

FAULT TOLERANCE

FROM A CELLULAR BIOLOGY PERSPECTIVE

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PLAN

- Background
- Immune system scenario
- How it works

The image features a minimalist background with a central horizontal band of medium blue. Above and below this band are lighter blue and white areas, creating a layered, ethereal effect. The word "BACKGROUND" is centered in a dark, serif font.

BACKGROUND

WHAT ARE WE TALKING ABOUT?

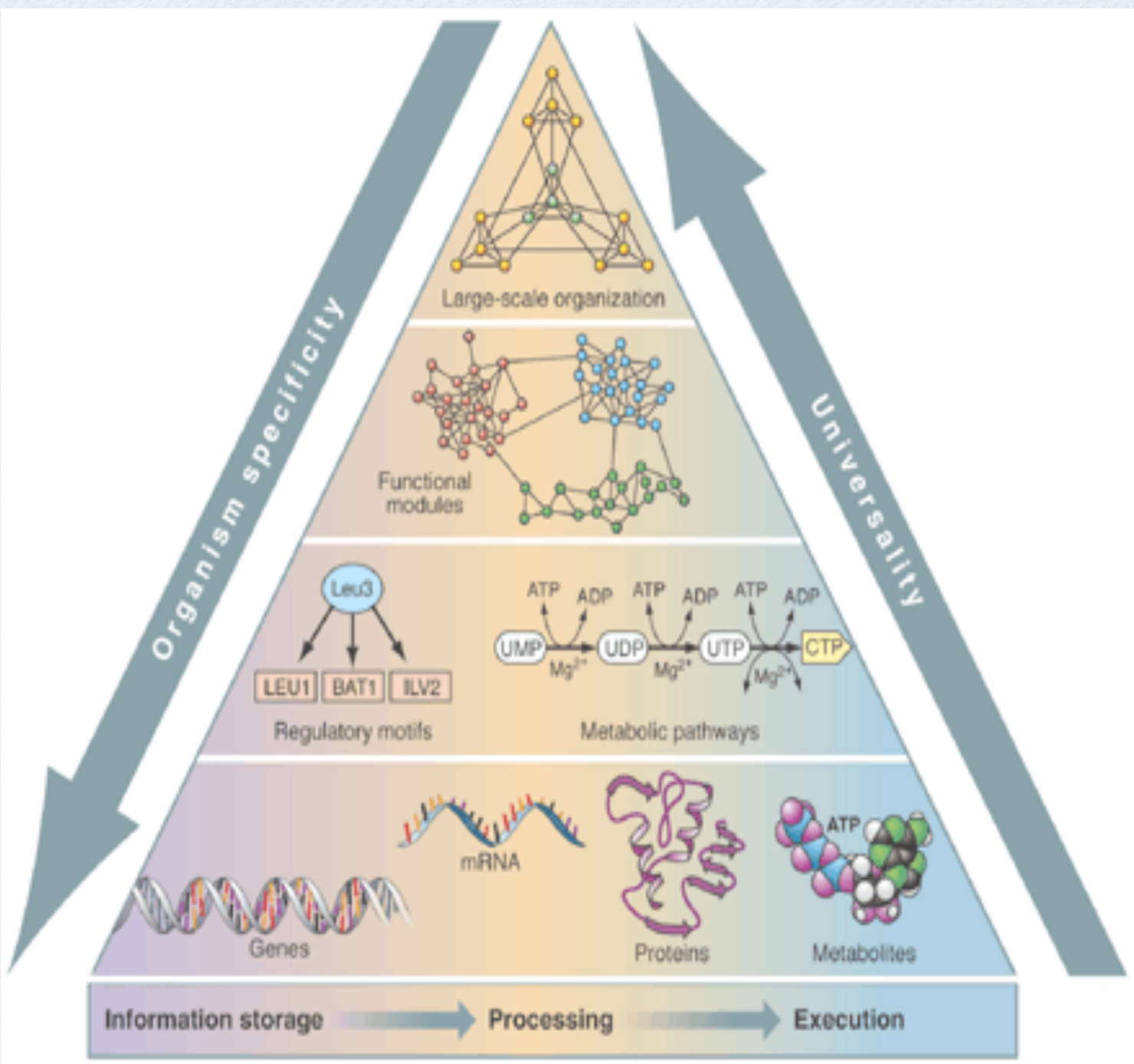
- What are faults?
 - stress conditions
 - invaders
 - misbehaving parts
- What is tolerance?
 - persist/survive
 - conquer/evade
 - repair/replace/destroy

BIO TOLERANCE EXAMPLES

- Persistent state of microbes
 - Some fraction non-deterministically 'go to sleep' (and wake up on schedule), thus providing a fraction of the community that will survive many attacks (by not reacting).
- Disintegrating invaders
- Error detection/Proof reading,
- Correction/DNA repair
- Apoptosis -- destroy the faulty (or unneeded) component and make a new one.

