Mechanics and tissues

Overview

Cells are not static beings – they must change shape, split in two, and effect movement

Communities of cells—**tissues**—must also exhibit mechanical strength

These mechanical properties of cells rely on both intracellular and extracellular networks of **protein fibrils**, and other components

These fibril systems are **regulated** just like other cellular systems, and are highly dynamic

Intracellular mechanics

The **cytoskeleton** in eukaryotic cells consists of three main networks of protein fibrils

- **intermediate filiments**
- **microtubules**
- **actin filaments**

Intermediate filaments

~10nm in diameter

Toughest and most durable intracellular filaments – enables cells to resist stretching

Composed of **coiled-coil** protein dimers wrapped around each other and bundled together

Anchored to nucleus and plasma membrane at cell-cell junctions

Provides mechanical strength in the cytoplasm in tissue cells (epithelia) – made of **keratins**

Forms a mesh around the nuclear envelope to strengthen it – the **nuclear lamina** made from **lamins**

Microtubules

~25 nm in diameter

Long, hollow tubes made of the protein tubulin

Responsible for

- anchoring organelles
- guiding intracellular transport (**kinesins** and **dyneins** walk along them, pulling attached organelles)
- facilitating cell division and chromosome allocation during mitosis
- basic unit in cilia and flagella

Microtubules are formed by the **self-assembly** of tubulin $\alpha\beta$ heterodimers

- dimers self-assemble head to tail to form filaments
- filaments associate to form tubes (about 13 filaments per tube)
- dimers can then add to the ends to "grow" a microtubule
- driven by highly specific and favorable **recognition** interactions of tubulin proteins with each other

Microtubules grow from the **centrosome**, typically close to the cell nucleus

- matrix of proteins
- γ-tubulin nucleation sites to promote formation of microtubules
- microtubules thus nucleate and grow from the centrosome outwards, towards the plasma membrane

Microtubule formation is highly dynamic!

- microtubules constantly growing and shrinking
- depends on GTP → GDP hydrolysis
    1. GTP binds a tubulin dimer
    2. Dimer adds to the microtubule
    3. Tubulin dimer hydrolizes GTP→GDP, which causes dimer not to want to be assembled into microtubule
    4. Microtubule dissociates
- cells need this dynamic assembly → provides way to explore connections to parts of the cell, like a fisherman casting a line

- addition of reagents that permanently stabilize or destabilize microtubules results in cell death

Actin filaments

~5-10 nm in diameter

Long, thin, flexible filaments made from the **self-assembly** of the protein **actin**

Responsible for:

- **cell movement**: cell crawling, muscle movement
- reinforcing cell cortex

Self-assembly very similar to microtubules

- associated with ATP→ADP hydrolysis
- dynamic assembly, which is essential to cell survival
- sea sponge toxins, for example, function by arresting cell movement through the inhibition of actin assembly or disassembly

Many proteins interact with actin to direct its assembly and form highly structured networks of actin filaments

Cell crawling uses actin polymerization to push out a part of the cell that reaches ahead and grabs onto a surface

Muscle contraction depends on actin interacting with **myosin** protein filaments

- actin and myosin filaments bundled together in sarcomeres in muscles
- myosin uses ATP→ADP hydrolysis coupled with conformational changes to **walk** along the actin filaments, pulling itself along
- result is net movement that produces **contractile** motion
- muscle contraction stimulated by Ca2+ signaling from neurons → opening of voltage-sensitive Ca2+ channels and sudden increase in intracellular Ca2+ concentrations

Extracellular mechanics

Cells organize themselves into many kinds of **tissues** that consists of the cells themselves plus an **extracellular matrix**

In plants, **cell walls** made of tough, strong **cellulose** fibrils greatly strengthen the cellular tissues and help the cells resist tremendous osmotic stress

In eukaryotes, tissues include

- **epithelial tissue** – sheets of side-by-side cells that line the outer surface of organs, etc
- **connective tissue** – strong layer of cells + matrix onto which epithelial cells are attached
- **muscle tissue**
- **nervous tissue**

Connective tissue

Connective tissue consists of large amounts of extracellular matrix, made of **collagen**

- helps the tissue resist extension (stretching)

Extracellular matrix is produced by specialized cells

- **fibroblasts** – skin, tendon, other tissues
- **osteoblasts** – bone tissue

Fibroblasts organize, align, and remodel collagen

The extracellular matrix protein **fibronectin** provides a sort-of clamp attachment that holds to collagen to which fibroblasts can adhere using transmembrane proteins called **integrins**

- Binding of integrins to fibronectin can activate subunits inside the cell → signal transduction

Extracellular matrix also consists of **proteoglycans**, amino-acid-sugar hybrid molecules

- highly negatively charged, and in an extended state → helps tissue resist compression

Epithelial tissue

Majority form of tissue for different cell types

"Close-packed" cells that can take on a variety of geometries

Two-sides to this tissue:

- **apical** – free surface (e.g., exposed to fluids or air)
- **basal** – attached to connective tissue

Close packing of cells creates various kinds of **cell junctions**:

- **tight junction** – seals neighboring membranes together, nothing can pass between cells
- **gap junction** – channels to actually allow passage of water, ions, small molecules
- **adherens** – joins actin filaments between cells
- **desmosomes** – joins intermediate filaments between cells
- **hemidesmosome** – anchors intermediate filaments to basal side

Understanding transport through epithelial layers is critical to drug delivery efforts

Epethelial sheets can roll over to form tubes

Tissue development

Major challenge to determine how complex, asymmetric tissues of multiple cell types emerge from simple homogeneous precursor cells → relies on complex signaling and regulation patterns

Also challenging to understand maintainence → how the structures of complex tissues are maintained, old cells replaced with the right new cells

How new cells are produced:

stem cells → precursor cells → differentiated cells

The process by which cells become specialized into a particular type is called **differentiation**

Stem cells can divide indefinitely, but have no explicit purpose other than to regulate the production of other cells that differentiate

Daughter cells of stem cells can become **precursor cells** that further differentiate (irreversibly) to a specific cell type

Different **stem cell systems** depending on the tissue

Embryonic stem cells are completely **pluripotent** → they can become any cell and have great potential for medicine

Cancer

Cancer essentially represents what happens when cell signaling in tissues goes awry, e.g., cells no longer receive and respond appropriately to signals

Cancer cells

- divide indefinitely regardless of signals not to do so → immortal cells
- colonize regions they would normally be regulated not to

Because cell signaling is so finely tuned to achieve balance between cell growth, maintenance, and degradation, one price we pay is that errors in cells can tip the balance to the cancerous side

Cancer emerges from accumulated mutations to DNA due to

- chemically active mutagens (e.g., tobacco smoke)
- radiation (e.g., skin cancer)
- viruses, though not common (e.g., cervical cancer)