Cellular Principles of Signaling: Living Cells as Biosensors

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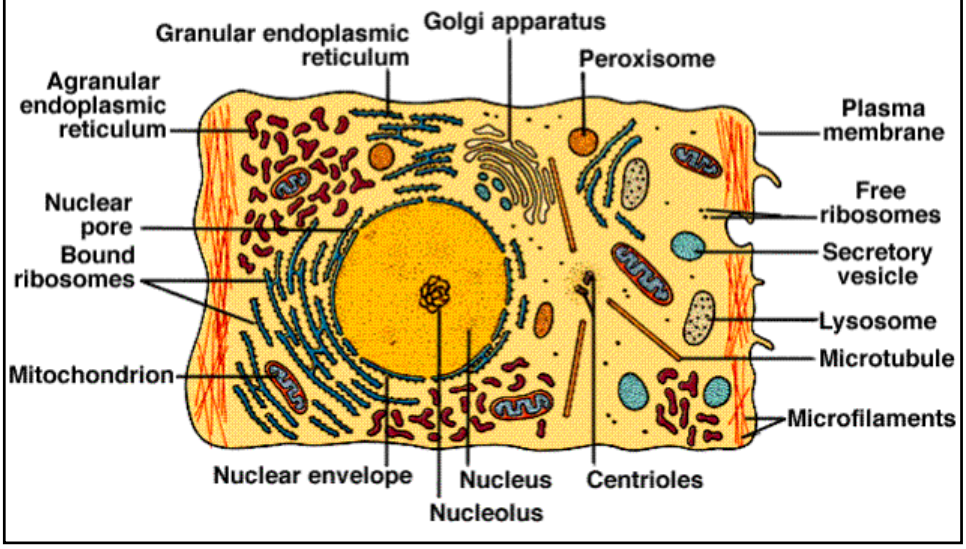
Cellular Principles of Signaling: Living Cells as Biosensors

- Cells
- Recognition of Stimulus
- Short term response
- Long term response
- Networking Cells
- Nanomachines and sensors

LAUR-07-1638

Human Cell



Cellular Principles of Signaling: Living Cells as Biosensors

- Heterogeneous Media
- Compartmentalization
  - Membrane
  - Cytosol
  - Specialized Organelles
  - Nucleus

Cellular Principles of Signaling: Living Cells as Biosensors

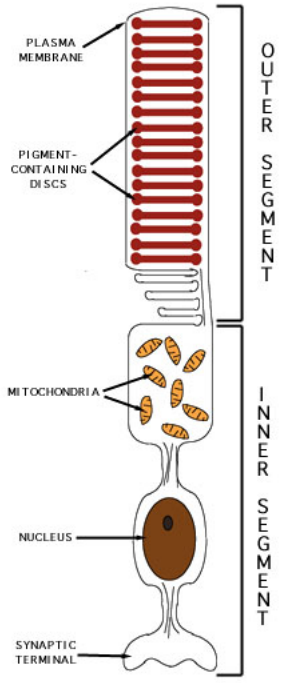
- Components and physical properties
  - ~10^4 proteins
  - Membranes 1/1 protein/lipid by mass; organized domains/rafts
- 2D diffusion
  - 0.01-1 um^2/sec
- 3D diffusion
  - "the 1-micron diffusion time tdiffuse >> tmeas (~1 microsec) for small molecules like amino acids or glucose (tdiffuse ~ 5000 microsec)
  - or for 100,000-dalton macromolecules measuring ~10 nm in diameter (tdiffuse ~ 130,000 microsec)"
  - Robert A. Freitas Jr., Nanomedicine, Volume I: Basic Capabilities, Landes Bioscience, Georgetown, TX, 1999