BIOLOGICAL SYSTEMS

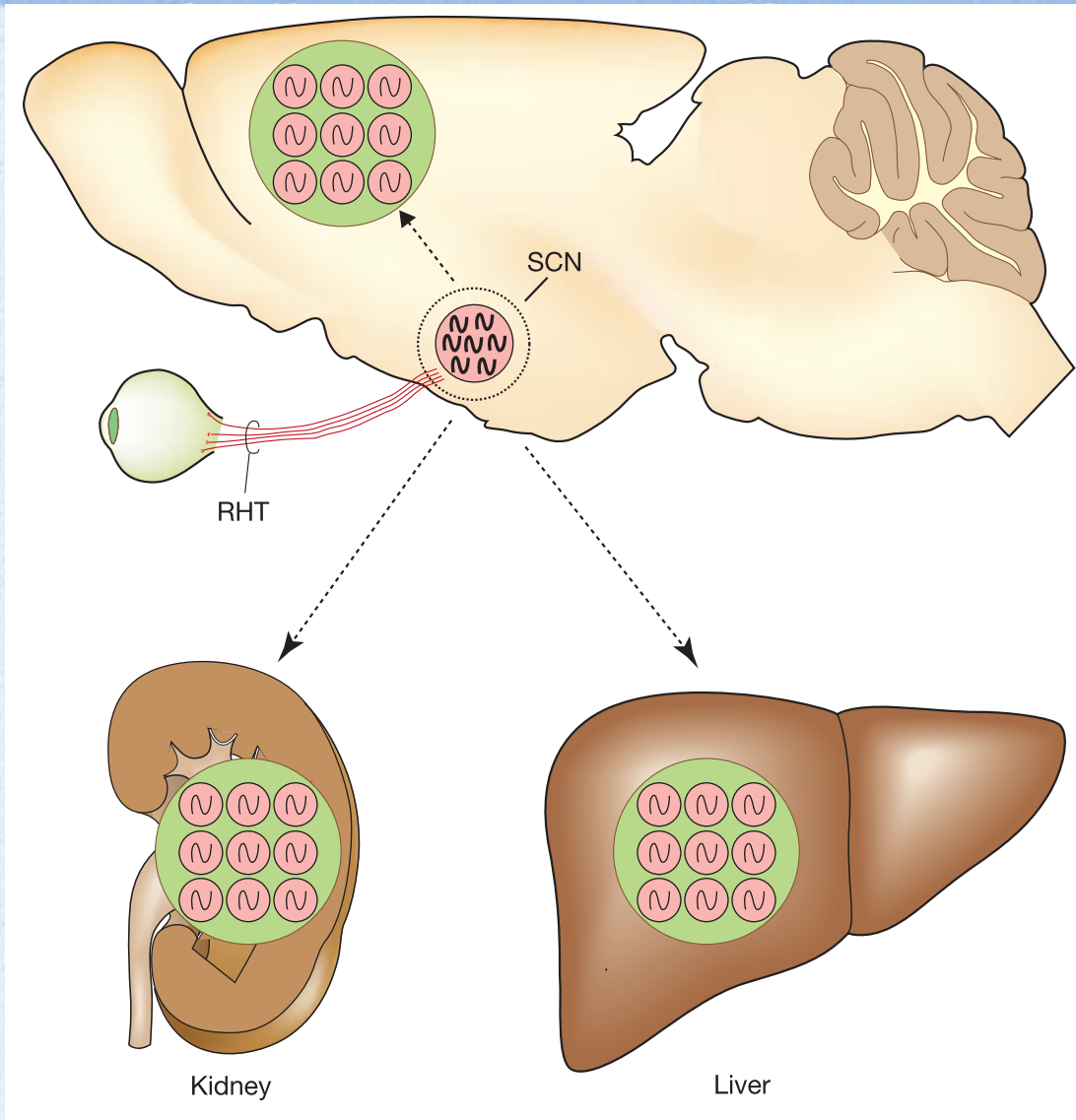
- Systems of systems of ... systems
- Including information and physical systems
 - (the ultimate CPS :-)
- Multiple levels of organization / abstraction
- Cross layer / system communication is crucial



