Here is a comprehensive note on the cytoskeleton, drawing on the provided sources:

Cytoskeleton: An Overview

The cytoskeleton is a crucial cellular structure that functions as a cellular "scaffolding" or "skeleton" within a cell's cytoplasm, composed of proteins. It is found in all cells, including prokaryotes, although it was once thought to be exclusive to eukaryotes.

Historical Context:

- The concept of the cytoskeleton was first proposed in **1903** by **Nikolai K Koltsov**, who suggested that a network of tubules determined cell shape.
- The French term "Cytosquelette" was introduced in **1931** by French embryologist **Paul Wintrebert**.

Overall Functions of the Cytoskeleton: The cytoskeleton is a dynamic structure that performs several vital roles within the cell:

- Provides a **structural framework** for the cell, helping to **maintain cell shape**.
- Facilitates **intracellular transport**.
- Supports **cell junctions** and transmits signals related to **cell contact and adhesion**.
- Enables **cellular motion** and permits **motility**.
- Plays a very important role in **cell division**.
- Often **protects the cell**.

Structural Elements of the Cytoskeleton: The cytoskeleton of each cell contains three main types of structural elements, along with many accessory proteins that link these structures to one another, to the plasma membrane, and to intracellular organelle membranes. These are:

1. **Microfilaments** (Actin filaments)
2. **Intermediate filaments**
3. **Microtubules**

The basic structure of the cytoskeleton involves **protein subunits**, **cross-linking proteins**, and **motor molecules**.

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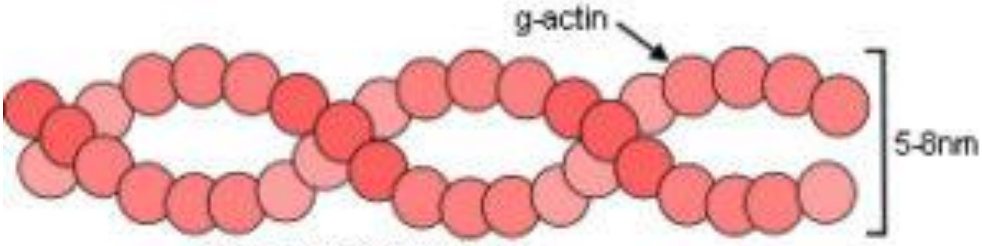
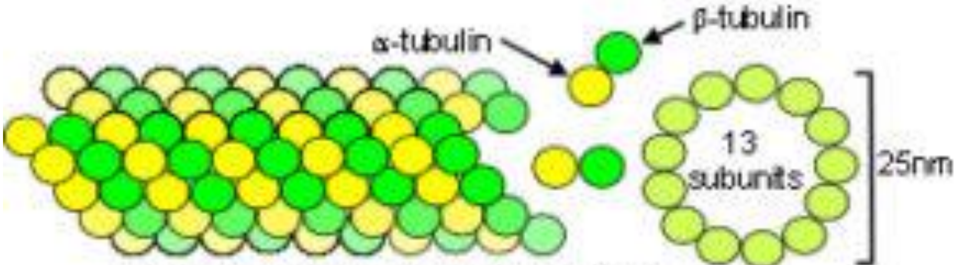
1. Microfilaments (Actin Filaments):