Cellular Principles of Signaling: Living Cells as Biosensors

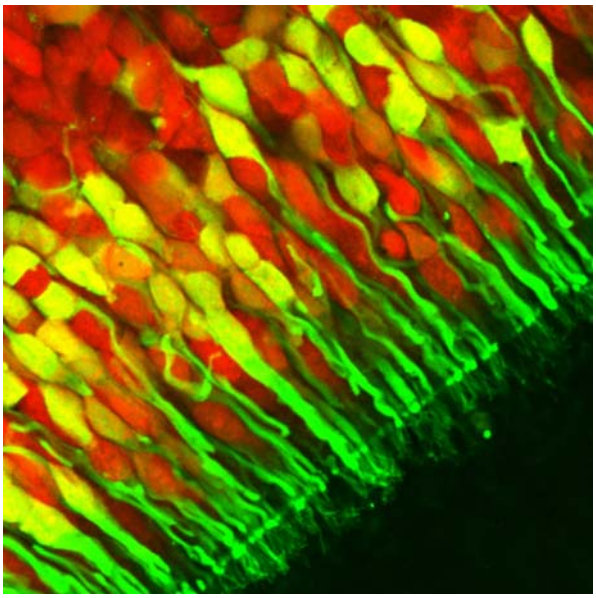
- Senses use arrays or "antennae"
  - Optimize collection
  - Optimize discrimination of multiple stimuli
- Response Highlights
  - Eye: 1 photon (rhodopsin)
  - Ear: 20 u Pascal, pN-nN forces cause nanometer deformation
  - Nose: >300 olfactory receptors including pheromones; array network allow detection of 10^4 smells
  - Taste buds arrayed on tongue: ~5 taste receptors: sweet, salty, sour, bitter, umami (glutamate)

Rod Outer Segment : Black and White Vision

http://www.chemistry.wustl.edu/~edudev/LabTutorials/Vision/images/Rodcell.jpg



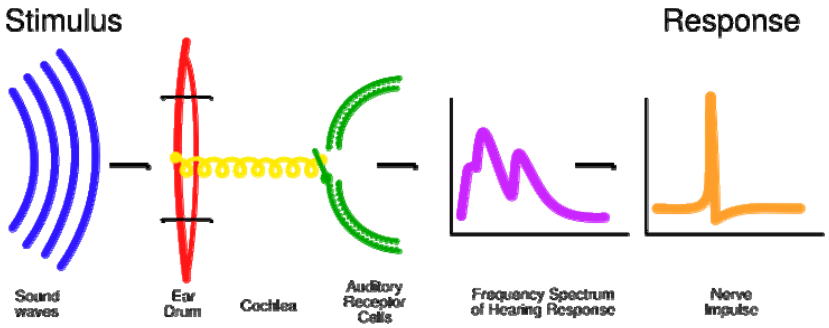
Olfactory receptor bulb – 347 receptors



grk.ukmn.gwdg.de/.../oe_detail_02.jpg

20 micropascal/piconewtons per hair cell?