BIOLOGICAL ORG-CHART

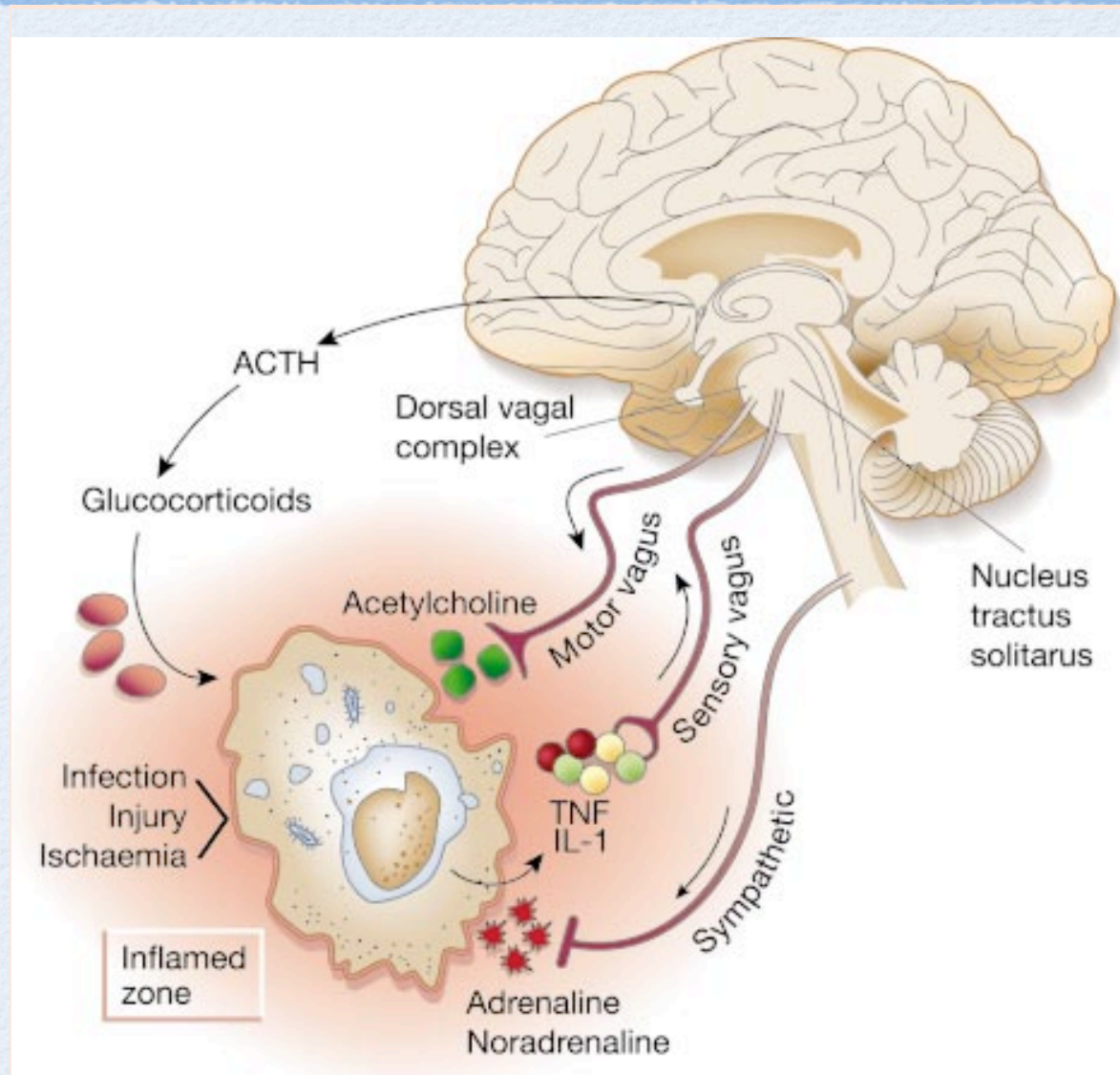
- Organism (microbe, celegans, ... rat ... human)
 - internal processes
 - community -- cooperation/competition
- Organ (brain, heart, liver ...)
 - intra organ (neuron patterns, pump, digest)
 - Organ-organ communication/coordination
- Cell
 - intra-cellular (transcriptional, signaling, metabolic processes)
 - cell system / cell-communication
- Protein

