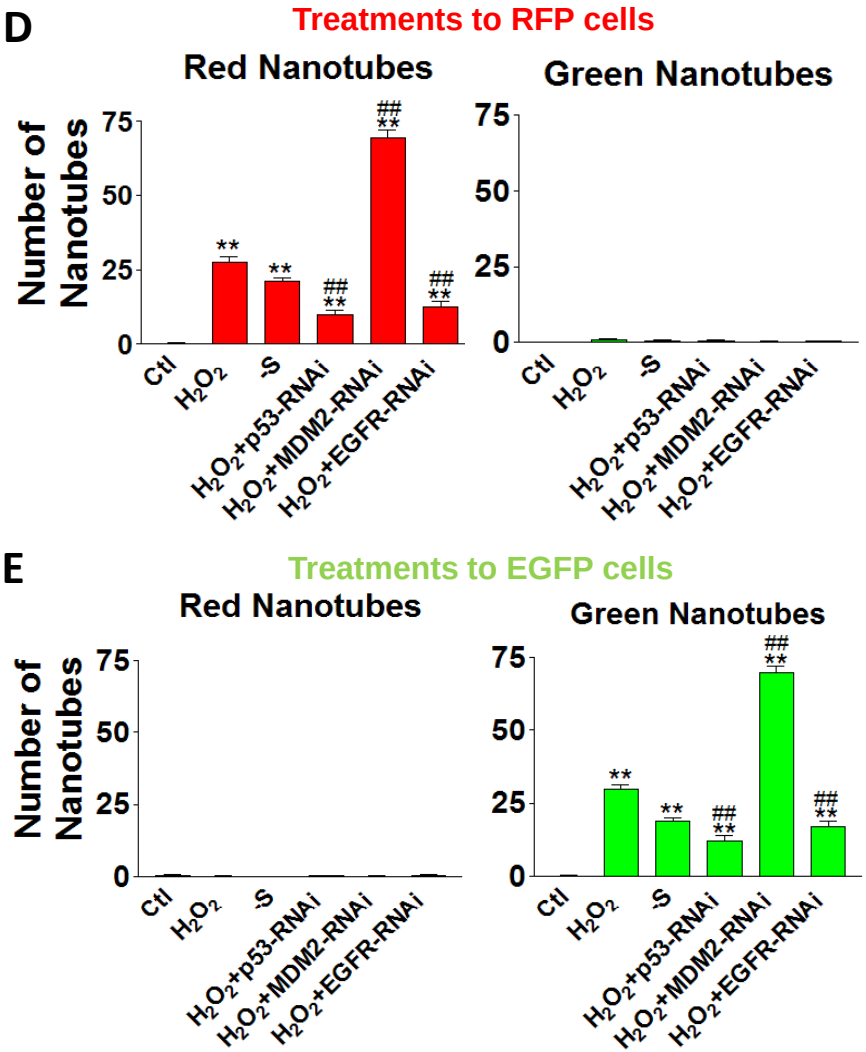

H
Ctl
I
H2O2
J
p53WT
K
p53DN
L
MDM2_RNAi
M
EGFR_RNAi
20 μm
H1
Ctl
I1
H2O2
J1
p53WT
K1
p53DN
L1
MDM2_RNAi
M1
EGFR_RNAi
5 μm

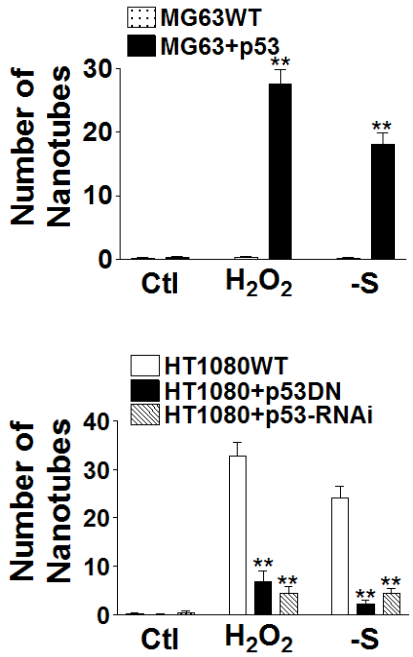

N
Astrocyte
Number of Nanotubes
Ctl
H2O2
Ctl
p53WT
p53DN
Bax 6A7
Bax 2D2
IgG
Z-VAD-fmk
O
Neuron
P
Ctl
NC
p53-1
p53-2
MDM2-1
MDM2-2
EGFR-1
EGFR-2
Ctl
H2O2

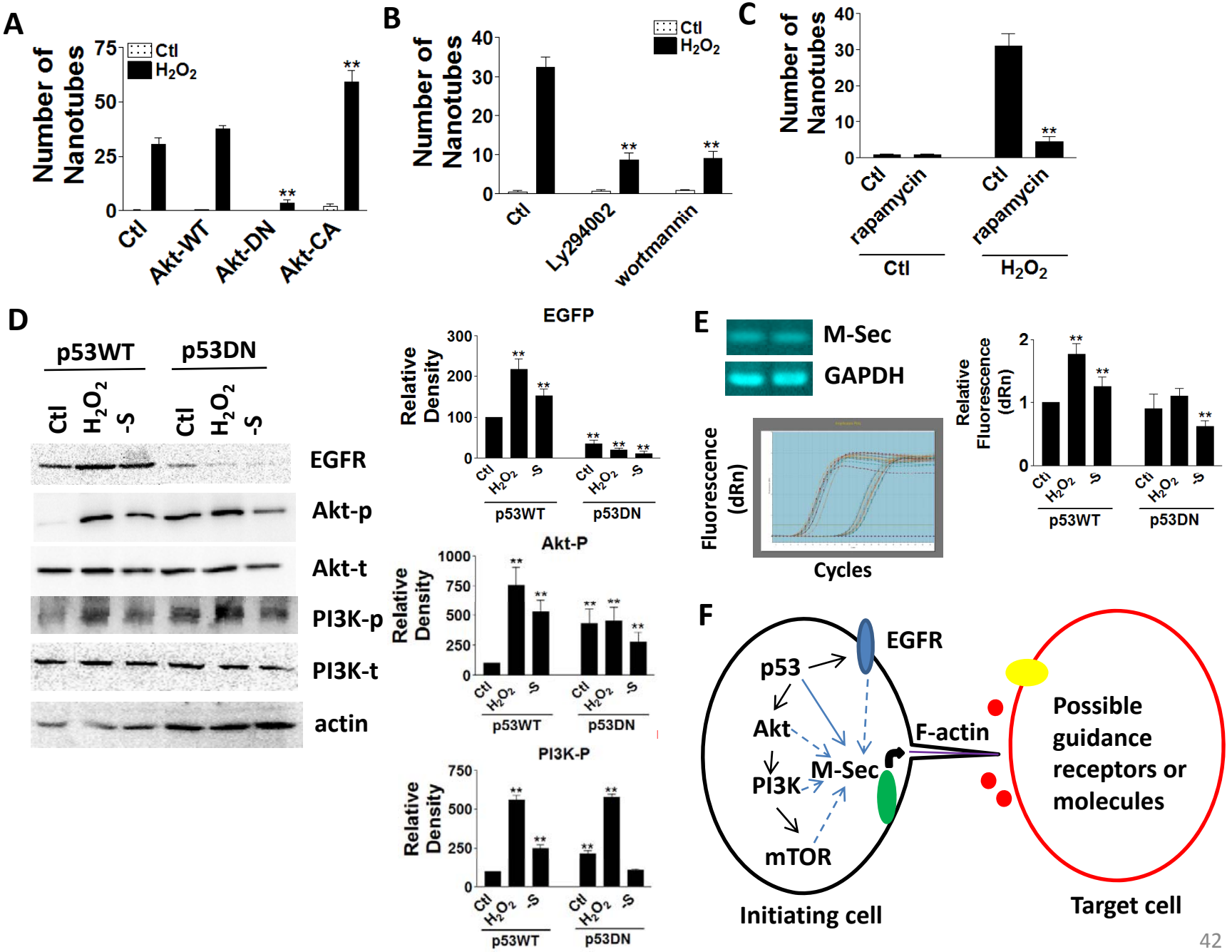

A
Number of Nanotubes
30
20
10
0
Astrocyte
Neuron
Ctl
CM
1/2 Ctl+1/2 CM


B
RFP
EGFP
After treatments, typsinize and wash the RFP cells and put onto the EGFP cells
treatments


