Lecture 07:
Neural Circuit Development

Zana Rafiq Majeed, Ph.D.

08 and 09-03-2023

Overview

- During development groups of neurons must become **interconnected** to form the **neural circuits**.
- The first step in this process is to establish **axons and dendrites**.
- Axons grow and begin to make the **synaptic connections** that will define **neural circuits**.
- The **guided growth** of axons and **recognition** of appropriate synaptic targets depend on **growth cones**.

Overview

- The **dynamic behavior** of growth cones depends in turn on **adhesive**, **attractive**, and **repulsive** molecular signals.

- Once axons find appropriate targets and form **synapses**, molecular **neurotrophic factors** influence **neuron survival**.

- Mature neural circuits allow animals to **behave** in various ways.

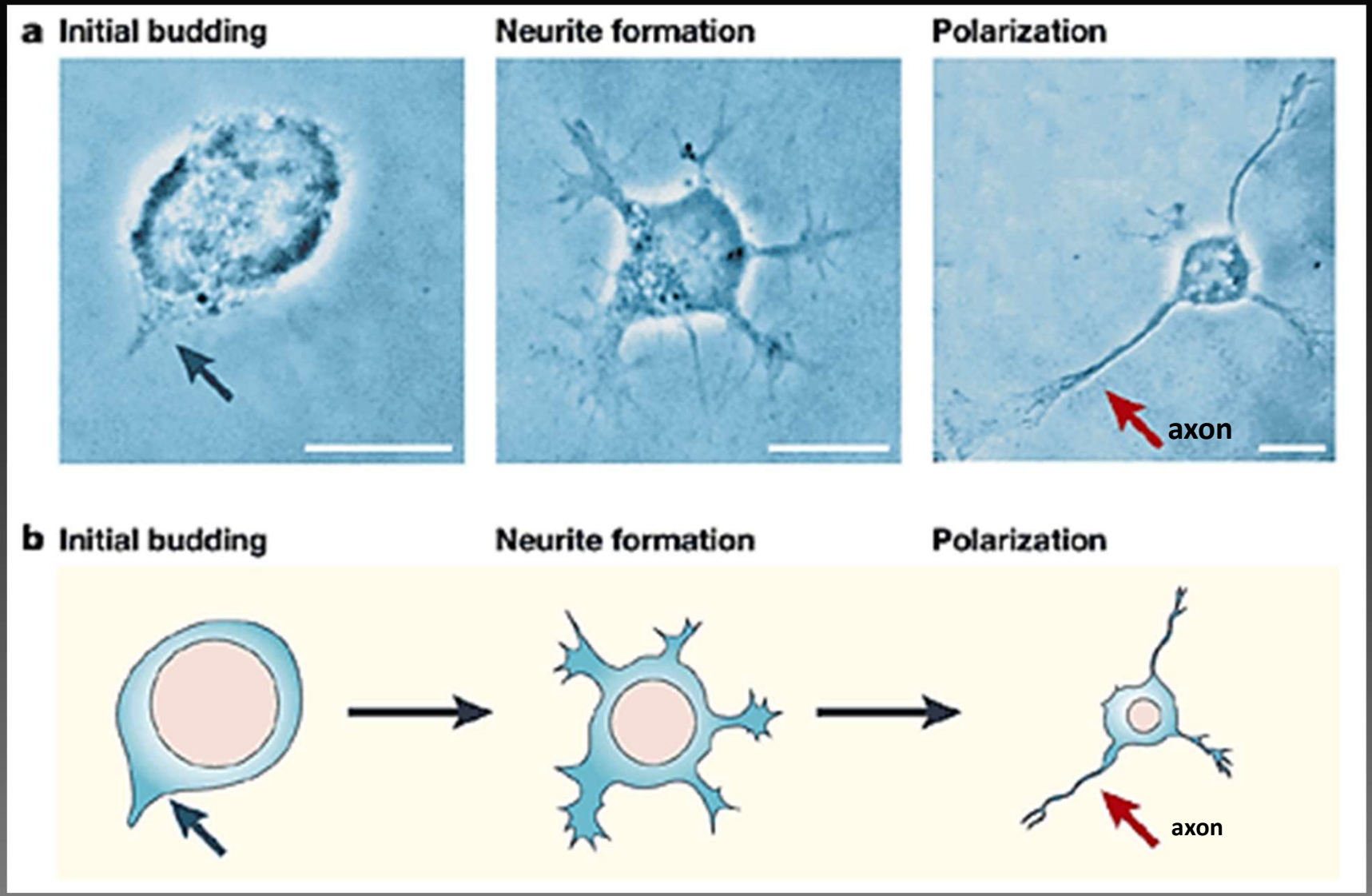
Neuronal Polarization: The First Step in Neural Circuit Formation

- A first step in neurons development is distinguishing their **polarity.**

- For the neuron, the fundamental polarity reflects the distinction between the **dendrites and the axon**.