COORDINATION OF CIRCADIAN TIMING



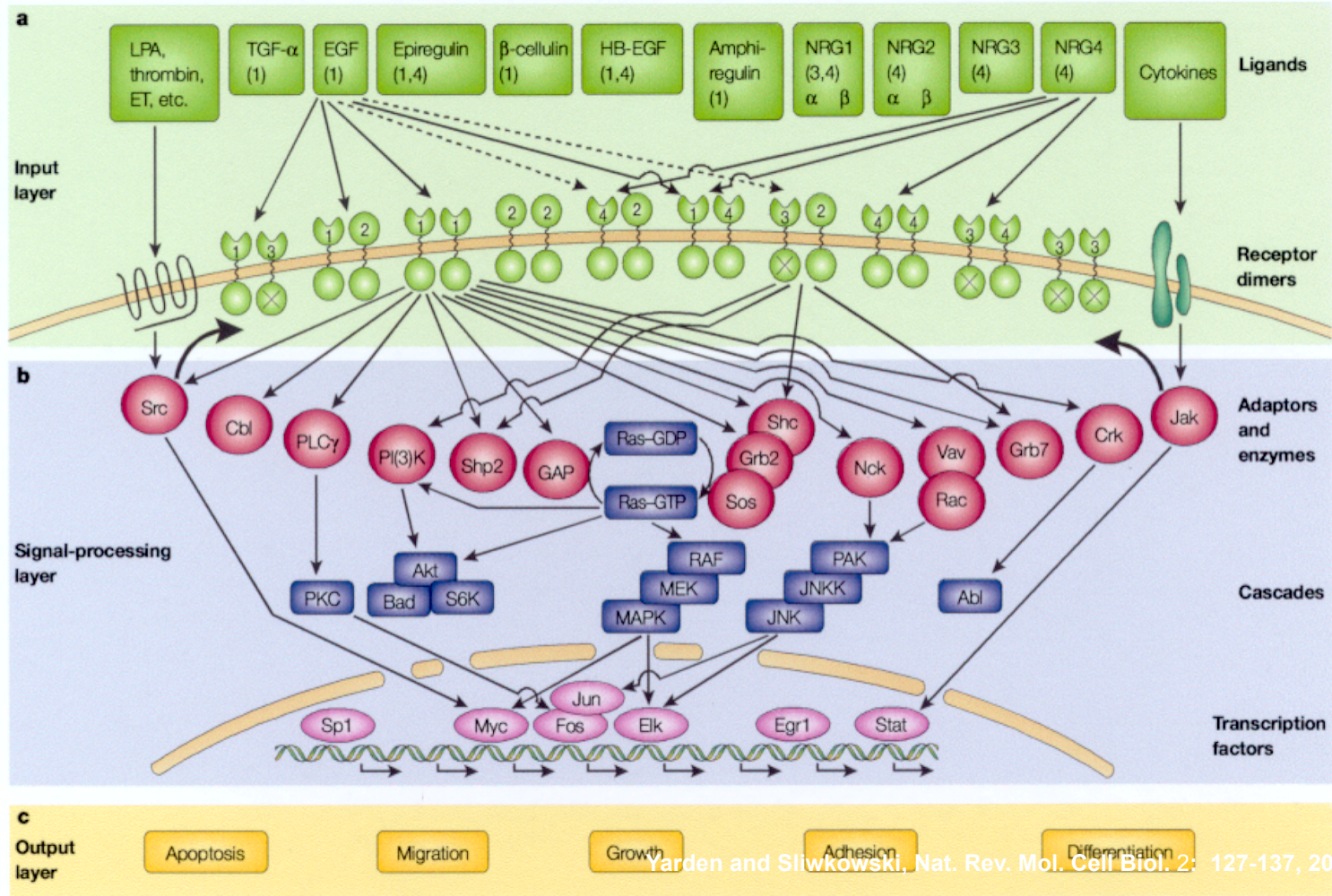
S. M. Reppert & D. R. Weaver
Nature Vol 18 2002

INFLAMMATORY REFLEX



Kevin J Tracey
Nature Vol 420 2002

THE ERBB NETWORK





CASE STUDY
THE IMMUNE SYSTEM

IMMUNE SYSTEM OVERVIEW

Job is protecting the organism from foreign entities

- Distributed
- Adaptive
- Risk/benefit trades
- Security mechanisms

Caveat smattering of observations -- not definitive

ANCESTRY

Where do immune system elements come from?

