

# Cytoskeleton - structure, function and tissue specificity, principles of biological motors

## The Cytoskeleton

The intricate cytoplasmic cytoskeleton comprises microtubules, microfilaments (actin filaments), and intermediate filaments. These proteinaceous frameworks not only define cell morphology but also facilitate organelle and cytoplasmic vesicle movement, as well as cell motility.

### Microtubules:

The microtubules have an outer diameter of 24nm, with a dense wall that is 5nm thick and a hollow lumen.

A microtubule's protein subunit consists of a heterodimer composed of  $\alpha$  and  $\beta$  tubulin molecules, which polymerize to form microtubules.

Microtubule organizing centers (MTOCs), including centrosomes and basal bodies of cilia, direct the polymerization of tubulins to form microtubules. These structures are polarized, with growth occurring more rapidly at one end.

Dynamic instability is exhibited by microtubules, with tubulin polymerization and depolymerization dependent on concentrations of chemical substances and specific microtubule-associated proteins (MAPs).

Cytoplasmic microtubules, rigid in nature, significantly contribute to cell shape formation and maintenance. They also facilitate intracellular transport of organelles and vesicles, such as chromosome movements during mitotic spindle formation and vesicle transport between cell compartments. Special MAPs known as motor proteins, like kinesins and cytoplasmic dyneins, control transport along microtubules by utilizing ATP to move molecules and vesicles.

Kinesins transport organelles away from microtubule organizing centers towards the plus end of microtubules, while cytoplasmic dyneins carry vesicles in the opposite direction.

Microtubules serve as the foundation for various cytoplasmic structures, including centrioles, basal bodies, cilia, and flagella.

Centrosomes consist of pairs of centrioles, which duplicate during the S phase before cell division. During mitosis, they divide into halves, move to opposite poles of the cell, and become organizing centers for the mitotic spindle's microtubules.

Cilia and flagella are motile structures covered by a cell membrane and possess a highly organized microtubule core. Cilia primarily function to sweep fluid along the cell surface, while flagella contribute to sperm cell motility. Both structures exhibit a 9+2 pattern of peripheral and central microtubules, known as the axoneme.

At the base of each cilia or flagella lies a basal body, responsible for axoneme assembly.

### Microfilaments

Microfilaments, also known as actin filaments, constitute the thinnest filaments of the cytoskeleton, measuring about 5-7nm in diameter. They are present in the cytoplasm of eukaryotic cells and consist of linear polymers of actin subunits that are flexible and relatively strong. These microfilaments are highly versatile and play crucial roles in processes such as cytokinesis and changes in cell shape.

Actin is typically found in cells as polymerized filaments of F-actin, which are intertwined with free globular G-actin subunits. Within cells, actin microfilaments (F-actin) can adopt various structural forms:

1. In skeletal muscle cells, they form stable arrays integrated with thick 16nm myosin filaments.
2. In most cells, microfilaments create a thin sheath or network just beneath the cell membrane (plasmalemma). These filaments are involved in shaping the cell during processes like endocytosis, exocytosis, and cell locomotion.
3. Microfilaments are closely associated with several cytoplasmic organelles, vesicles, and granules, and play a role in moving or repositioning cytoplasmic components, a process known as cytoplasmic streaming.
4. Microfilaments also contribute to cytokinesis, the division of the cytoplasm during cell division.

Numerous actin-binding proteins with diverse functions have been identified in various cells, including:

- Actin motor proteins like myosin (II, I, V), which transport other molecules or vesicles along microfilaments.
- Actin-capping proteins such as tropomyosin, which bind to the free ends of actin filaments.
- Actin filament-severing proteins like gelsolin, which cleave microfilaments into shorter fragments.
- Actin-bundling proteins including fimbrin, villin, and actinin, which crosslink microfilaments.

- Actin-branching proteins like formin, which generate branch points along microfilaments.

## **Intermediate filaments**

Intermediate filaments, falling in size between the other two components of the cytoskeleton, typically have an average diameter ranging from 10 to 12 nanometers.

Intermediate filament proteins are classified into four main groups based on their chemical and genetic organization:

- Keratins (cytokeratins): This diverse family comprises more than 20 proteins present in all epithelial cells and in the rigid structures produced by epidermal cells. Keratins serve to reinforce tissue and offer protection against abrasion and loss of water.

- Vimentin: Among the most prevalent intermediate filament proteins, vimentin is found in mesenchymal cells originating from the middle layer of the early embryo. Desmin, a protein akin to vimentin, is prevalent in nearly all muscle cells, while Glial fibrillary acidic protein (GFAP) is present in astrocytes, the supportive cells of CNS tissues.

- Neurofilaments: These are specific intermediate filaments present in nerve cells.

Lamins: The nuclear lamina forms a dense fibrillar network (~30 to 100 nanometers thick) inside the nucleus of most cells. Comprising intermediate filaments and membrane-associated proteins, the nuclear lamina offers mechanical support and regulates crucial cellular processes such as DNA replication and cell division. Additionally, it plays a role in organizing chromatin and serves as an anchor for nuclear pore complexes.

The cytoskeleton, with its intricate network of protein filaments, plays crucial roles in cell structure, movement, and signaling. In a diagnostic context, abnormalities or dysfunctions in the cytoskeleton can indicate various diseases and conditions. Here are some diagnostic applications related to the cytoskeleton:

1. **Cancer Diagnosis**: Changes in cytoskeletal organization and dynamics are commonly observed in cancer cells. Diagnostic techniques such as immunohistochemistry and fluorescence microscopy can detect aberrant cytoskeletal structures, aiding in cancer diagnosis and classification.
2. **Neurological Disorders**: Cytoskeletal defects are associated with neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's disease. Biomarkers related to cytoskeletal proteins may be utilized for early detection and monitoring of these conditions.
3. **Muscle Disorders**: Disorders affecting the cytoskeleton in muscle cells, such as muscular dystrophy, can be diagnosed through genetic testing, muscle biopsy analysis, and imaging techniques like MRI (Magnetic Resonance Imaging).
4. **Hematological Diseases**: Abnormalities in the cytoskeleton of blood cells can lead to various hematological disorders, including anemias and leukemias. Examination of blood smears and flow cytometry analysis can reveal cytoskeletal defects indicative of these conditions.
5. **Cellular Migration Disorders**: Dysfunctions in cytoskeletal components can impair cell migration processes critical for wound healing, immune response, and embryonic development. Analysis of cell motility using live-cell imaging and migration assays can aid in diagnosing related disorders.
6. **Drug Development and Testing**: Pharmaceutical companies utilize cytoskeletal assays to screen potential drugs for their effects on cytoskeletal dynamics. Compounds that modulate cytoskeletal function may be developed as therapeutics for various diseases.
7. **Genetic Disorders**: Inherited conditions affecting cytoskeletal proteins, such as microtubule-associated disorders and actinopathies, can be diagnosed through genetic testing and molecular analysis techniques.
8. **Cellular Aging**: Changes in the cytoskeleton are associated with cellular senescence and aging. Diagnostic markers related to cytoskeletal alterations may provide insights into age-related diseases and conditions.

In summary, the cytoskeleton serves as a diagnostic indicator for a wide range of diseases and conditions, from cancer to neurological disorders. Various molecular, cellular, and imaging techniques are employed to detect cytoskeletal abnormalities and aid in disease diagnosis and treatment.