- Once **neurogenesis** is complete and the **neuroblast** has entered a fully committed **postmitotic state**, the outgrowth of neuronal processes begins.

Neuronal Polarization: The First Step in Neural Circuit Formation



The Axon Growth Cone

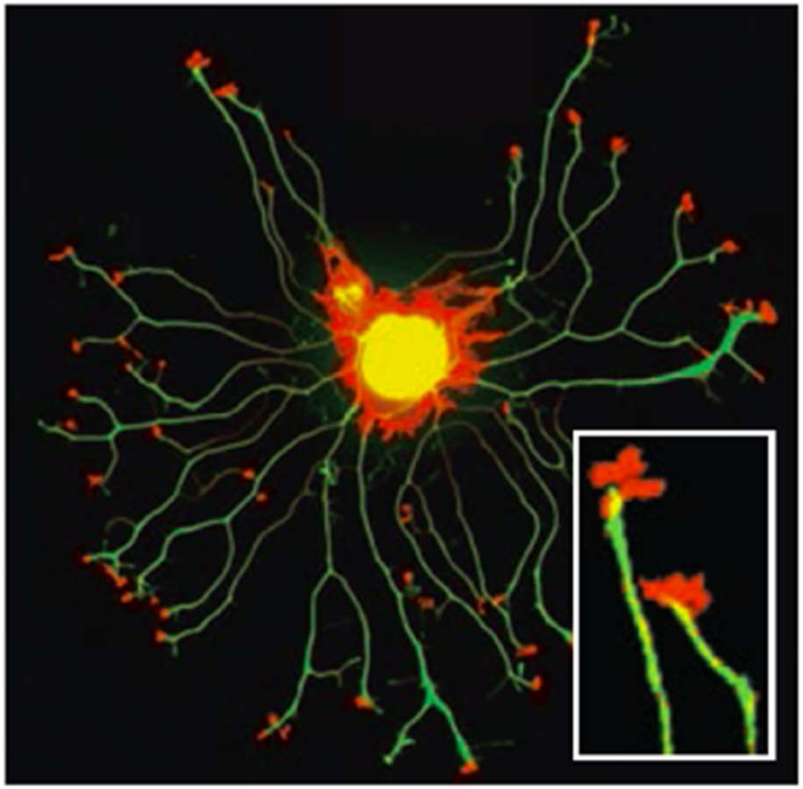
- **Growth cones** are highly motile. They explore the extracellular environment, determine the direction of growth, and then **guide the extension** of the axon in that direction.

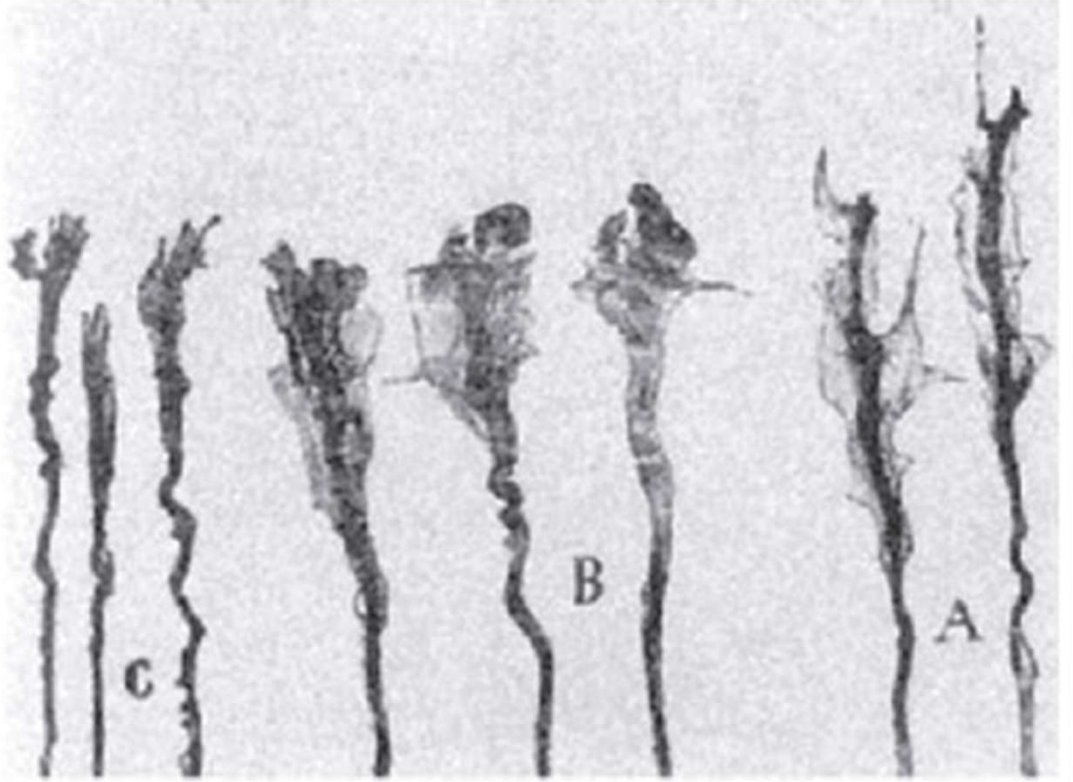
- The primary morphological characteristic of a growth cone is a sheet-like expansion of the growing axon at its tip called a **lamellipodium.**