C
RFP
EGFP
Merge
20 μm


D
Treatments to RFP cells
Red Nanotubes
Green Nanotubes
Number of Nanotubes
75
50
25
0
Ctl
H2O2
-S
H2O2+p53-RNAi
H2O2+MDM2-RNAi
H2O2+EGFR-RNAi
E
Treatments to EGFP cells
Red Nanotubes
Green Nanotubes

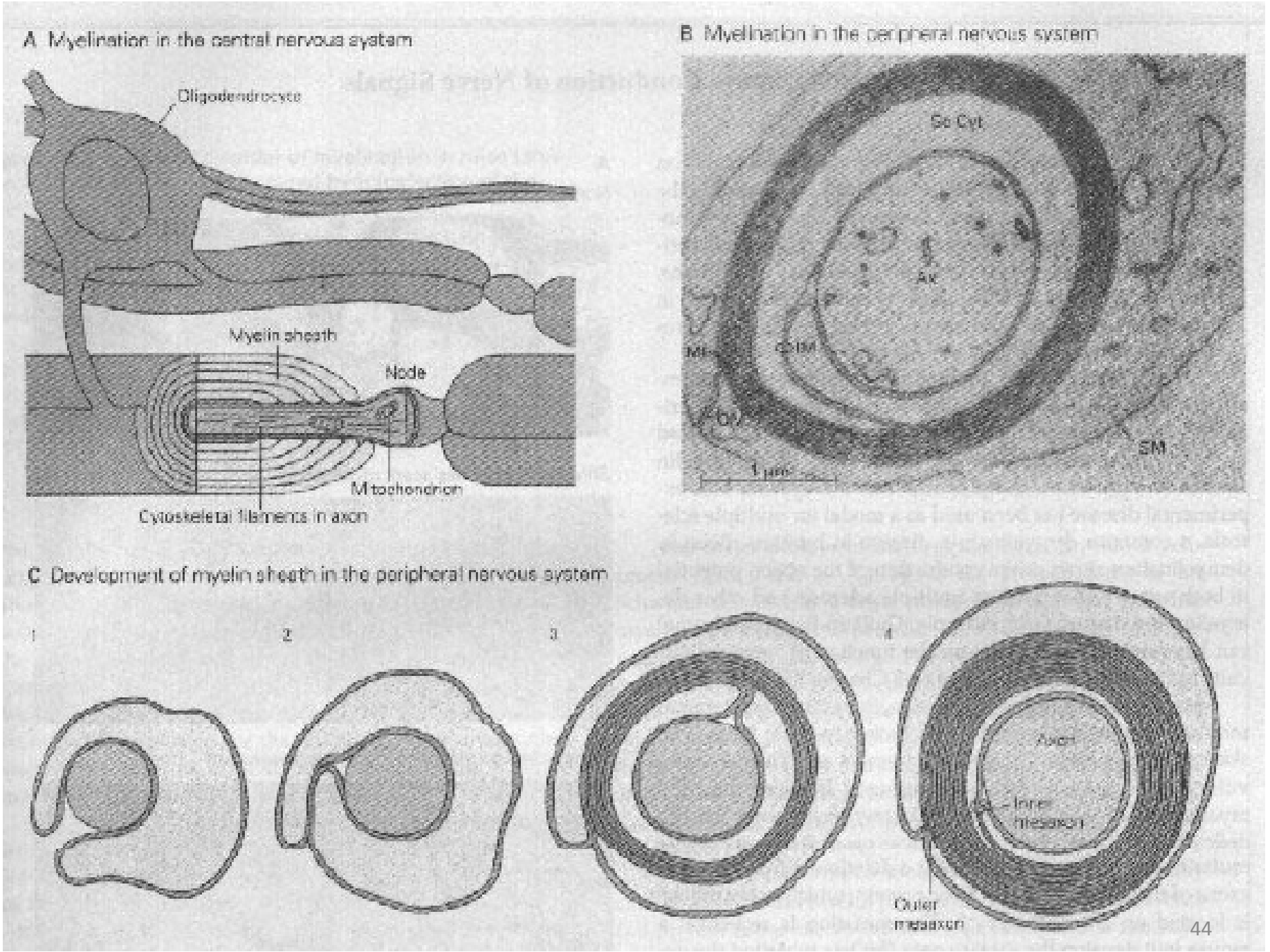

F
MG63WT
MG63+p53
Number of Nanotubes
30
20
10
0
Ctl
H2O2
-S
HT1080WT
HT1080+p53DN
HT1080+p53-RNAi
40


A
Number of Nanotubes
Ctl
H2O2
Ctl
Akt-WT
Akt-DN
Akt-CA
B
Number of Nanotubes
Ctl
H2O2
Ctl
Ly294002
wortmannin
C
Number of Nanotubes
Ctl
rapamycin
Ctl
rapamycin
Ctl
H2O2
D
p53WT
p53DN
Ctl
H2O2
-S
EGFR
Akt-p
Akt-t
PI3K-p
PI3K-t
actin
EGFP
Relative Density
Akt-P
PI3K-P
p53WT
p53DN
E
M-Sec
GAPDH
Fluorescence (dRn)
Cycles
Relative Fluorescence (dRn)
F
EGFR
p53
Akt
PI3K
mTOR
M-Sec
F-actin
Possible guidance receptors or molecules
Initiating cell
Target cell