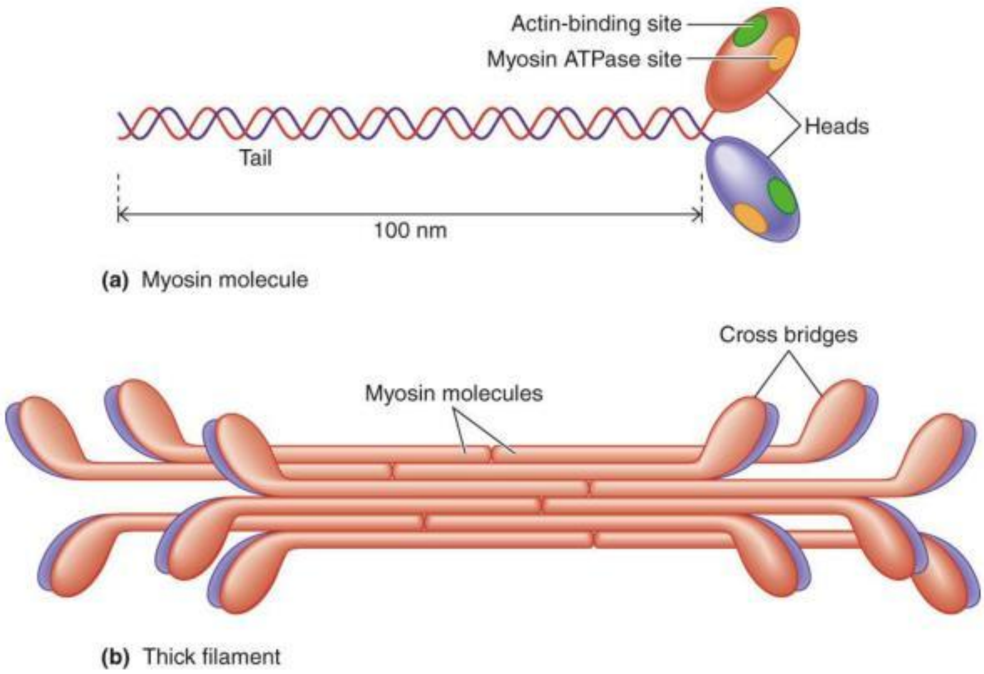
- **Structure:** They are **6 to 8 nm in diameter** and consist of **actin filaments**. Actin exists in two states: **monomeric G-actin** and **filamentous F-actin**. Actin monomers polymerize to form filaments, a process stimulated by nucleation.
- **Polarity:** Actin filaments exhibit **polarity**, with each microfilament possessing a **fast growing or "plus" end** and a **slow growing or "minus" end**. Actin monomers orient with their cleft towards the minus end.

- 

F-actin polymer filament.


Microtubule polymer of globular tubulin.
- **Functions:**
  - **Cell Migration:** Rapid polymerization of actin monomers on the plus ends can produce **protrusions on the cell surface called Pseudopods**, which are critical for directional cell migration.
  - **Contractility:** Microfilaments organised as stress fibres serve as **contractile elements**, responsible for generating directional force during cell motility.
  - **Cell Division (Cytokinesis):** A microfilament-based structure called the **contractile ring** is essential for the separation of a cell into two progeny during cytokinesis.
  - **Adhesion:** Adherens junctions and focal contacts, associated with the actin cytoskeleton, are involved in **adhesion between cells or between a cell and its surface**. Focal contacts possess specific transmembrane receptors of the integrin family, linking the cell to the extracellular matrix on the outside and microfilaments on the inside.
- **Associated Proteins:**
  - **Myosin:** One of the actin-associated proteins, myosin, converts chemical energy into movement. **Myosin motors** bind to actin filaments in the presence of ATP to produce movement. Myosin motors, some of which are two-headed, are involved in cytokinesis and cell motility, including the movement of membrane-bound vesicles along actin tracks.
  - **Cross-linking proteins:** These proteins organise actin filaments into bundles or networks. Examples include **alpha-actinin, villin, and fimbrin**, which bind actin filaments into parallel bundles. **Filamins** organise actin filaments into loose networks, giving some areas of the cytosol a gel-like consistency.

Structure and Arrangement of Myosin Molecules Within Thick Filament



- **Clinical Considerations:**
    - **Mutations in actin-binding proteins** can lead to **defects in motility** and **impaired cytokinesis**.
    - These mutations can also cause **hypertrophied cardiomyopathy**.