The Axon Growth Cone

- Numerous fine processes called **filopodia** extend from each lamellipodium.
- Filopodia rapidly form and disappear from the terminal expansion, like fingers reaching out to **sense the environment**.
- The lamellipodium and filopodia are distinguished from the axon shaft by different cytoskeletal molecules.

The Axon Growth Cone





The Molecular Basis of Growth Cone Motility

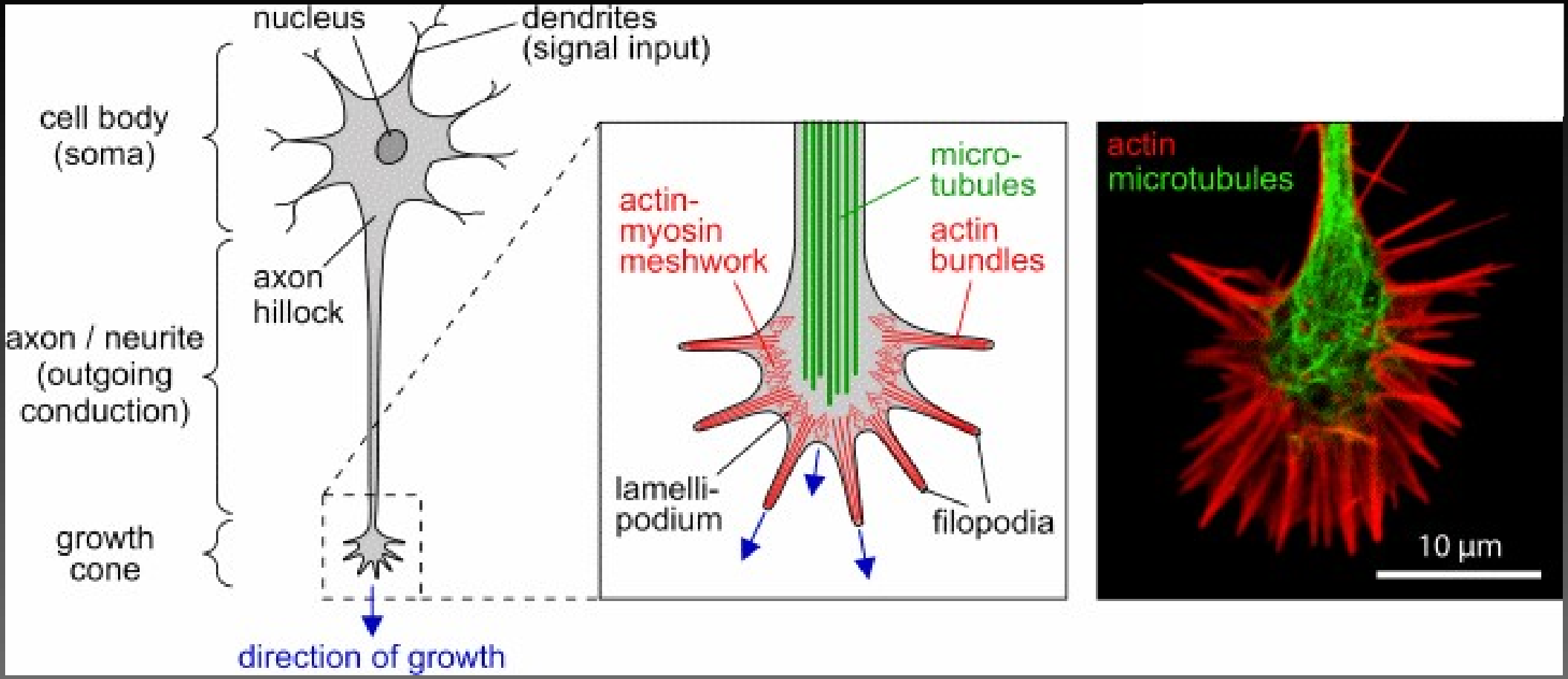
- The **actin cytoskeleton** regulates changes in lamellipodial and filopodial shape for directed growth, while the **microtubule cytoskeleton** is responsible for elongation of the **axon shaft**.