http://en.wikipedia.org/wiki/Image:Processing-of-sound.svg

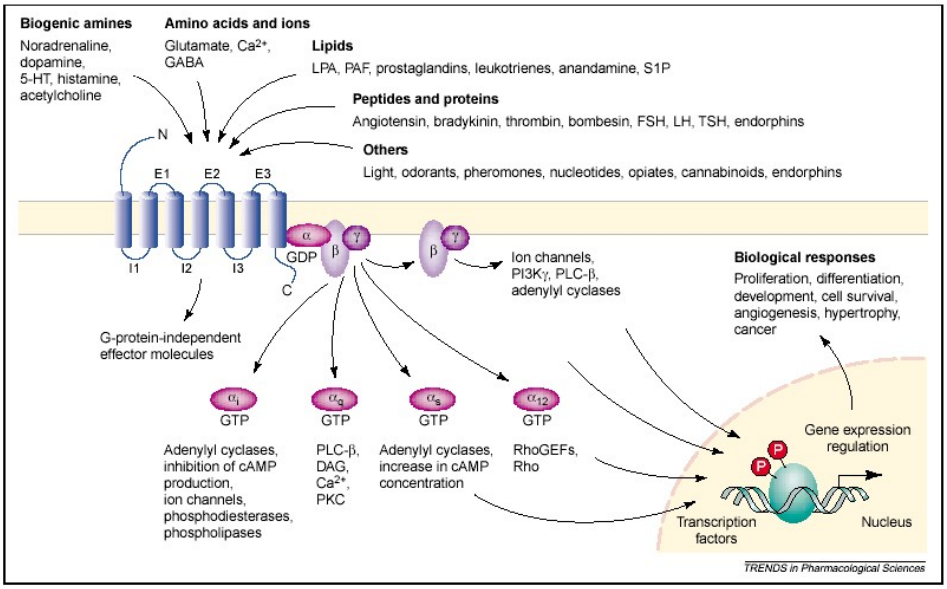


Ca^{2+} Changes the Force Sensitivity of the Hair-Cell Transduction Channel
Biophysical Journal, Jan 1, 2006 by Cheung, Eunice L M, Corey, David P

Cellular Principles of Signaling: Living Cells as Biosensors

- Recognition
  - Display of receptors
  - Display antigens
  - Diversity of antibodies
- Pathways
- Photosynthetic arrays
  - making light do work

The GPCR Family



http://nlp.postech.ac.kr/Research/POSBIOTM/image/GPCR/gpcr1_fig1.jpg

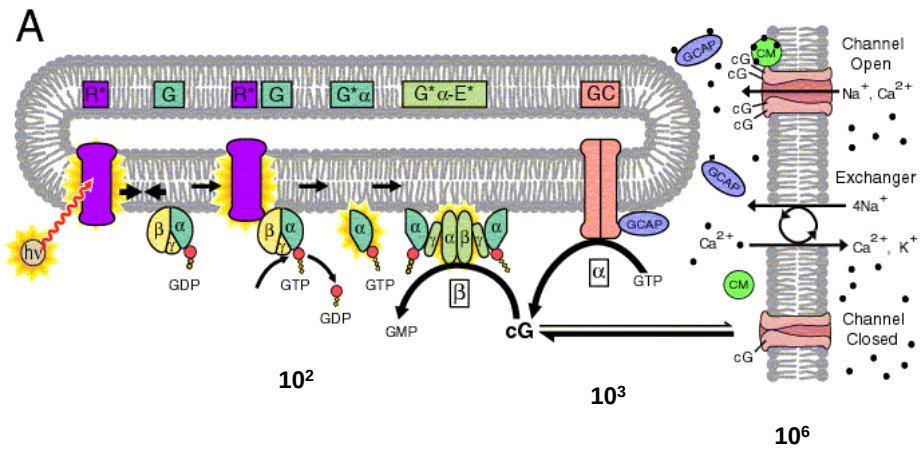
Cellular Principles of Signaling: Living Cells as Biosensors

- Recognition
  - Families of receptors
    - Redundancy
    - Differential display (tissue specificity)
    - Opposing Activities
  - Diversity:
    - Different Recognition Principles: monomers/dimers
  - Valency
    - Different Biophysical Principles