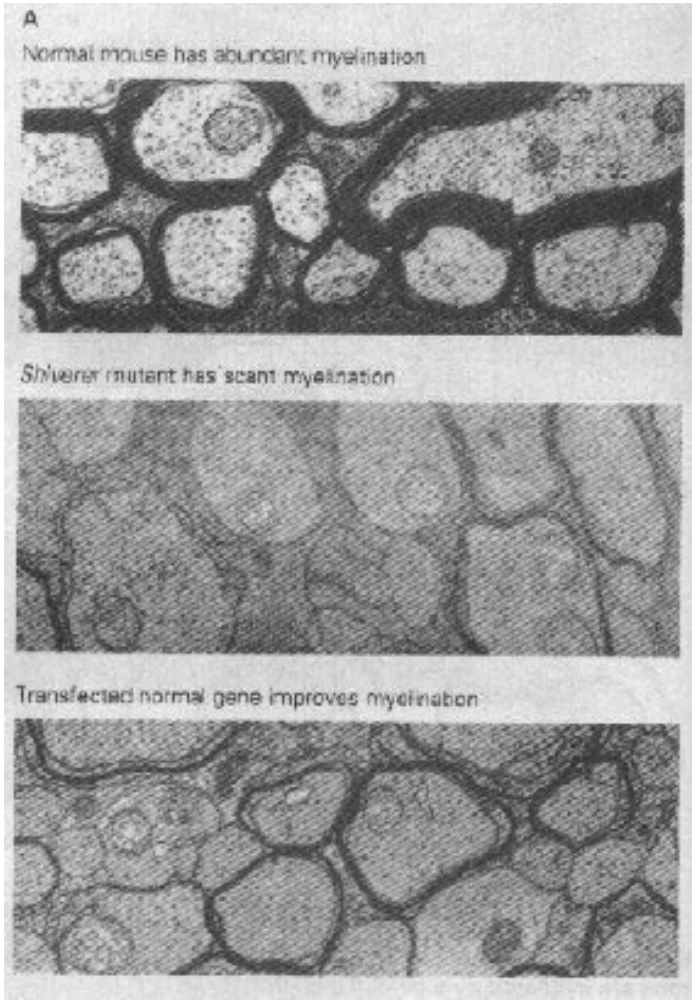
# Other cell types 其他细胞类型

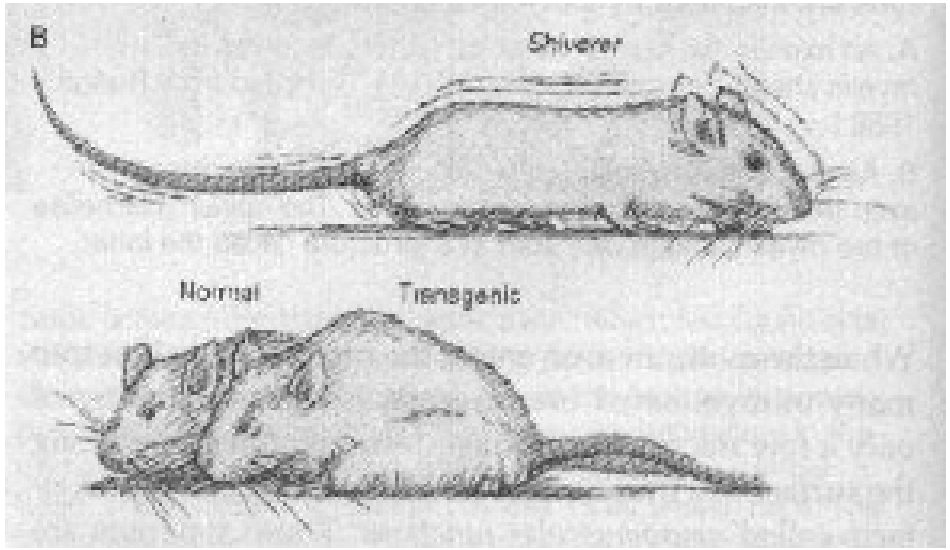
- Astrocytes 星形胶质细胞
- Microglias 小胶质细胞
- Oligodendrocytes 少突胶质细胞
  - Myelination 髓鞘化
  - Defects in myelin proteins disrupt conduction of nerve signals

    髓磷脂蛋白的缺失扰乱神经信号传导

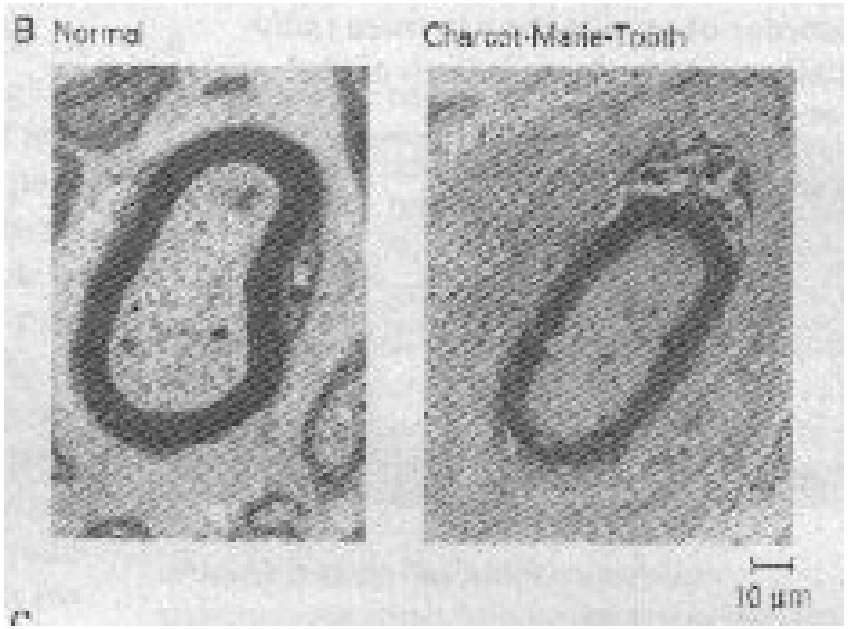

A Myelination in the central nervous system
Oligodendrocyte
Myelin sheath
Node
Mitochondrion
Cytoskeletal filaments in axon
B Myelination in the peripheral nervous system
Sc Cyt
Ax
ML
IM
BM
SM
1 μm
C Development of myelin sheath in the peripheral nervous system
1
2
3
4
Axon
Inner mesaxon
Outer mesaxon

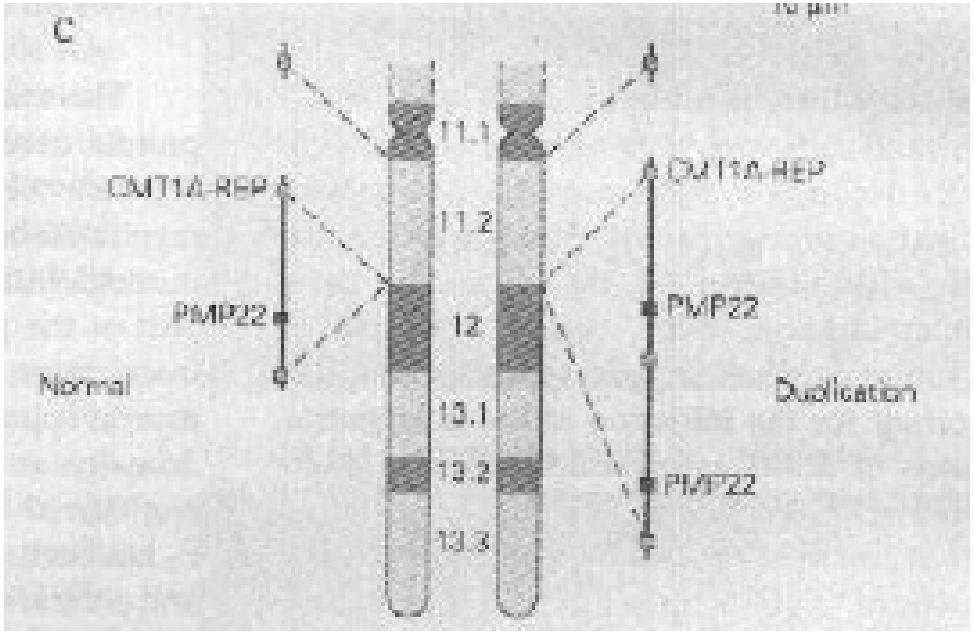
# Partial deletion of myelin basic protein causes *shiverer* phenotype
# MBP部分缺失导致颤栗表型



# Increased production of peripheral myelin protein induces Charcot-Marie-Tooth disease
# 外周髓磷脂蛋白导致腓骨肌萎缩症



# Synthesis and Trafficking of Neuronal Protein
# 神经元蛋白的合成和运输

- Most proteins are synthesized in the cell body and dendrites

  多数蛋白在细胞体和树突合成

  - Information for the synthesis of proteins is encoded in the DNA within the cell's nucleus

    蛋白合成信息被编码在细胞核内的DNA中

  - Only a selected portion of this genetic information is transcribed in a given cell to generate mRNAs and eventually proteins

    细胞中的这些信息只有选择性的一部分被转录成mRNA，最终合成蛋白

  - Regulated by DNA-binding proteins (transcription factors) synthesized in the cytosol and taken up into the nucleus through the nuclear pores

    由DNA结合蛋白（转录因子）调控。转录因子在细胞质中合成，通过核孔进入细胞核内。

- The brain expresses about 200,000 mRNA sequences: 10-20 times more than in the kidney or liver

  脑表达约200,000种mRNA序列，比肾和肝中多10-20倍
- In mature neurons, the chromosomes no longer duplicate and functions only in gene expression