- The dynamic **polymerization** and **depolymerization** of actin at the membrane of the lamellipodium, as well as within the filopodium, sets the direction of growth cone movement.

The Molecular Basis of Growth Cone Motility

- Similarly, the polymerization and depolymerization of tubulin into microtubules consolidate the **direction of movement** of the growth cone by stabilizing the axon shaft.
- **Globular actin** (G-actin) can be incorporated into **filamentous actin** (F-actin) at the **leading edge** of a filopodium in response to **attractive cues**.
- **Repulsive cues** support disassembly of F-actin and **retrograde flow** of G-actin toward the lamellipodium.

The Molecular Basis of Growth Cone Motility



Non-Diffusible Signals for Axon Guidance

- The **complex behavior** of growth cones suggests the presence of **specific cues** that cause the growth cone to move in a **particular direction**.

- The cues comprise a large group of proteins associated with **cell adhesion** and **cell-cell recognition**.

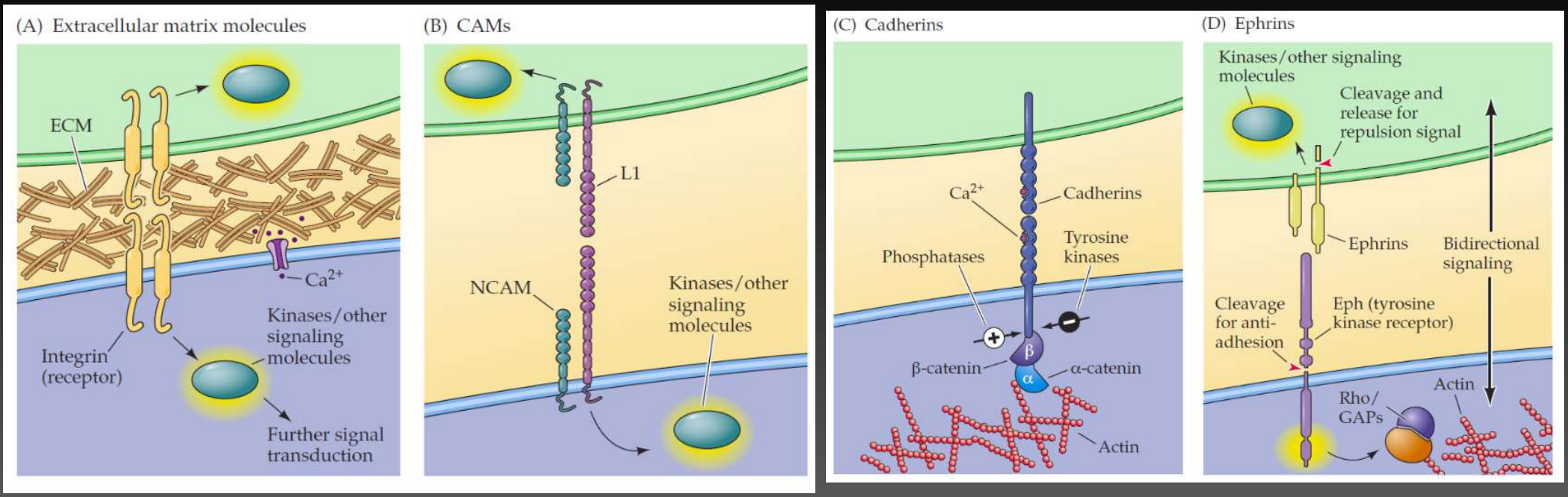
Non-Diffusible Signals for Axon Guidance

- The major classes of **non-diffusible axon guidance molecules** are: the extracellular matrix (**ECM**) molecules (**laminins**, **collagens**, and **fibronectin**) and their **integrin** receptors; the Ca^{2+}-independent cell adhesion molecules (**CAMs**); the Ca^{2+}-dependent cell adhesion molecules (**cadherins**); and the **ephrins and Eph** receptors.
- The binding of laminin, collagen, or fibronectin to integrins triggers a cascade of events that can stimulate **axon growth and elongation**.
- The CAMs and cadherins are found on growth cones and growing axons as well as on surrounding cells and targets.