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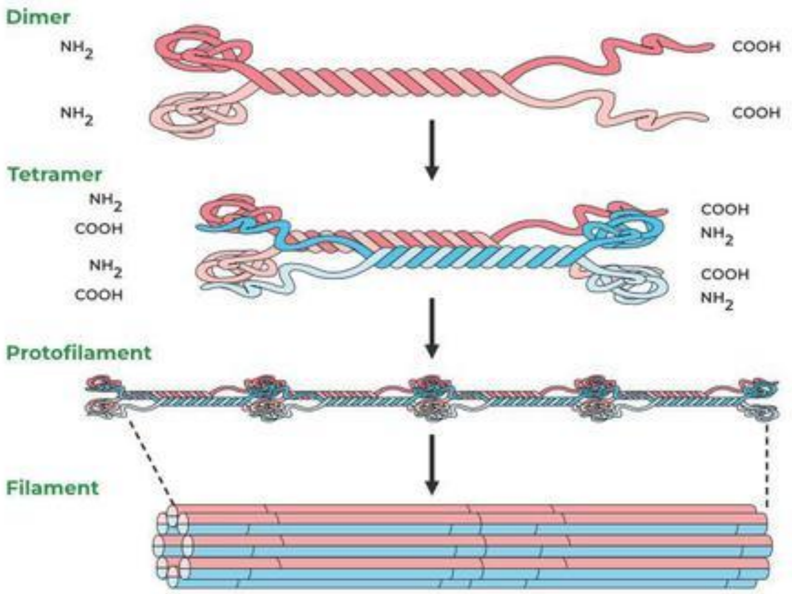
2. Intermediate Filaments:

- **Structure:** They are **8-10 nm in diameter** and are rope-like structures constructed from **tetramers of rod-like proteins** that are tightly bundled into long helical arrays. They self-assemble into larger filaments.
- **Key Characteristics:** Unlike microfilaments and microtubules, intermediate filaments **do not have polarity**. They are also **more stable** than other cytoskeletal elements and **do not have molecular motors**.
- **Functions:**
    - Intermediate filament binding proteins link them into a **3-dimensional network** that facilitates cytoskeleton formation.
    - They bind intracellular structures to each other and to plasma membrane proteins.
    - They link **cell surfaces and the nucleus**.

- They **stabilise the structural integrity of the cell** due to their **highest tensile strength**.
- At the cell surface, intermediate filaments attach to specific junctions called **desmosomes and hemidesmosomes**, which attach cells to neighbouring cells or the extracellular matrix.
- 

- **Types of Intermediate Filaments:**
  - **Keratins:** Type I (acidic) and Type II (basic). Found in epithelial cells and cells of hair and nails. They form bundles called **tonofilaments** that anchor on desmosomes.
  - **Desmin:** Found in all types of muscle cells.
  - **Vimentin:** Found in cells of the embryo and cells of mesenchymal origin, such as fibroblasts, leucocytes, and endothelial cells.
  - **Glial Fibrillary Acidic Protein (GFAP):** Expressed in the central nervous system (CNS) in astrocyte cells. Involved in CNS processes like cell communication and the functioning of the blood-brain barrier.
  - **Neurofilaments:** Found in neurons, forming the cytoskeleton of axons and dendrites.
  - **Nuclear Lamins:** Lining the nuclear envelopes of all cells.
- **Clinical Considerations:**
  - **Skin Diseases:** Mutations in keratin cause blistering diseases like **epidermolysis bullosa simplex (EBS)**, resulting from a loss of cellular integrity. This makes keratinocytes of the epidermal basal layer fragile due to mutations in keratins K5 or K14.
  - **Squamous Cell Carcinoma:** K8 and K18 are prototype keratin pairs of simple epithelia, not typically found in stratified adult epithelial tissues. However, their aberrant expression in carcinomas, including oral squamous cell carcinoma (OSCC), correlates with invasion and poor prognosis. A marked increase in **tonofilaments** in

tumor cells is noted, which may provide motive force for tumor cell deformation and invasiveness.

  - **Vimentin expression** is regarded as a sign of mesenchymal differentiation. Vimentin-positivity in carcinomas indicates an epithelial-mesenchymal transition and an **increased metastatic potential**.
  - **Desmin-related myofibrillar myopathy:** Results from a mutation in the desmin gene, preventing it from forming protein filaments and leading to desmin aggregates.
  - **Alexander disease:** A genetic disorder affecting the central nervous system (midbrain and cerebellum), caused by mutations in the gene for **glial fibrillary acidic protein (GFAP)**.
  - **Mandibuloacral dysplasia:** A rare genetic disorder caused by mutations in genes encoding **nuclear lamins**.