Photoreceptor Response Kinetics

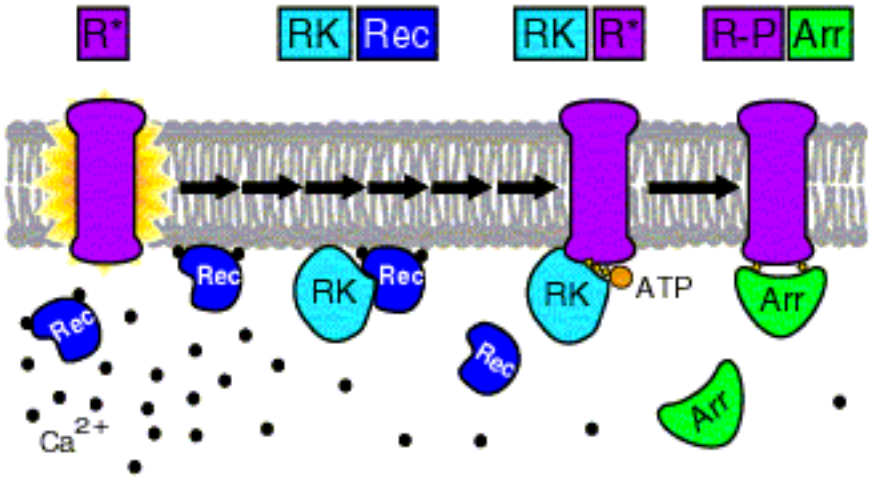
- Gedanken Experiments
  - How fast is activating biochemistry?
  - How fast is inactivating biochemistry?
  - How rapid is adaptation?
  - What is the range of adaptation?