Non-Diffusible Signals for Axon Guidance

- Cadherins are important determinants of final target selection in the transition from **growing axon to synapse**.
- In the developing nervous system, immature axons use ephrins and Eph receptors to recognize **appropriate pathways** for growth as well as appropriate sites for **synaptogenesis.**
- Mutations in these signaling molecules can lead to the partial absence of the **corpus callosum** (referred to as **callosal agenesis**).

Non-Diffusible Signals for Axon Guidance



Chemoattraction and Chemorepulsion

- A growing axon must eventually find an **appropriate target** while avoiding **inappropriate** ones.

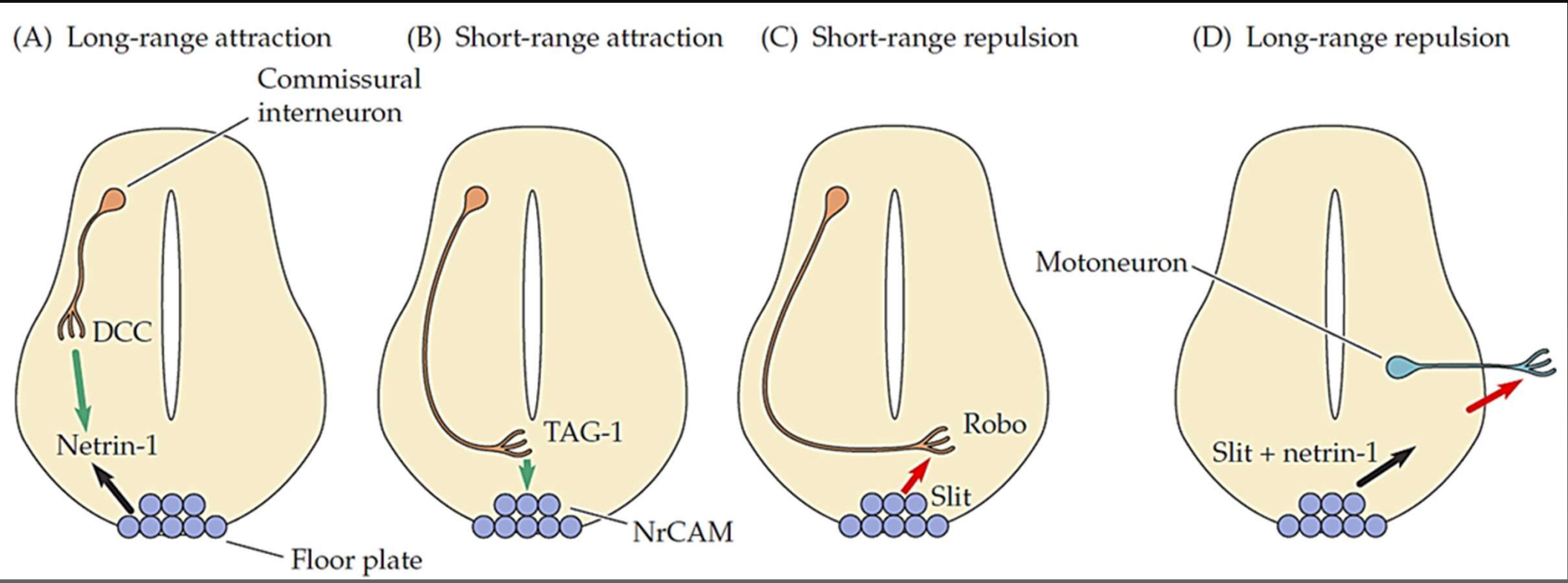
- One of the chemoattractant molecules is the **netrins** (Sanskrit: he who guides).

- Netrin chemoattractant signals are transduced by specific receptors, including the molecule DCC (***d*eleted in *c*olorectal *c*ancer**).