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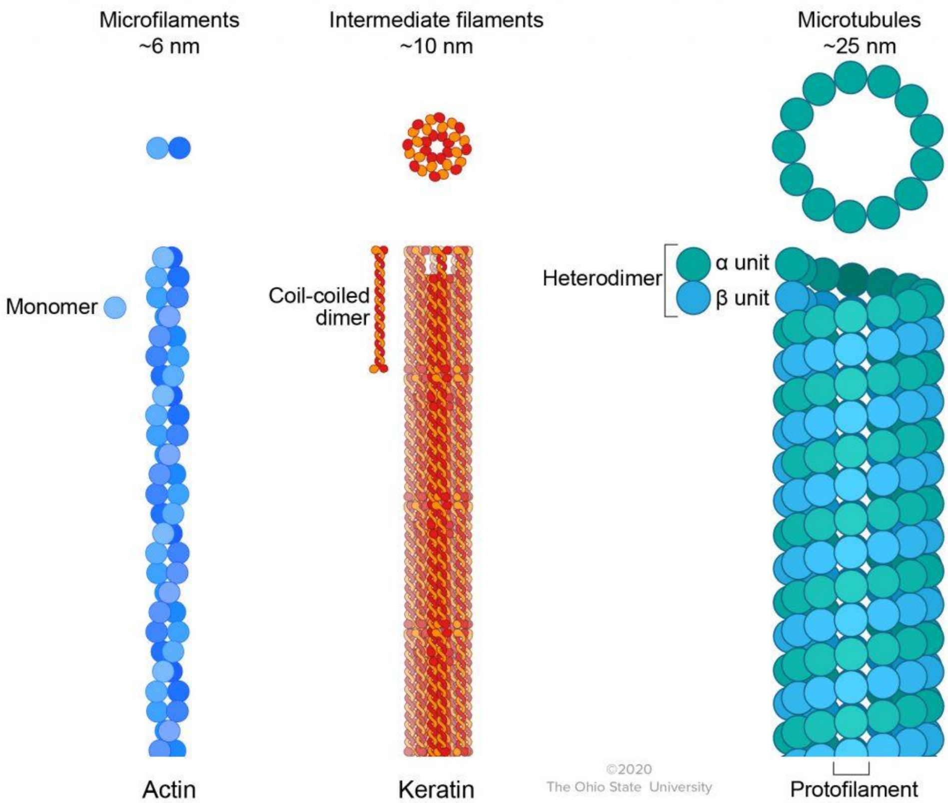
3. Microtubules:

- **Structure:** They are the **largest of all cytoskeletal elements**, measuring **25 nm in diameter**. They are composed of two globular protein subunits, **alpha- and beta-tubulin**. These subunits form heterodimers, which aggregate to form long tubes made of stacked rings, with each ring usually containing 13 subunits.
- **Dynamics:** Microtubules have a **fast growing or "plus" end** and a **slow growing or "minus" end**. Due to their constant assembly and disassembly, microtubules are a **dynamic portion of the cell skeleton**.
- **Origin:** They originate from a specialized **microtubule organising centre called the centriole**. In most cells, microtubules are organised in a radial array extending from a single centriole site.
- **Functions:**
  - **Intracellular Transport:** Microtubules provide **tracks for the transport of vesicles, organelles** (e.g., secretory granules, mitochondria) from one part of the cell to another, and also function as tracks for **mRNA transport**.
  - **Cell Division (Mitosis):** They form the **spindle**, which moves chromosomes during mitosis.
- **Associated Proteins (Motor Proteins):**
  - The functions of microtubules in vesicle transport and chromosome segregation depend on **molecular motors** that bind to and move along microtubule tracks.
  - These motor proteins, which convert chemical energy from ATP into mechanical work, include **kinesin and dynein**.



- **Kinesin and dynein** actively transport vesicles along microtubules: kinesin typically moves towards the **MT plus-end** (cell periphery), while dynein moves towards the **MT minus-end** (cell nucleus).

- **Clinical Considerations:**
  - **Diseases associated with motor protein defects:**
    - **Kinesin deficiencies** cause **Charcot-Marie-Tooth disease**, leading to defective axonal transport.
    - **Dynein deficiencies** can cause **chronic infections of the respiratory tract**, as cilia fail to function without dynein.
  - **Anticancer Drug Paclitaxel:** This drug binds to microtubules, making them so stable that organelles cannot move, mitotic spindles cannot form, and cells die.
  - **Tumor Cells and Oxygen:** Tumor cells often experience low oxygen conditions. Microtubules help control the production of **Hif-1alpha**, a transcription factor essential for a cell's response to low oxygen. Hif-1alpha mRNA is transported along microtubules and translated into protein, which assists tumor cells in coping with low oxygen. Disrupting the microtubule cytoskeleton with drugs like taxol or nocodazole shifts Hif-1alpha mRNA into P-bodies in the cytoplasm, where its translation is repressed by micro RNAs, suggesting an additional way these drugs can kill tumor cells.

