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Lecture 17 - Cell motility
The Range of Cell Movement

- Velocities of moving cells span more than 4 orders of magnitude
- Each cell has evolved the speed and mechanism of its migration to match:
  - The cell’s unique energy requirements
  - The way the cell acquires nutrients
  - The cell’s unique energy requirements
  - The way the cell acquires nutrients
- The direction of cell migration is usually not random...
Cell movement according to an environmental cue

- **taxis**

  • Can be an attracting or repelling signal

  1. **Chemotaxis** - soluble factor (molecule or protein)
  2. **Haptotaxis** - same as chemotaxis, but the signal is immobilized on a surface
  3. **Durotaxis** - rigidity of the cell's substrate

Kinds of signals

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"Taxis," a form of cell signaling

1. Reception of signal
2. Transduction of signal
3. Cellular response

Cell motility towards or away from the signal
Cellular locomotion is an essential part of life for many organisms. Single-celled protozoa - Dictyostelium discoideum

http://www.youtube.com/watch?v=VWGA7kIeE0Q
Cellular locomotion is an essential part of life for many organisms.

Dictyostelium discoideum - Single celled protozoa

http://www.youtube.com/watch?v=VWGAtKleEDQ

Mahadeo and Parent, 2006
Embryonic development in animals

Movements of autonomous cells or specialized cellular structures are an essential part of life for many organisms.

Early development - neurons migrating from their point of origin have found their home within the cerebral cortex. They send out axons that stretch into other parts of the brain.

Later development - once the neurons have found their home within the cerebral cortex, they send out axons that stretch into other parts of the brain.

Chemorepellent

Chemottractant
Cellular locomotion is an essential part of life for many organisms. Embryonic development in animals involves collective movement of groups of cells. How are cohorts of cells able to stay together as they migrate through tissue (also made of cells) and how do they know when (or if) they're to come apart?
Cellular locomotion is an essential part of life for many organisms.

Wound healing and tissue remodeling.

Cells sense the loss of epithelial integrity (neighbors) which triggers cell motility and gene transcription.
Cellular locomotion is an essential part of life for many organisms. Immune cells - Macrophages and Neutrophils migrate toward chemical signals from bacteria and other pathogens.
Cellular locomotion is an essential part of life for many organisms.

Immune cells - Macrophages and Neutrophils migrate toward chemical signals from injured, inflamed, and dead tissue (called Necrotaxis).
Cellular locomotion is an essential part of life for many organisms. Pollen Tube Growth is required to transport non-motile sperm to ovule tissue.
Misregulation of cell migration contributes to:

- Atherosclerosis & heart disease
- Cancer (metastasis) & arthritis
- Chronic inflammatory diseases (asthma &
- Congenital birth defects
Rolling leukocytes are recruited to sites of injury or inflammation.
How do cells move?
Cellular migration is a cycle of 4 processes:

1. Polarization of the cell (defining front vs. back)
2. Protrusion of the leading edge
3. Formation of adhesive contacts with the surface
4. De-adhesion and retraction of the trailing edge
Cell polarity is regulated by signaling molecules that create a "leading edge" and "trailing edge".

1. Membrane receptors (GPCRs, RTKs) detect an asymmetric signal from outside the cell.
2. Receptors activate Ras-like small G proteins (Rho-family proteins) to induce cytoskeletal changes at the leading (Rac, Cdc42) and trailing (Rho) edges of the cell.
3. Rho-family proteins induce cytoskeletal changes at the leading (Rac, Cdc42) and trailing (Rho) edges of the cell.
Rho family members are Ras-like proteins that regulate cell morphology and polarity.
Rho protein localizes to the trailing edge of crawling neutrophils.
Signaling during cell polarization
Cell polarization requires the orientation and capture of microtubules at the leading edge.
2. Protrusion

Protrusion is driven primarily by forces that are produced by actin polymerization.

There are 2 types of protrusive structures in motile cells: lamellipodia (sheet-like) and filopodia (finger-like).
The structure of protrusions is dictated by actin organization.
Actin dynamics in lamellipodia
Lamellipodia are composed of branched networks of short actin filaments.
Actin dynamics in lamellipodia

- ARP complex - nucleates growth of new filaments
- Capping proteins - halt growth of filaments to keep them short
- Depolymerizing proteins - break down network away from leading edge

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Filopodia dynamics

http://www.youtube.com/watch?v=VWGA7kIeE00
Filopodia are composed of long, unbranched, and bundled actin filaments.
The model for filopodia formation
3. Formation of adhesive contacts with the substrate
Cells bind to the ECM (Extra-Cellular Matrix) using transmembrane receptors called integrins.
Integrins bound to ECM cluster to form "focal adhesions"
Integrins form an indirect linkage between the ECM and actin network. This link to the substrate allows the cell to exert force and gain traction in motility. The amount of tension between the cytoskeleton and the ECM is how cells "feel" the rigidity of their substrate (Durotaxis).
The ECM is secreted and maintained by fibroblasts.
A Cancer cell migrates in vitro through a 3-D collagen matrix

Lecaudey, et al., 2008
4. De-adhesion and retraction of the trailing edge

• Cells use actin and myosin II to pull on the trailing edge

• Myosin II is activated at trailing edge by Rho

• Old adhesions in the rear are degraded by a calcium-dependent protease called calpain

Further, when force of tension in the cell is greater than the strength of adhesions, the rear of the cell shortens elastically and contracts.
Myosin II is activated at the rear of migrating neutrophils.
An exaggerated example of a leading and trailing edge:

Fish keratocyte motility

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A model for how forces generated by the actin cytoskeleton move cells forward.