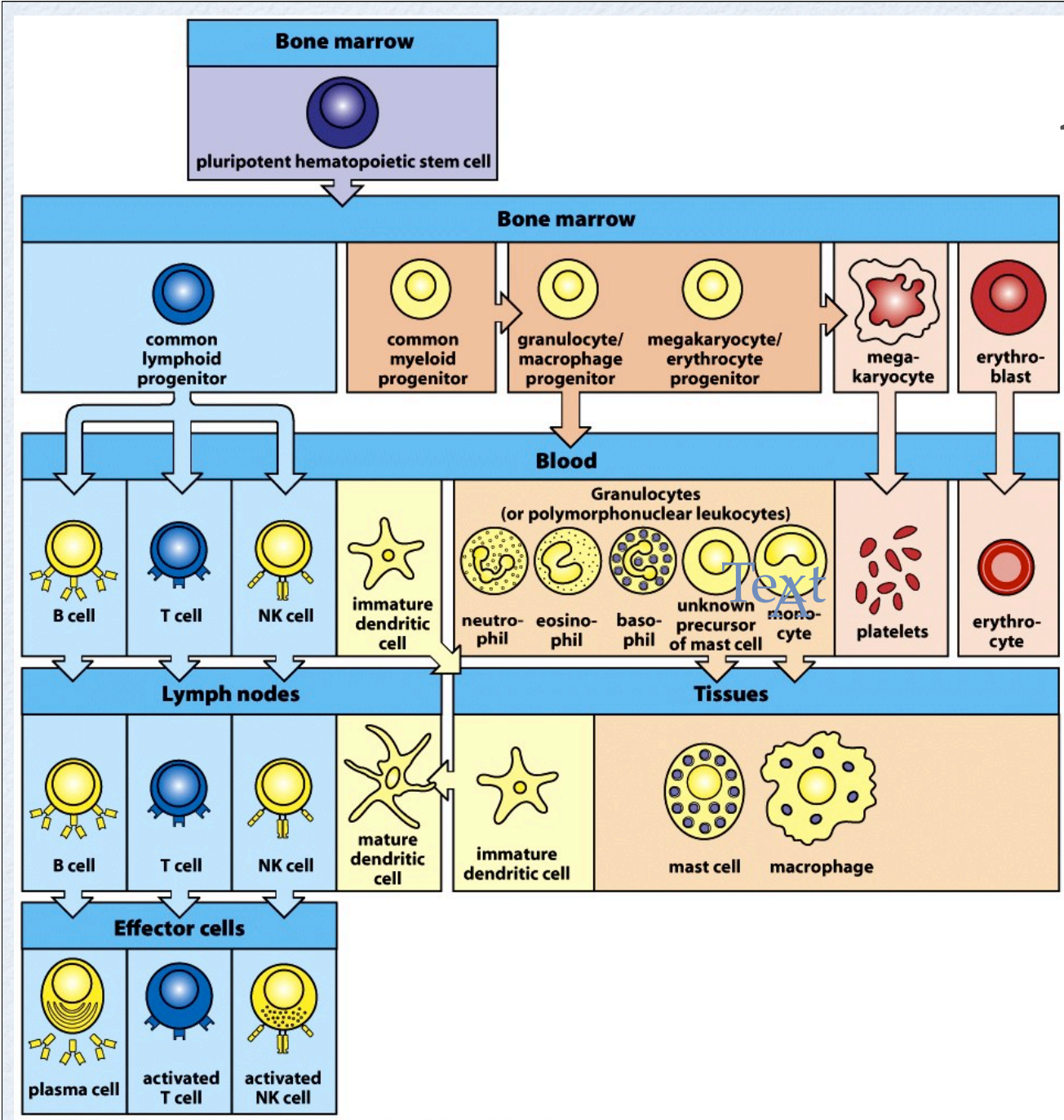


Figure 1-3 Immunobiology, 7ed. (© Garland Science 2008)

ROLES

- Phagocyte (P) -- eater
- Antigen Presenting Cells (APC)
 - sample of inside / surroundings
- Killer (K) -- by signal or poison
- Coordination (C) -- activate, signal
- Tagging

PLAYERS : CELLS

- General purpose
 - Macrophage (P, APC)
 - garbage collection / eating invaders / signal
 - Dendritic Cell (APC)
 - carries sample with pathogen to show T cells
 - Neutrophils (P aggressive)
 - circulating in blood looking for infection sites
 - Natural Killer Cells (K) -- drill holes in target
- Pathogen specific
 - B cells -- antibody factory (APC) -- mature in bone marrow
- T cells: -- mature in thymus,
 - (C) T helper (Th)
 - (K) CytoToxic Lymphocytes (CTL)