Rhodopsin Amplification



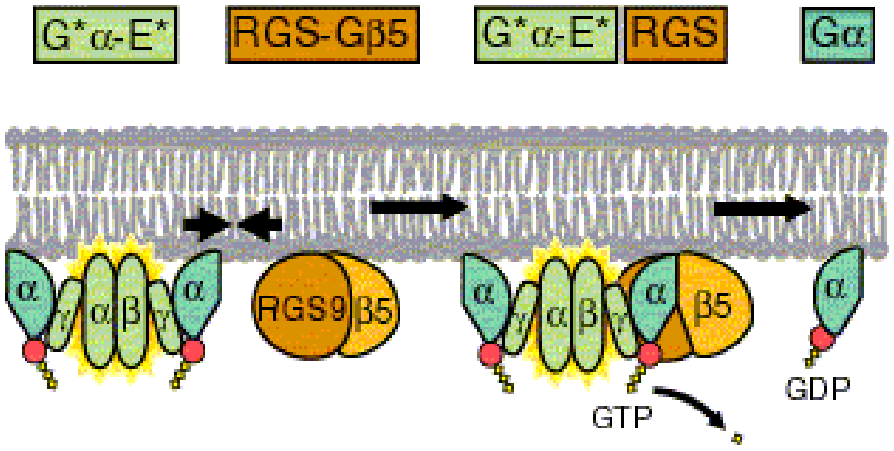
dolphin.upenn.edu

Rhodopsin Desensitizaton



dolphin.upenn.edu

G Protein Termination

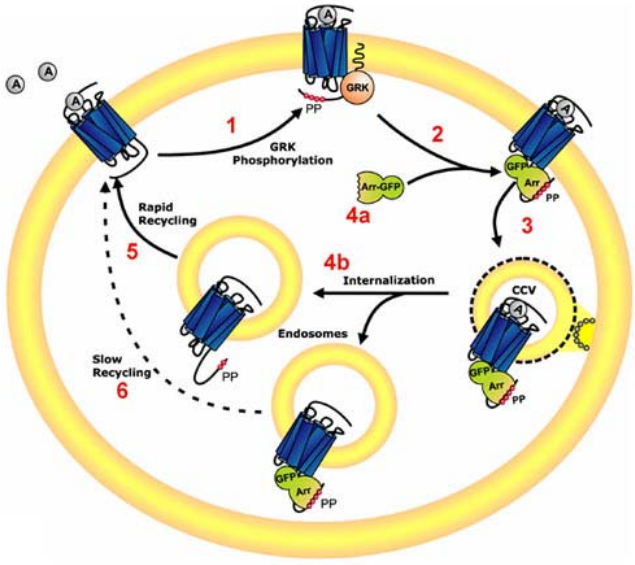


dolphin.upenn.edu

Amplification and Termination

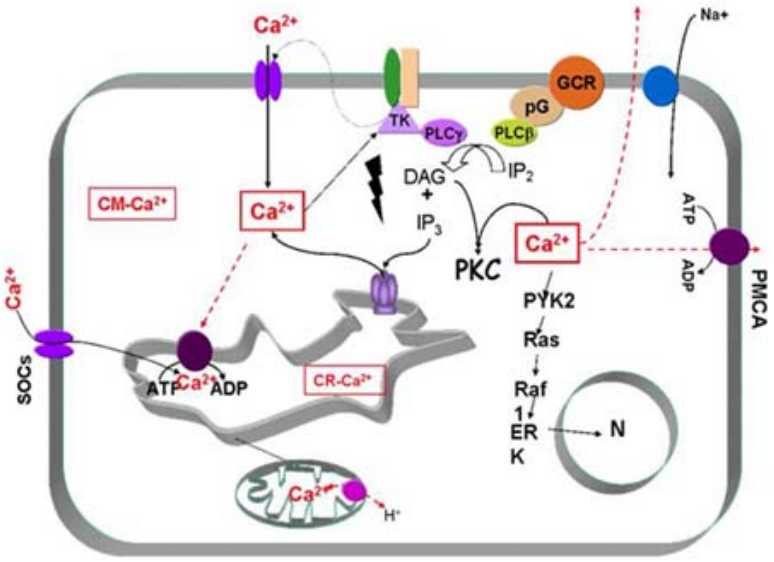
- Steps are amplified
  - Stoichiometry: if rhodopsin is in excess, response is non linear
- Steps that are amplified must be terminated
  - Rhodopsin phosphorylation and regeneration
  - G protein
  - Second messenger
- Gain can be adjusted

Processing/recycling of signaling elements



www.dddmag.com/images/0507/cel1_lrg.jpg

Second messenger regulation



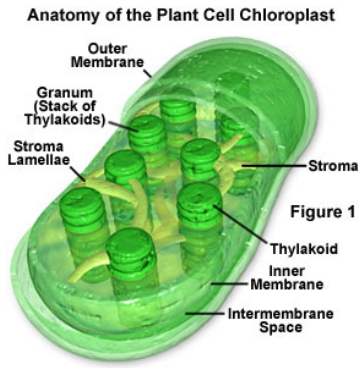
www.sct.ub.es:802/Tutorial/imagenes/casignal.jpg

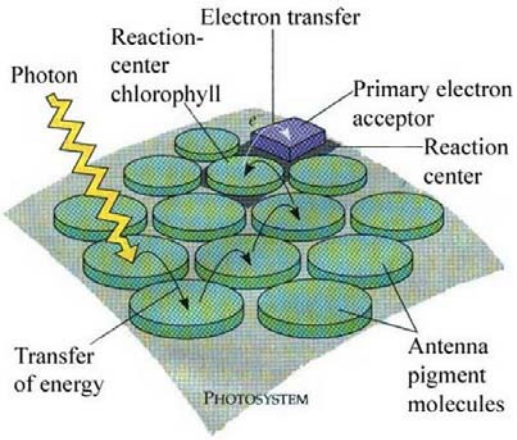
Cellular Principles of Signaling: Living Cells as Biosensors

- Signal Amplification
- Differential Amplification depends upon stoichiometry and bifurcation
- Differential Display
- Redundancy
- Gain Modulation/second messenger regulation
- Signal Termination
- Pathways can be additive, subtractive, synergistic