Chemoattraction and Chemorepulsion

- Netrin directs axons to cross the midline but they do not cross back.
- The secreted **factor slit** and its **receptor robo (roundabout)** are important for **preventing** an axon from **crossing back** the midline once it has crossed initially in response to netrin.
- The successful completion of such crossing by axons is essential for the **construction** of all major **sensory**, **motor**, and **associational pathways** in the mammalian nervous system.

Chemoattraction and Chemorepulsion



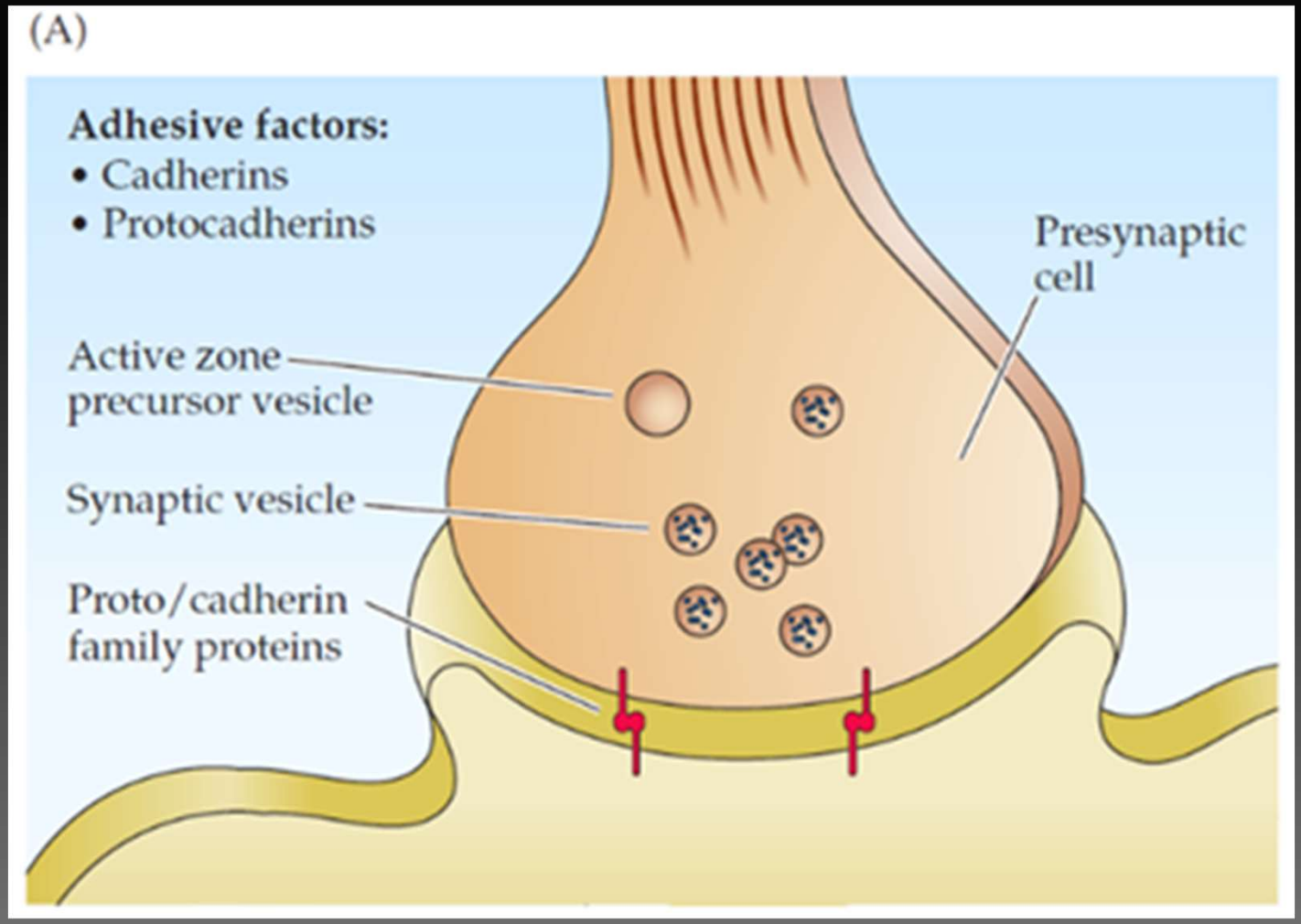
Selective Synapse Formation

- Once an axon reaches its **target region**, additional cell-cell interactions dictate which target cells to **innervate** from among a variety of **potential synaptic partners.**
- In the first stages of synapse formation, the ephrins, the CAMs, and the cadherin molecules influence **recognition** of any suitable postsynaptic positions on dendrites, cell bodies, or other appropriate targets (i.e., muscle fibers) by a **nascent presynaptic process**.
- Several signals have been implicated in this process, including **growth factors** and **neurotransmitters** themselves.