  在成熟神经元中，染色体不再复制，只有表达基因的功能
- Chromosomes exit in a relatively uncoiled state

  染色体以相对非螺旋形式存在
- Circular mitochondria DNA

  环状线粒体DNA
- The synthesis of all proteins starts in the cytosol

  所有蛋白的合成均在细胞质中起始

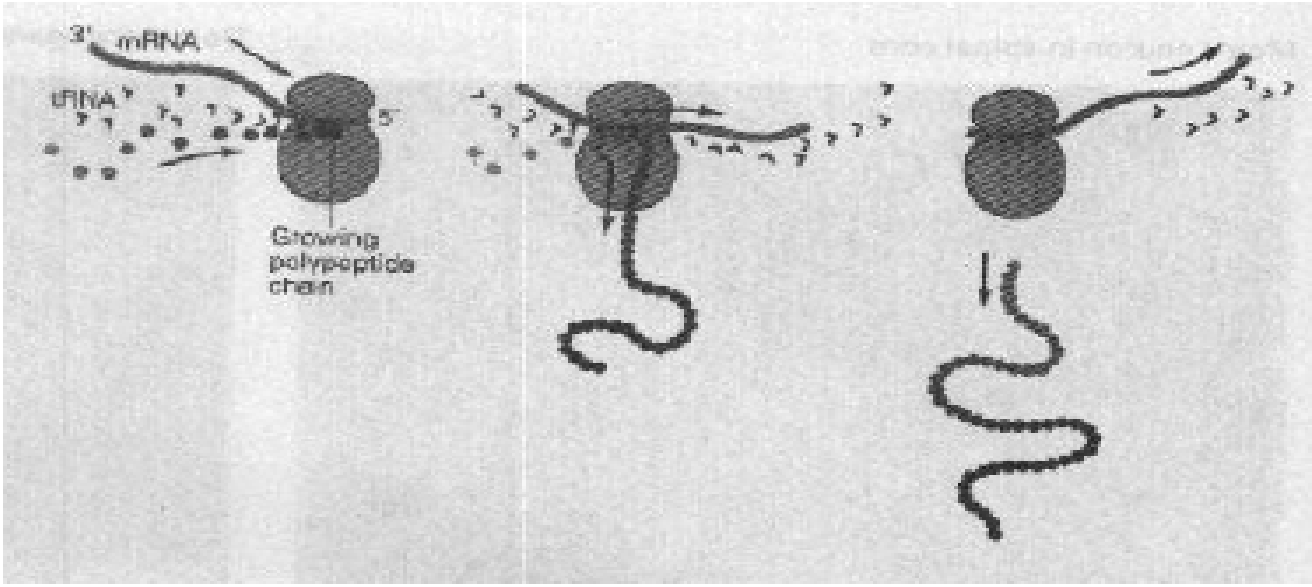
# Protein translation and synthesis
# 蛋白翻译和合成

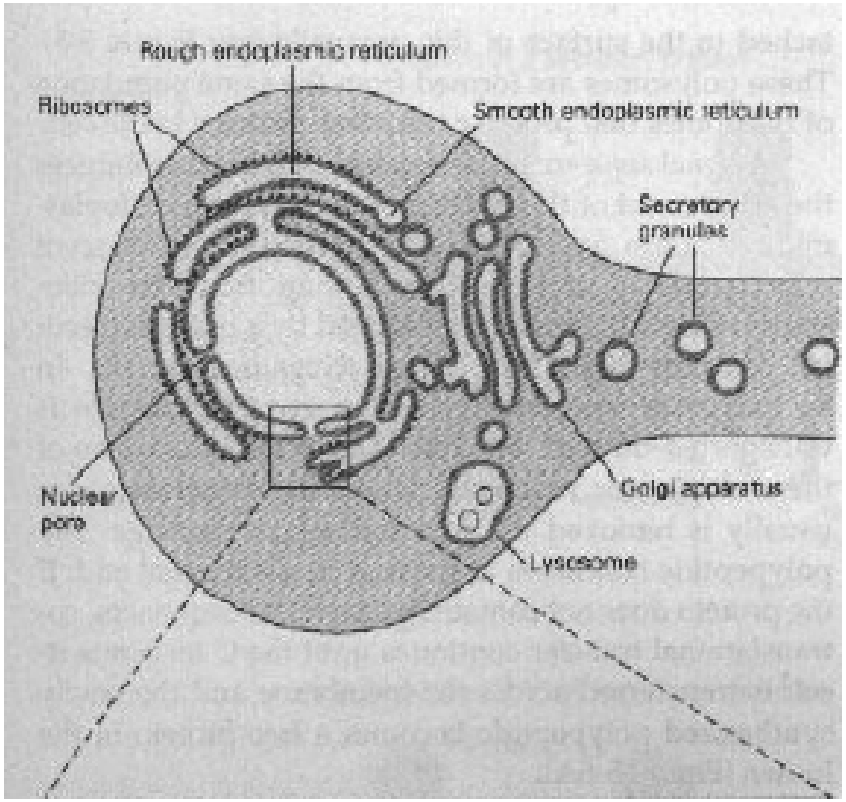
- Translation of mRNA starts from the 5’ end, which encodes the N-terminal end of the protein

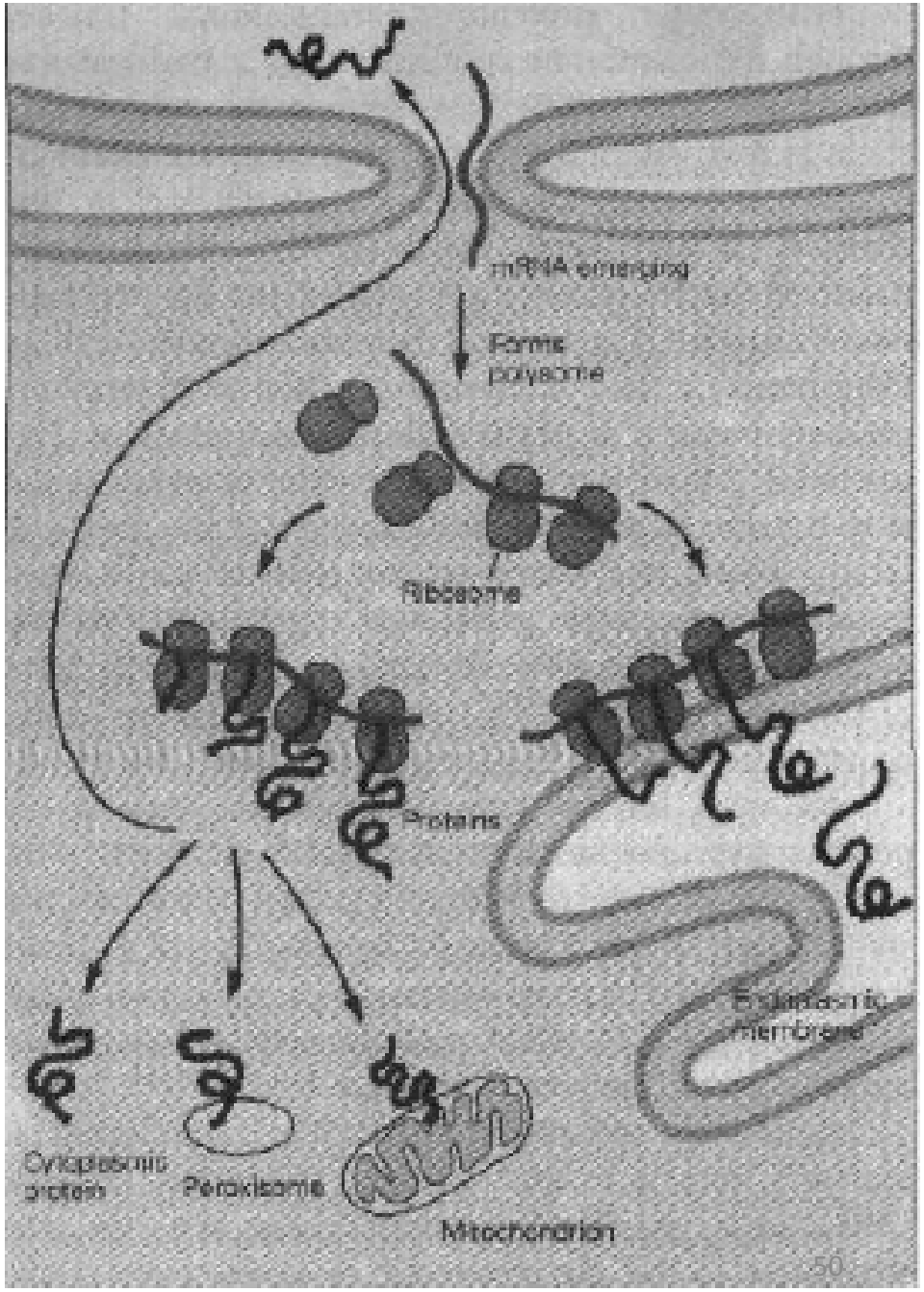
  mRNA翻译开始于5’端，此端编码蛋白N端

- N-terminal signal peptides: location (NLS), modification (palmitoylation, isoprenylation), degradation (ubiquitinylation)