Photosynthetic Arrays

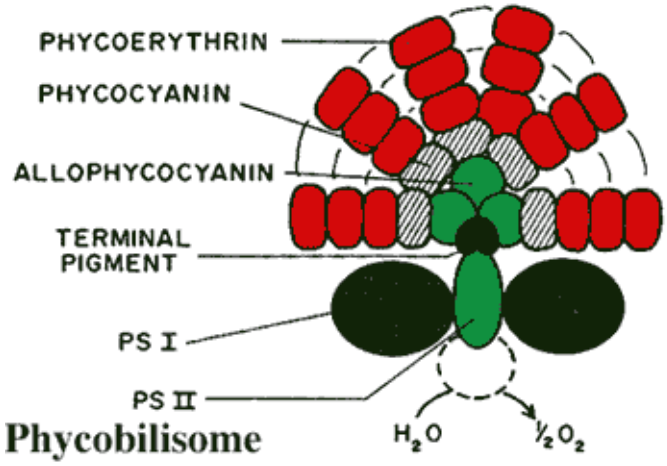
http://micro.magnet.fsu.edu/primer/java/photosynthesis/javaphotosynthesisfigure1.jpg





http://kvhs.nbed.nb.ca/gallant/biology/photosystem.jpg

Light harvesting in algae and marine bacteria



www.palaeos.com

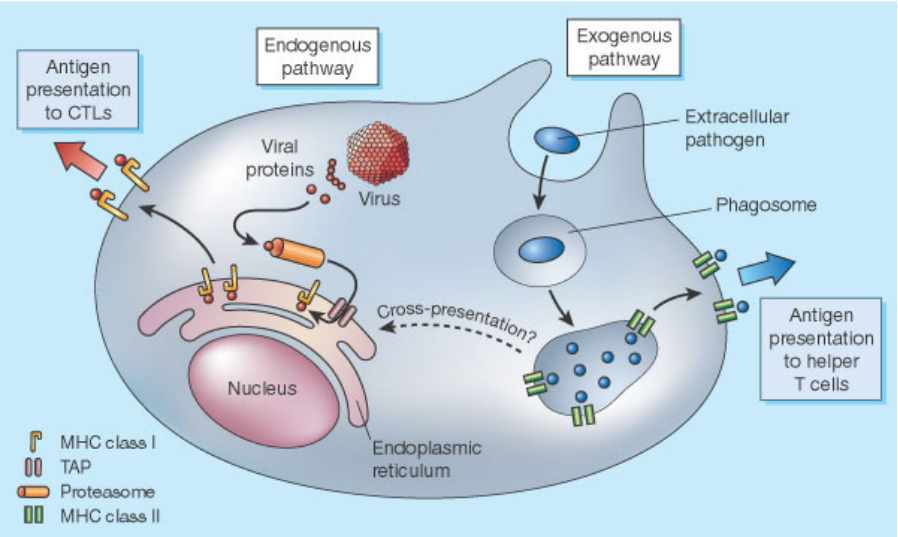
Cellular Principles of Signaling: Living Cells as Biosensors

- Long Term Responses
  - Proliferation
  - Differentiation
  - Necrosis
  - Apoptosis

Cellular Principles of Signaling: Living Cells as Biosensors

- Intercellular communication
  - Autocrine: self-signaling
  - Endocrine: circulating hormones
  - Juxtracrine: nearest neighbor
    - Antigen presentation
    - Leukocyte trafficking