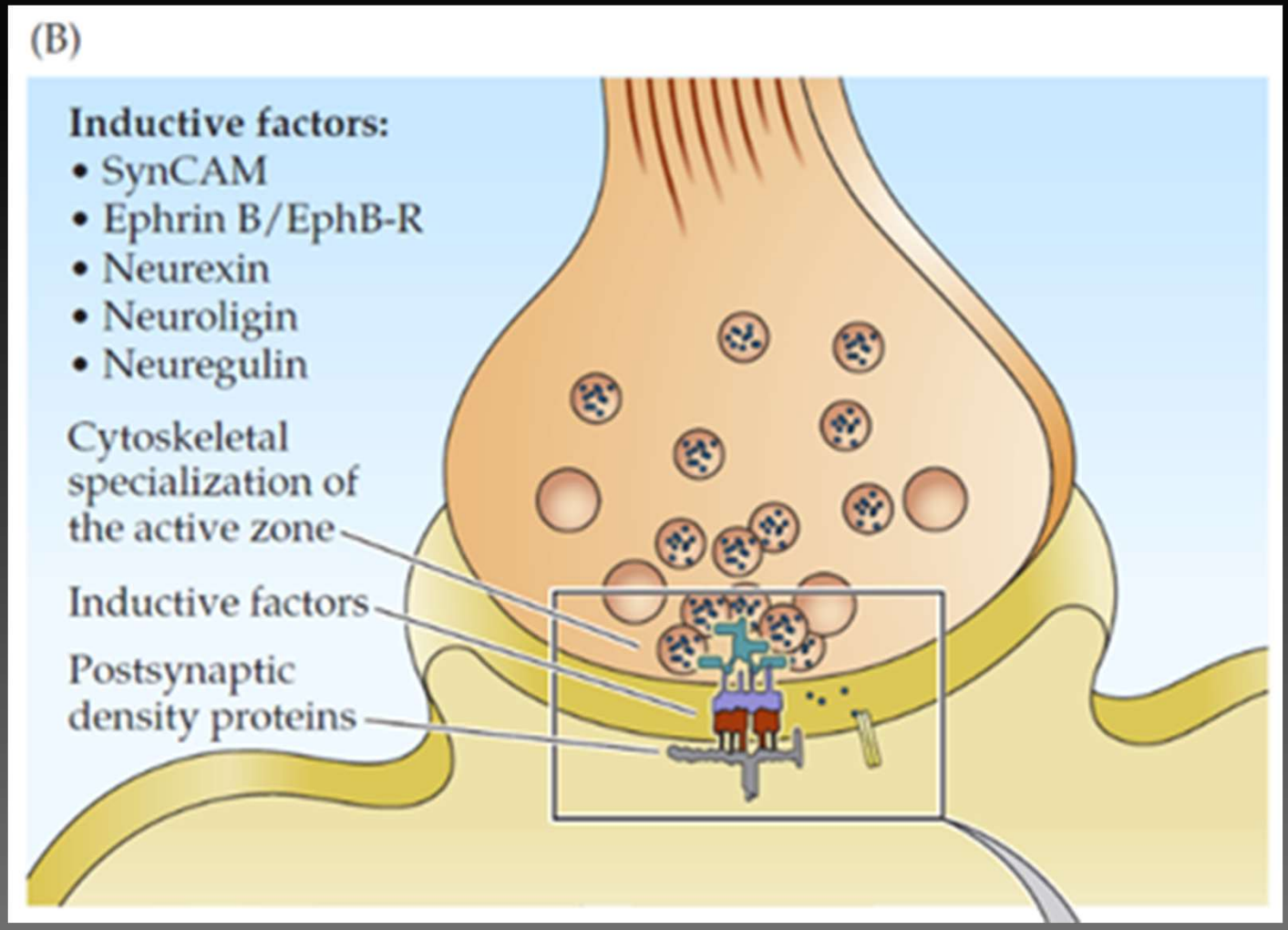
Selective Synapse Formation

- Two adhesion molecules are particularly central to the **construction** of all synapses: **neurexins**, found in the presynaptic membrane; and their binding partners the **neuroligins**, found in the postsynaptic membrane.
- Neurexins helps localize **synaptic vesicles**, docking proteins, and fusion molecules contributed by active zone vesicles in the presynaptic terminal.
- Neuroligins interact with specialized postsynaptic proteins to promote the **clustering of receptors** and **channels** of the postsynaptic density.
- The association of **polymorphisms** in neurexin and neuroligin **genes** with increased risk for **autism** and **schizophrenia** shows that these molecules are key for establishing **appropriate connectivity**.