  N端信号肽：位置（核定位序列），修饰（棕榈酰化、异戊二烯化），降解（泛素化）




Rough endoplasmic reticulum
Ribosomes
Smooth endoplasmic reticulum
Secretory granules
Nuclear pore
Golgi apparatus
Lysosome


mRNA emerging
Forms polysome
Ribosome
Proteins
Cytoplasmic protein
Peroxisome
Mitochondrion

# Protein synthesis in the cytosol
# 蛋白在细胞质中的合成

- Nuclear, peroxisomal and mitochondrial proteins encoded by the cell's nucleus, are formed in the cytosol

  核蛋白、过氧化物酶体蛋白和线粒体蛋白由细胞核编码，在细胞质中形成
- Import into nucleus: through nuclear pores (<10 nm, NLS, NES, requires ATP), after folding, not involve transport through a membrane

  入核：通过核孔（<10 nm,核定位序列、出核信号，需要ATP），在折叠之后发生，不包括跨膜转运
- The cytosol and nucleoplasm are theoretically continuous

  细胞质和核质理论上互通

- Mitochondrial and peroxisomal proteins: reach their native conformation only after import into the target organelle

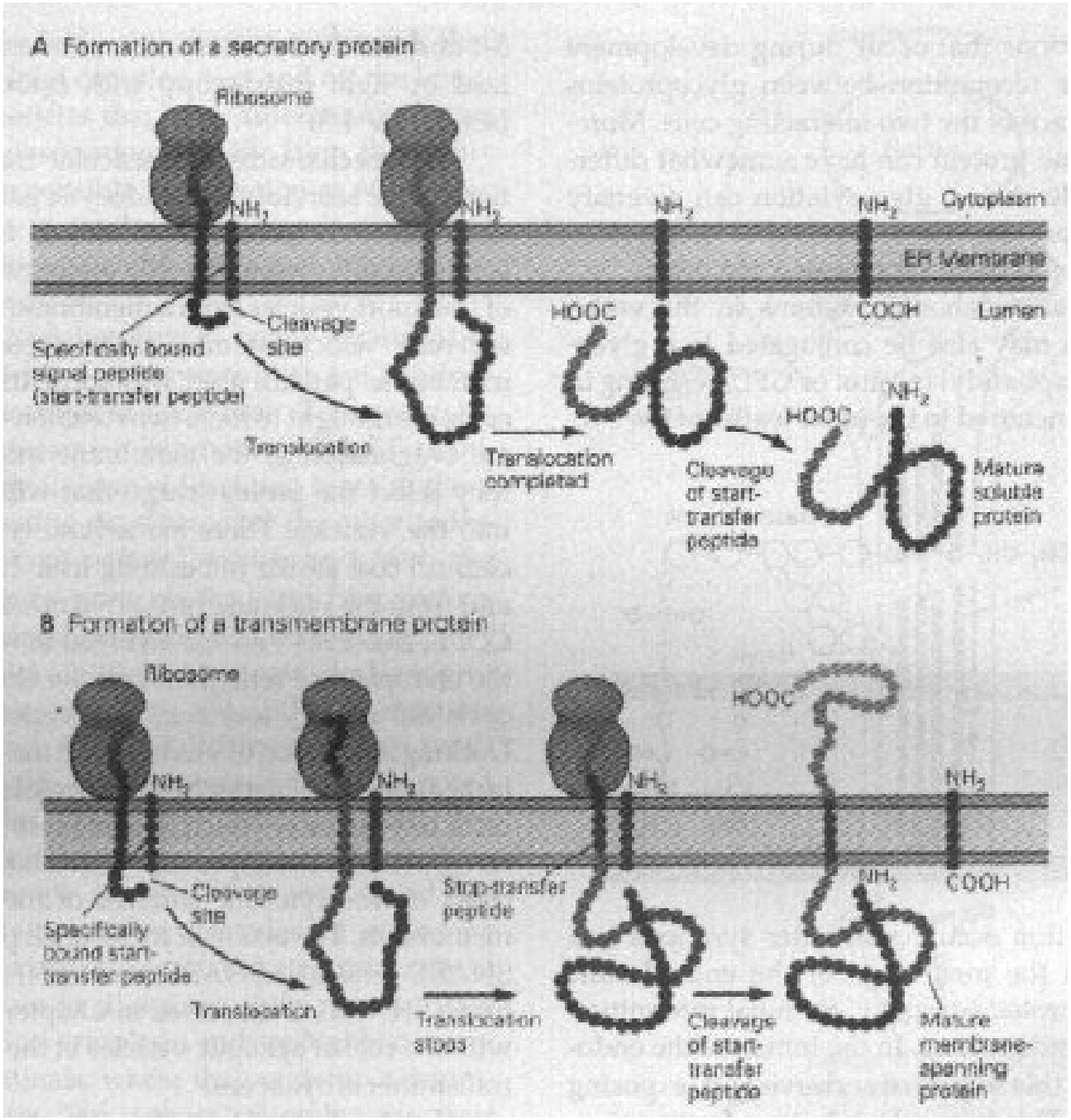
  线粒体蛋白和过氧化物酶体蛋白：到达目标细胞器后折叠成天然构象

- Movement of the polypeptide chain through the bilayer of mitochondrial membranes requires chaperones

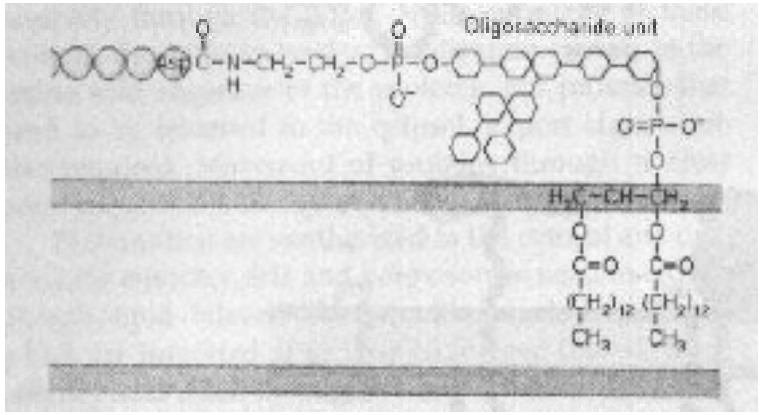
  多肽链通过线粒体双层膜的运动需要分子伴侣

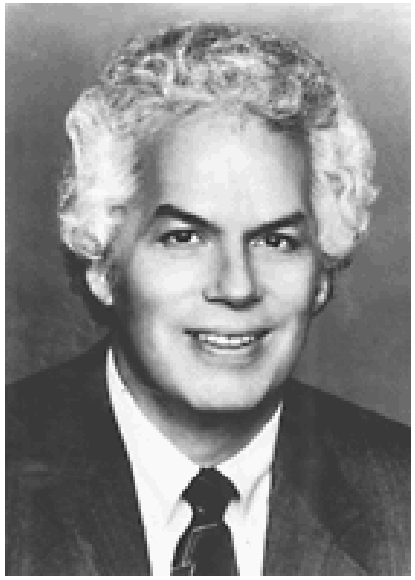
# Protein synthesis in the ER
# 蛋白在内质网中的合成