Antigen Presentation

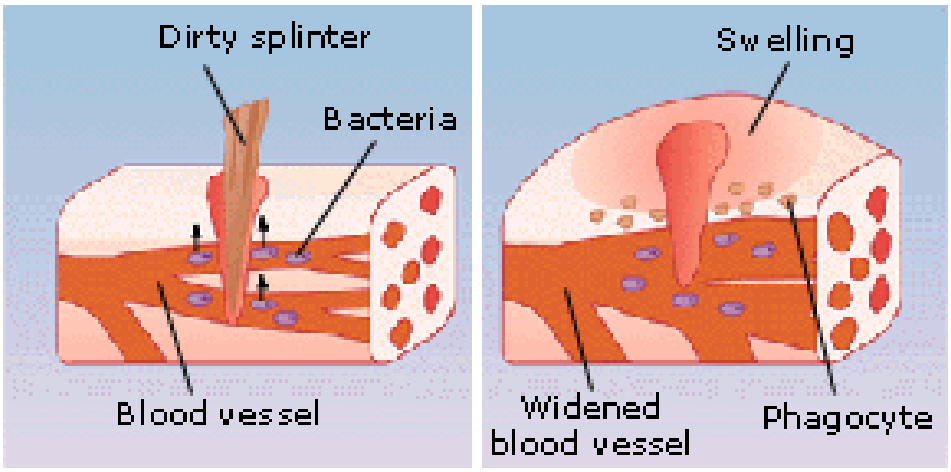


www.vetmed.wsu.edu

Leukocyte Trafficking

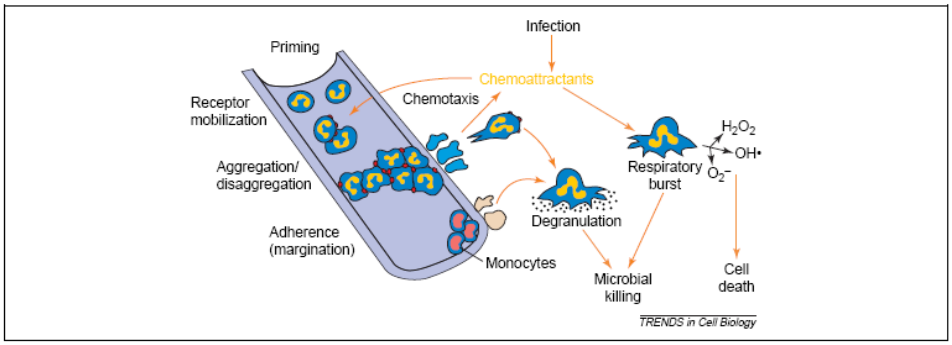
- Splinter Physiology
- Neutrophil Physiology and Machinery
- Blood Vessel Adhesion Physiology
- Integrins as nanomachines

Splinter Physiology



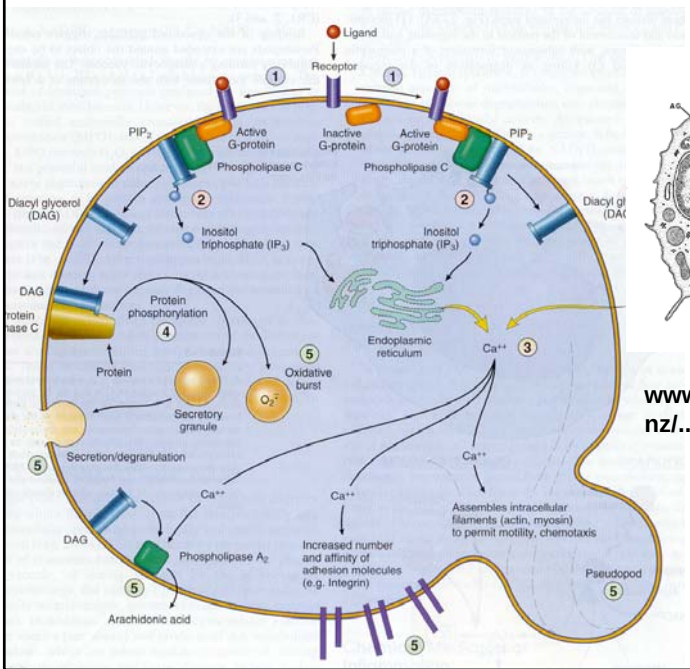
http://www.drugdigest.org/dd/images/splinter.gif