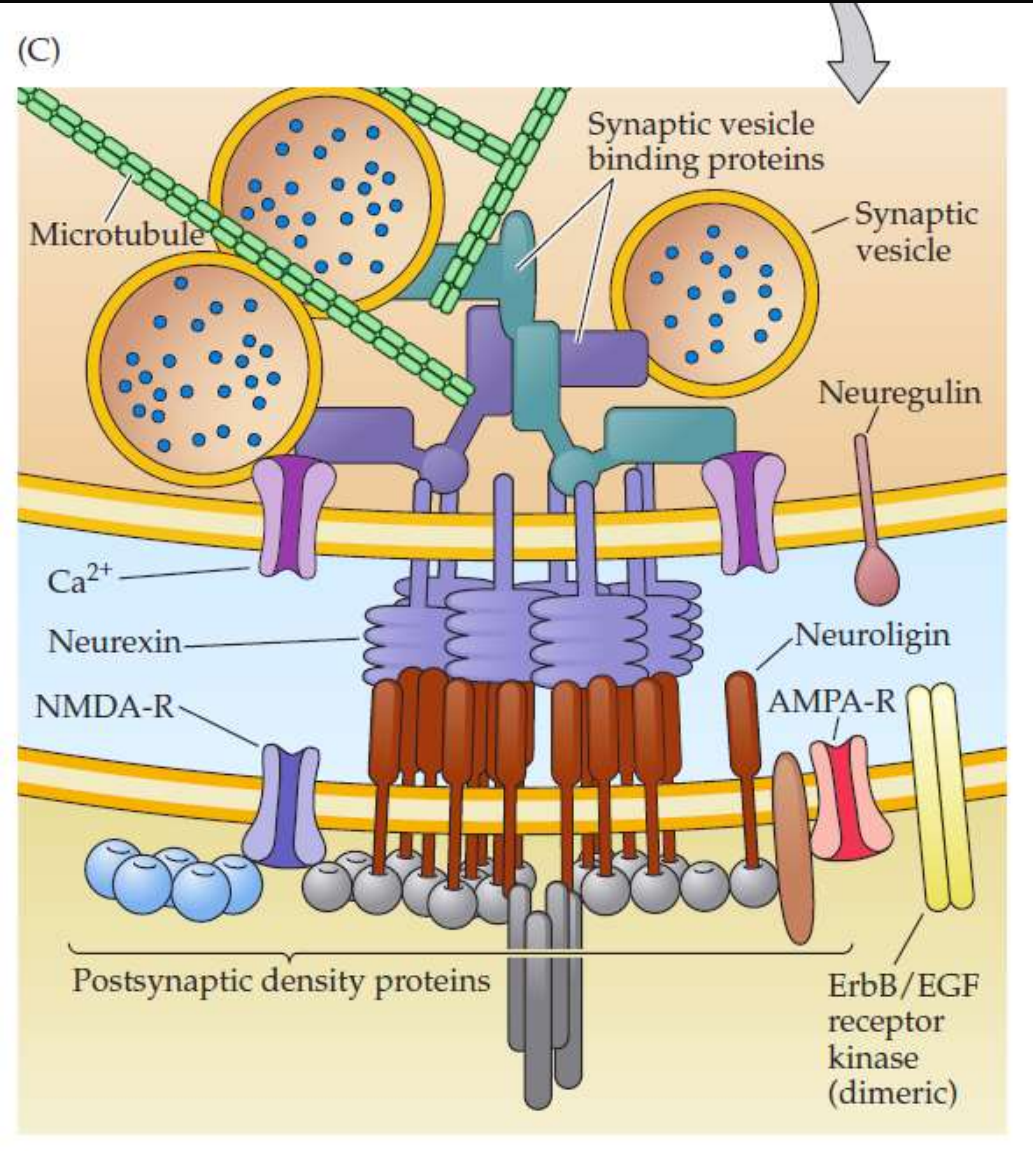
Selective Synapse Formation



Selective Synapse Formation



Selective Synapse Formation

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