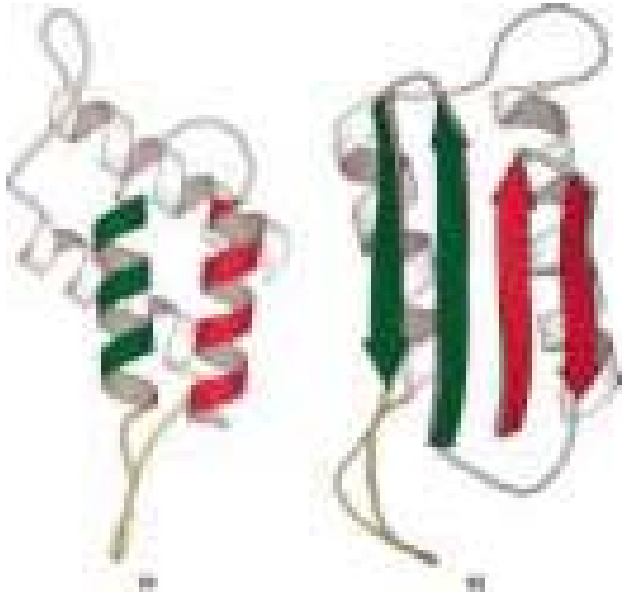
- Secretory proteins 分泌蛋白
  - Signal sequence 信号序列
- Proteins of the vacuolar apparatus and plasmalemma
  空泡状细胞器蛋白和质膜蛋白
  - Hydrophobic stop-transfer segment
    疏水终止运输信号
  - Neurotransmitter receptors and ion channels
    神经递质受体和离子通道
  - Glycosylphosphatidyl inositol (GPI) anchored proteins
    磷脂酰肌醇（GPI）锚定蛋白


A Formation of a secretory protein
Ribosome
NH2
Cytoplasm
ER Membrane
Lumen
COOH
HOOC
Cleavage site
Specifically bound signal peptide (start-transfer peptide)
Translocation
Translocation completed
Cleavage of start-transfer peptide
Mature soluble protein
B Formation of a transmembrane protein
Ribosome
Stop-transfer peptide
Specifically bound start-transfer peptide
Translocation stops
Mature membrane-spanning protein

# GPI anchored protein
# GPI锚定蛋白





# Secretory proteins are further processed in the Golgi
# 分泌蛋白在高尔基体的进一步加工

- N-linked oligosaccharides, O-linked glycosylation, phosphorylation, sulfation

  N-连接寡糖基化、O-连接糖基化、磷酸化、硫酸盐化
- Constitutive secretion

  固有分泌
- Regulated secretion

  受调分泌
  - Peptide neurohormones

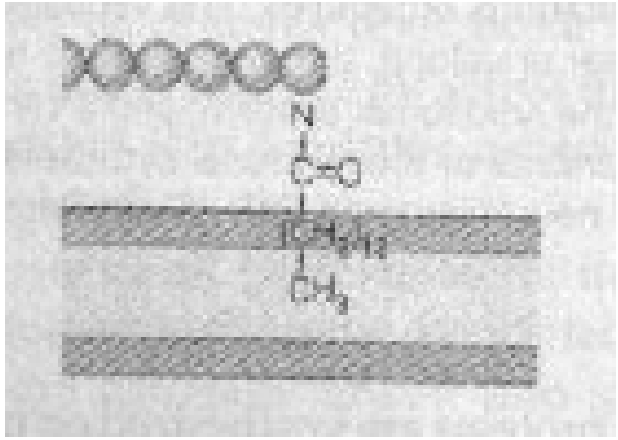
    神经激素肽

# Protein modification
# 蛋白修饰

- Proteins may be modified during (co-translational) or after (post-translational) synthesis

  蛋白可以在翻译中或翻译后被修饰
- Cotranslational modification: N-acylation, 80% of a cell's proteins are acylated

  共翻译修饰：N-酰化，细胞蛋白80%被酰化

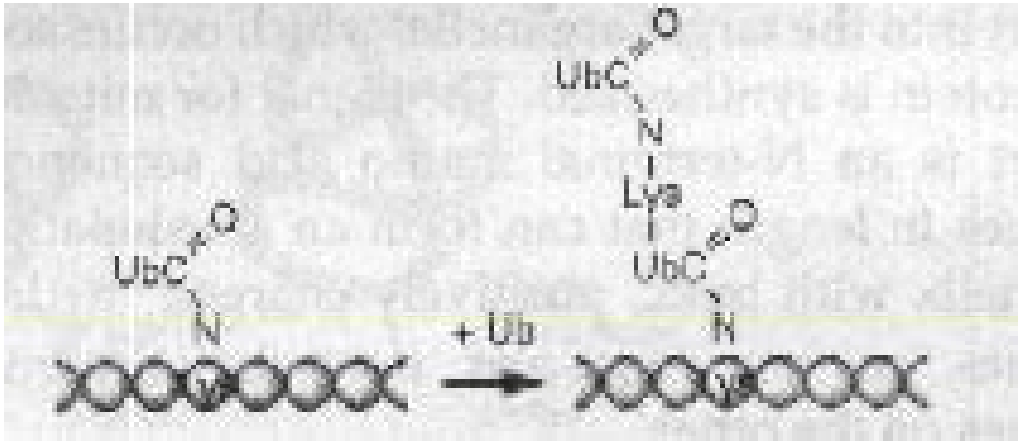


- Post-translational modifications: thioacylation, isoprenylation

  翻译后修饰：硫代酰化、异戊二烯化
- Some post-translational modifications are readily reversible and are used to regulate the function of a protein transiently: phosphorylation and dephosphorylation

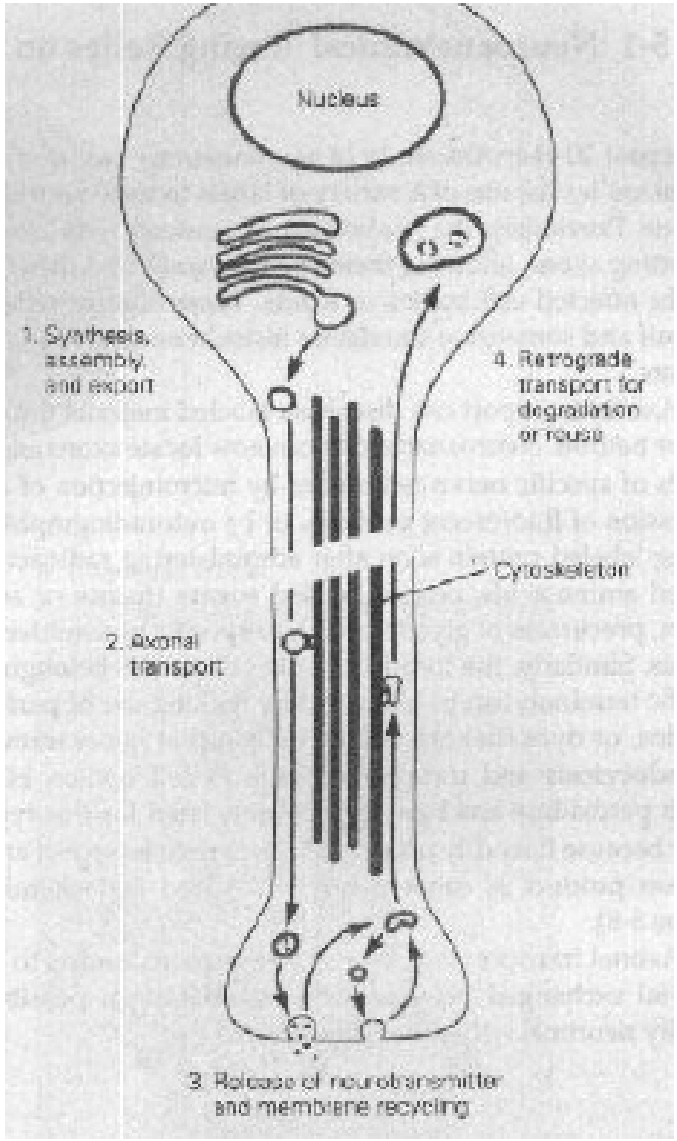
  一些翻译后修饰容易擦除，用作瞬间调节蛋白功能：磷酸化和去磷酸化
- Important post-translational modification: ubiquitination