Cytoskeleton-Based Structures: The cytoskeleton is integral to several cellular structures:

- **Centrosomes:** Located near the nucleus in the cytoplasm of eukaryotic cells, a centrosome is made of two centrioles. Each centriole has nine triplets of microtubules arranged in a ring. Centrioles replicate during cell division. Centrosomes are microtubule-organising centres containing gamma-tubulin. They duplicate and move apart during cell division to form the poles of the mitotic spindle.
- **Cilia:** These are dynein-driven motile processes used by unicellular organisms for propulsion and by multicellular organisms to propel mucus and other substances over epithelial surfaces. They resemble centrioles but have a pair of microtubules in the centre, with two rather than three microtubules in each of the nine circumferential structures.
- **Microvilli:** These are bundles of actin filaments found as protrusions from the surface of intestinal epithelial cells. These protrusions increase the surface area of intestinal cells.

Comparison of Cytoskeletal Elements:

Feature	**Microfilament**	**Intermediate Filament**	**Microtubule**
Proteins	Actin	Keratin, Desmin, Vimentin, GFAP, Neurofilament	α-Tubulin, β-Tubulin
Motor Molecule	Myosin	-----	Kinesin, Dynein
Cross-linking Proteins	Alpha-actinin, Villin, Fimbrin, Filamin	Filaggrin, Plectin	MAP-1, MAP-2, MAP-4