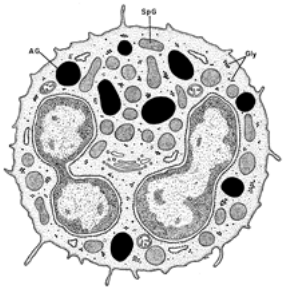
Neutrophil Physiology



TRENDS in Cell Biology Vol.15 No.3 March 2005

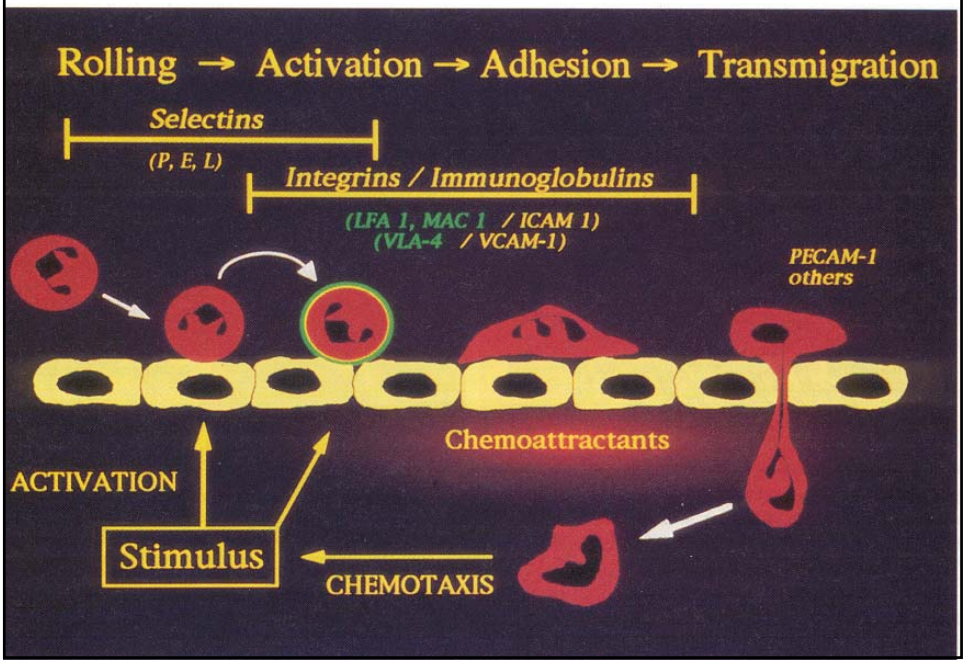
Neutrophil Machinery Robbins Pathologic Basis of Disease 6, Fig. 2-10, 11





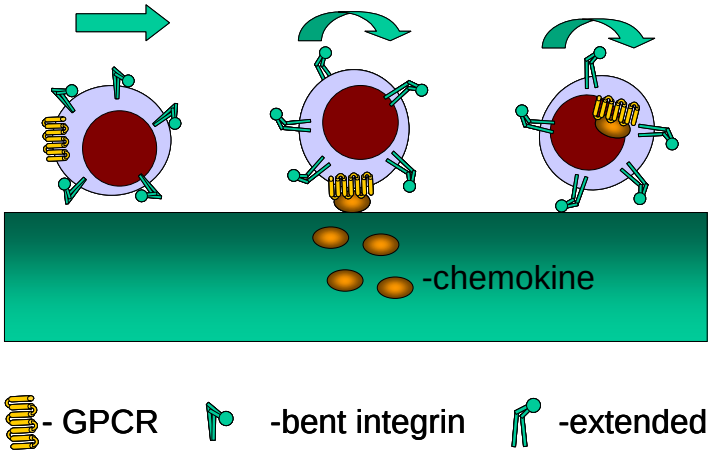
www.bioeng.auckland.ac.nz/.../neutrophil2.gif

Vascular Physiology (Robbins PBD6 Fig. 2-6)



An integrin as nanomachine with a memory

pNewtonforces, nmeter deformation, log fold affinity changes



Nanomachine Sensors

- Inside Out Signaling
  - Molecular rearrangements of nanometers
  - Changes in ligand affinity/duration of adhesion/efficiency of adhesion
  - Memory of particular stimulus
- Outside In Signaling
  - Ligand binding alter conformation and signaling
  - Mechanotransduction: Response to force alters affinity (catch bond) and generates signals
- Can protein engineering lead to generic two way sensor?