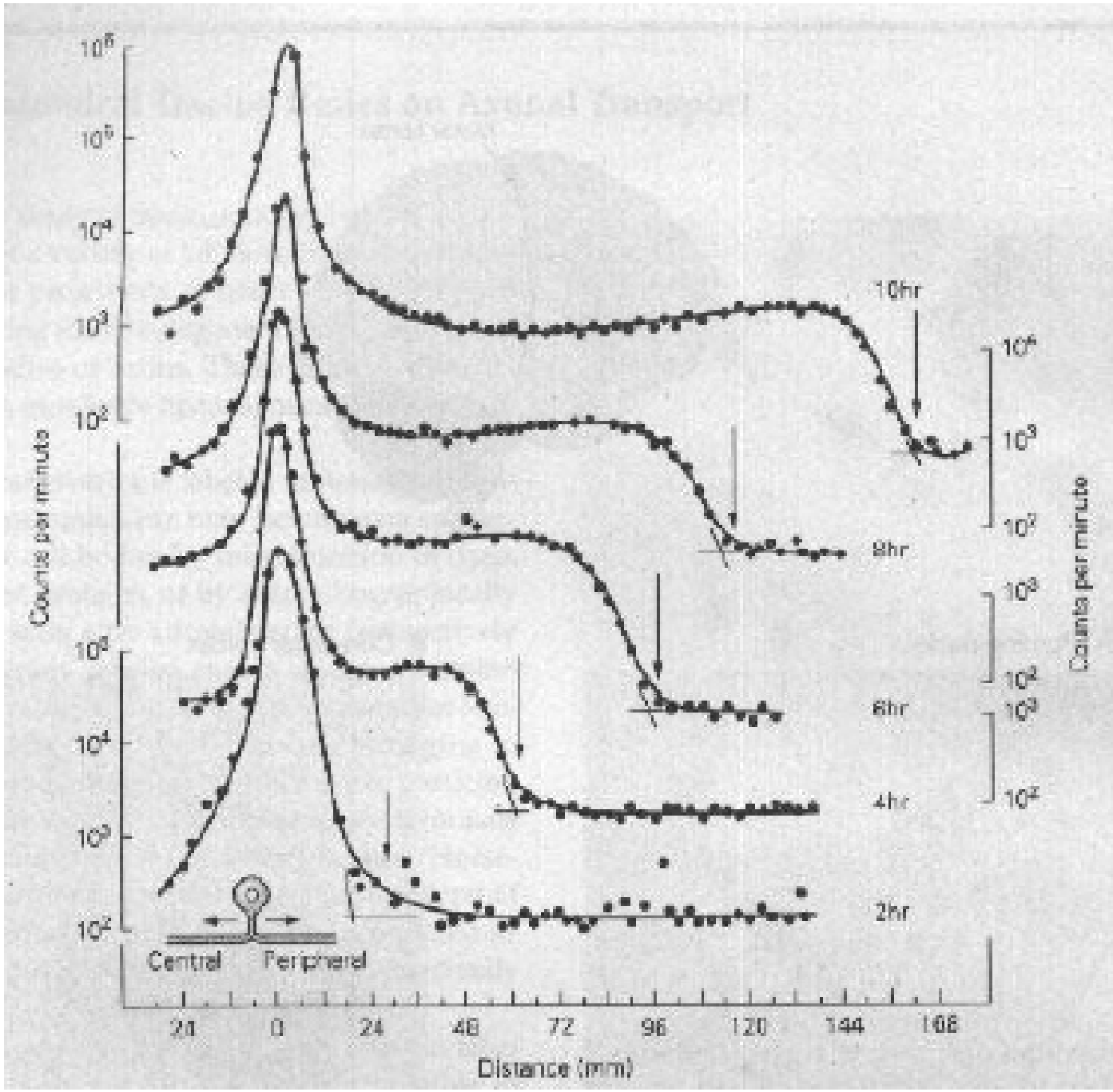
  重要翻译后修饰：泛素化

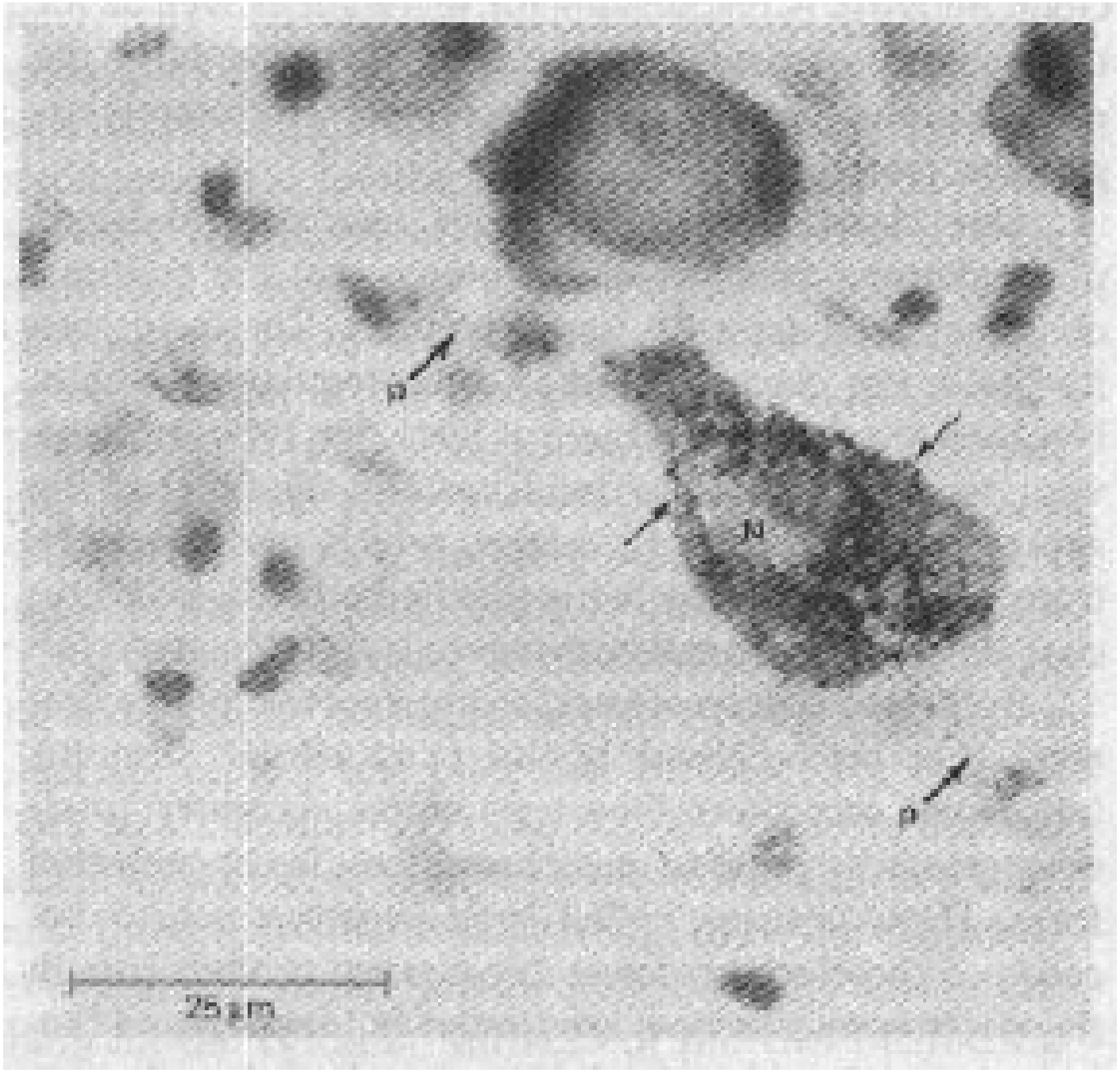


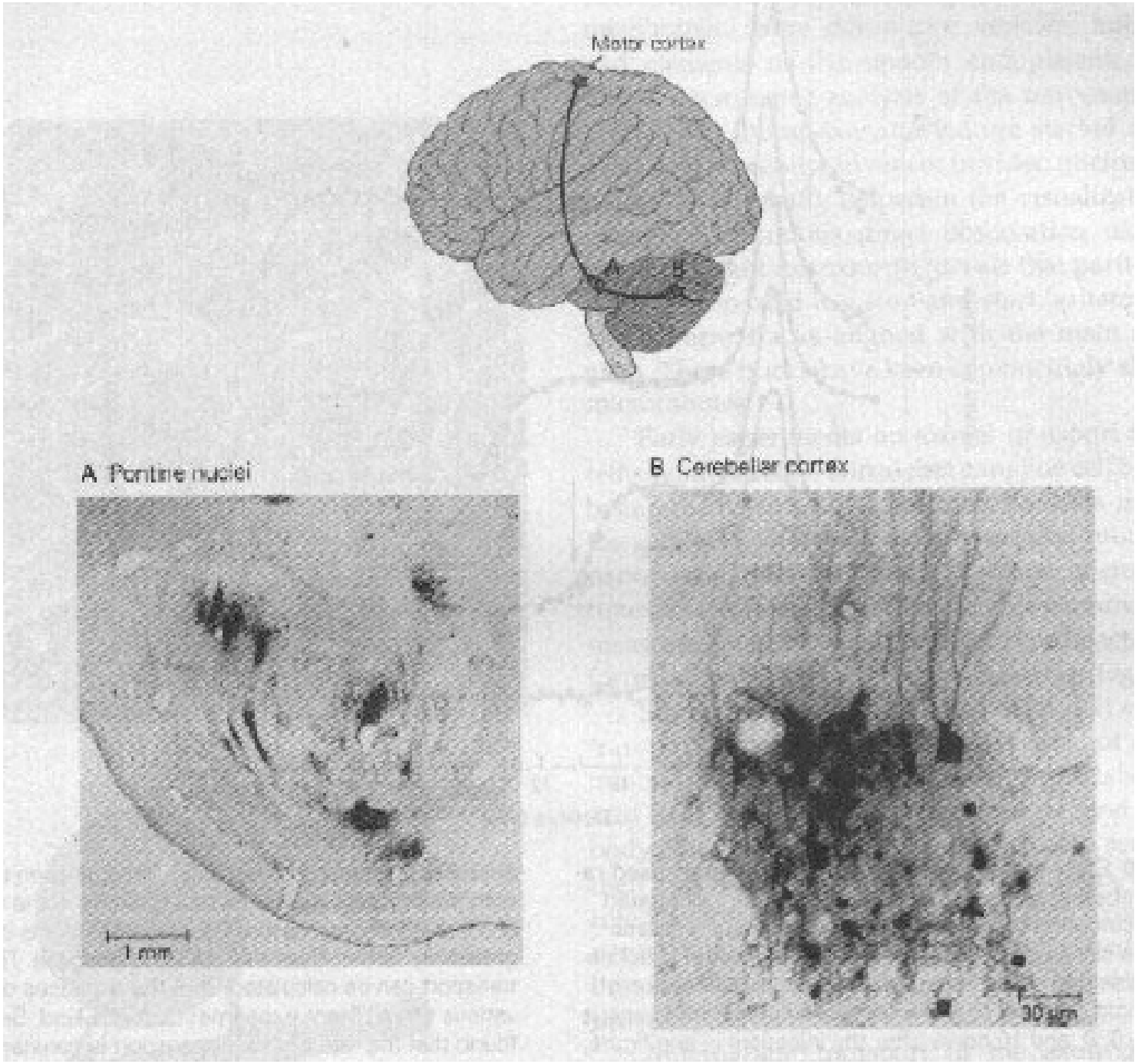
# Protein trafficking 蛋白质运输

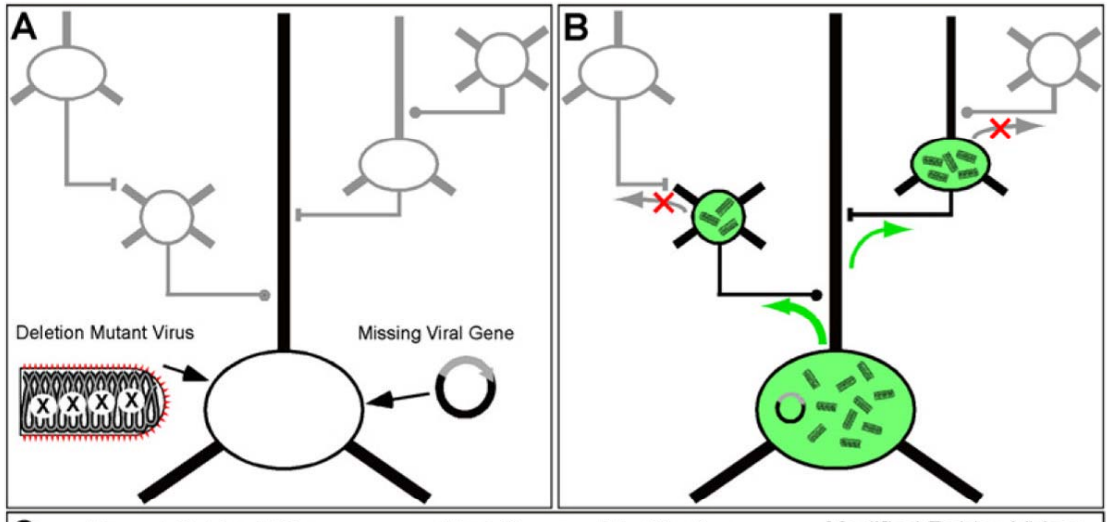
- Exportation
  运出
- Endocytosis
  胞吞
- Exocytosis
  胞吐

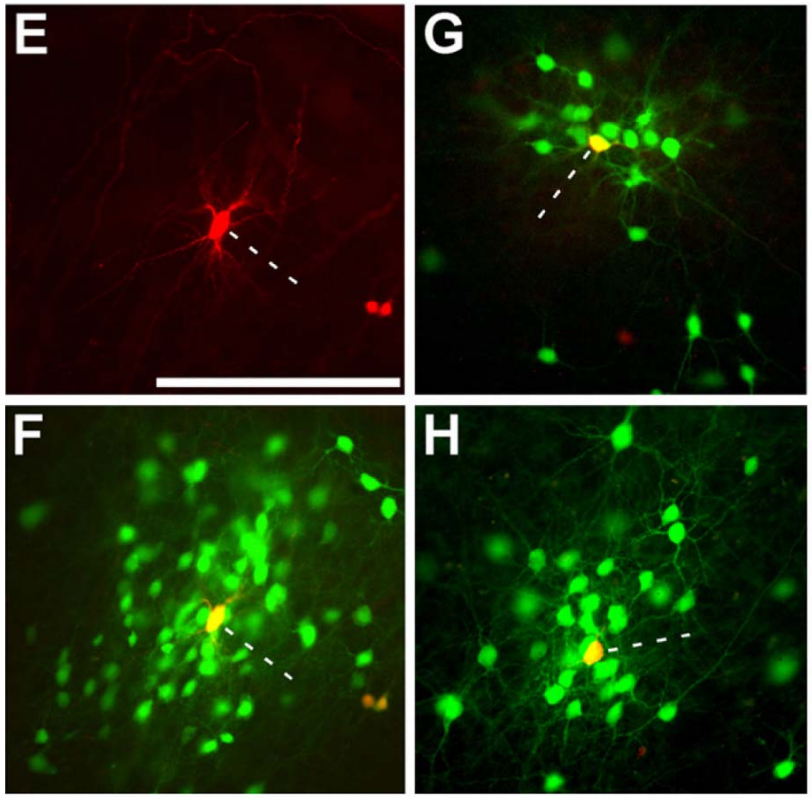



Counts per minute
10hr
8hr
6hr
4hr
2hr
Central
Peripheral
24
0
24
48
72
96
120
144
168
Distance (mm)


25 µm


Motor cortex
A Pontine nuclei
1 mm
B Cerebellar cortex
30 μm


A
B
Deletion Mutant Virus
Missing Viral Gene


E
G
F
H

# Proteins and organelles are transported along the axon
# 蛋白和细胞器在轴突中的运输

- Fast axonal transport: membranous organelles (>400 mm/day)

  快速轴突运输：膜细胞器（ >400 mm/天 ）
  - Anterograde: move toward the nerve terminal

    顺行：朝向神经末端
  - Retrograde: move back toward the cell body

    逆行：返回细胞体
- Slow axonal transport: cytosolic and cytoskeletal proteins, only in the anterograde direction (0.2-2.5 mm/day)

  慢速轴突运输：细胞质蛋白和细胞骨架蛋白，仅在顺行方向（ 0.2-2.5 mm/天）

# Fast axonal transport carries membranous organelles
# 快速轴突运输携带膜细胞器