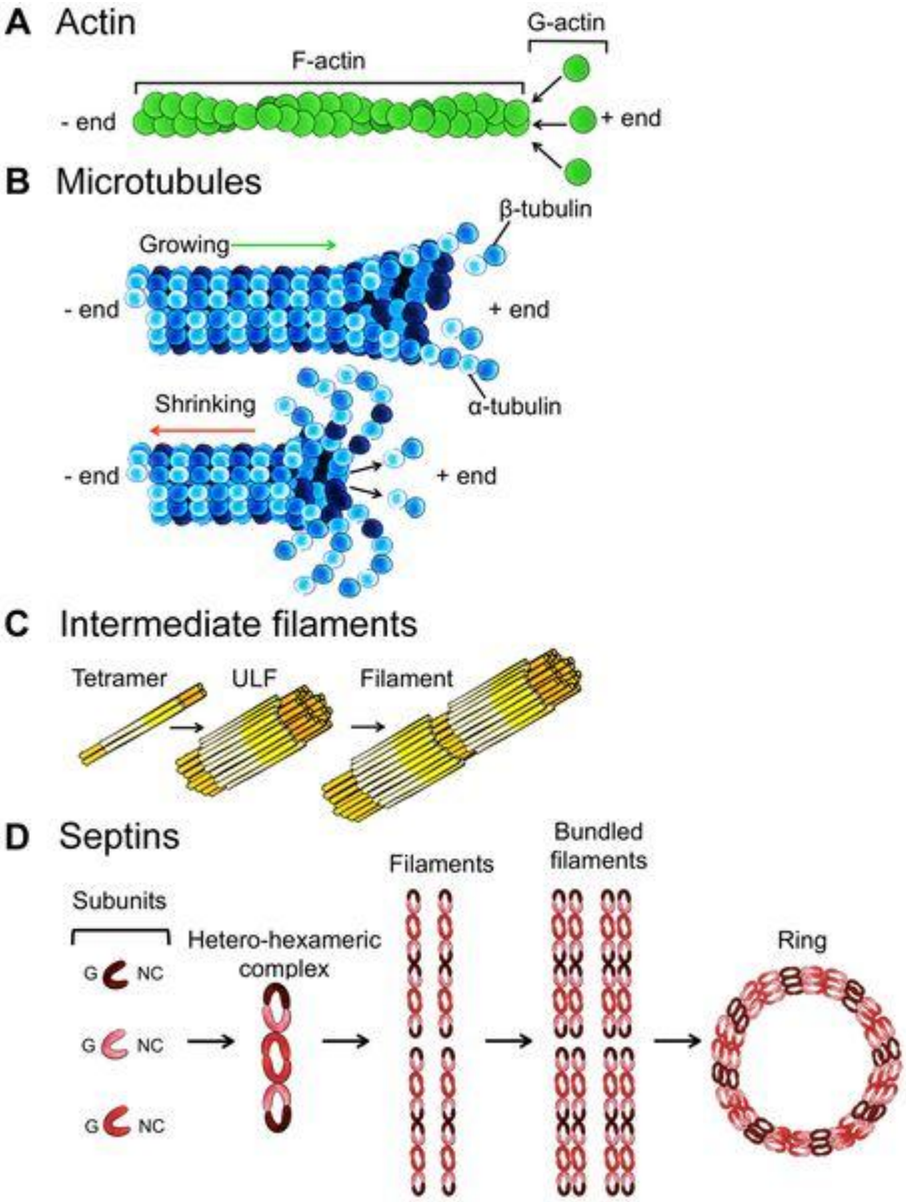
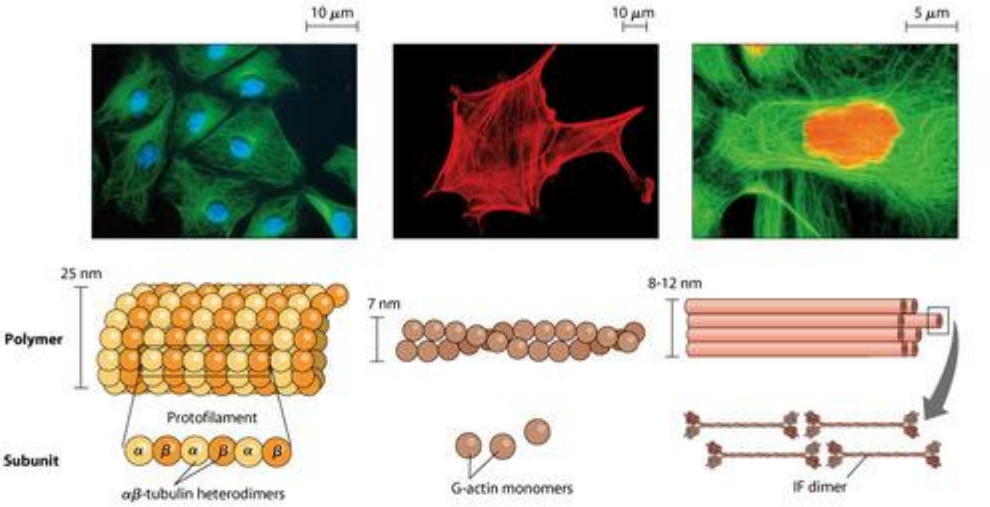

A Actin
G-actin
F-actin
- end
+ end
B Microtubules
β-tubulin
Growing
- end
+ end
α-tubulin
Shrinking
- end
+ end
C Intermediate filaments
Tetramer
ULF
Filament
D Septins
Bundled filaments
Filaments
Subunits
Hetero-hexameric complex
Ring
G
NC
G
NC
G
NC

Table 15-1 **Properties of Microtubules, Microfilaments, and Intermediate Filaments**

	Microtubules	Microfilaments	Intermediate Filaments



	Microtubules	Microfilaments	Intermediate Filaments
Structure	Hollow tube with a wall consisting of 13 protofilaments	Two intertwined chains of F-actin	Eight protofilaments joined end to end with staggered overlaps
Diameter	Outer: 25 nm Inner: 15 nm	7 nm	8–12 nm
Monomers	α-tubulin β-tubulin	G-actin	Several proteins; see Table 15-4
Polarity	(+), (−) ends	(+), (−) ends	No known polarity
Functions	Cytoplasmic: Organization and maintenance of animal cell shape and polarity Chromosome movements Intracellular transport/trafficking, and movement of organelles Axonemal: Cell motility	Muscle contraction Cell locomotion Cytoplasmic streaming Cytokinesis Maintenance of animal cell shape Intracellular transport/trafficking	Structural support Maintenance of animal cell shape Formation of nuclear lamina and scaffolding Strengthening of nerve cell axons (neurofilament protein) Keeping muscle fibers in register (desmin)