PLAYERS : PROTEINS

- Complement system -- rapid response
 - opsonize or kill pathogens
- Antibodies -- each antibody binds specific target
- Major histocompatibility complexes (MHC)
 - present bug bits (and other peptides)
- Cytokines/Chemokines
 - signals, attractants

SCENARIO

IMMUNE SYSTEM DYNAMICS

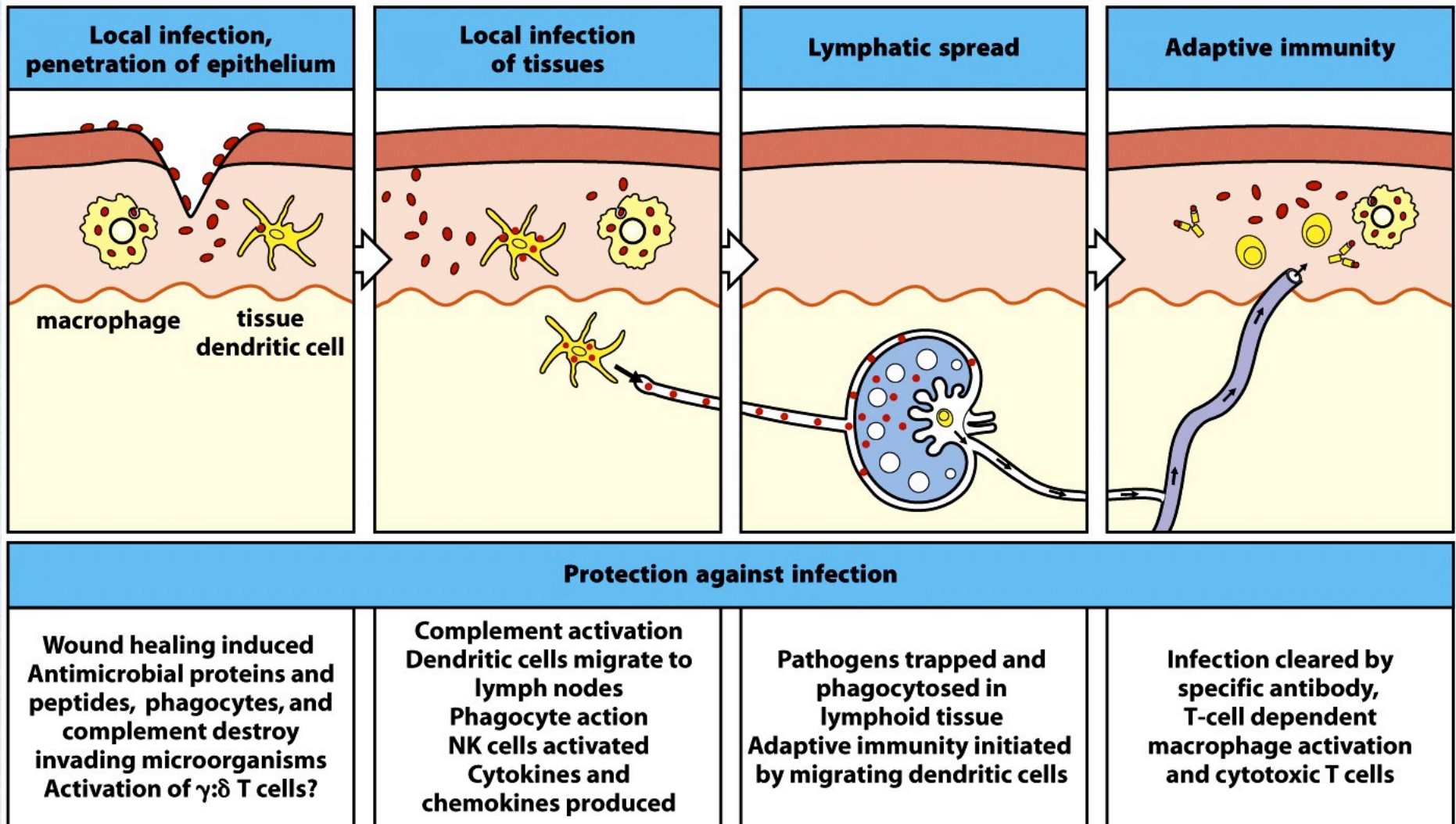
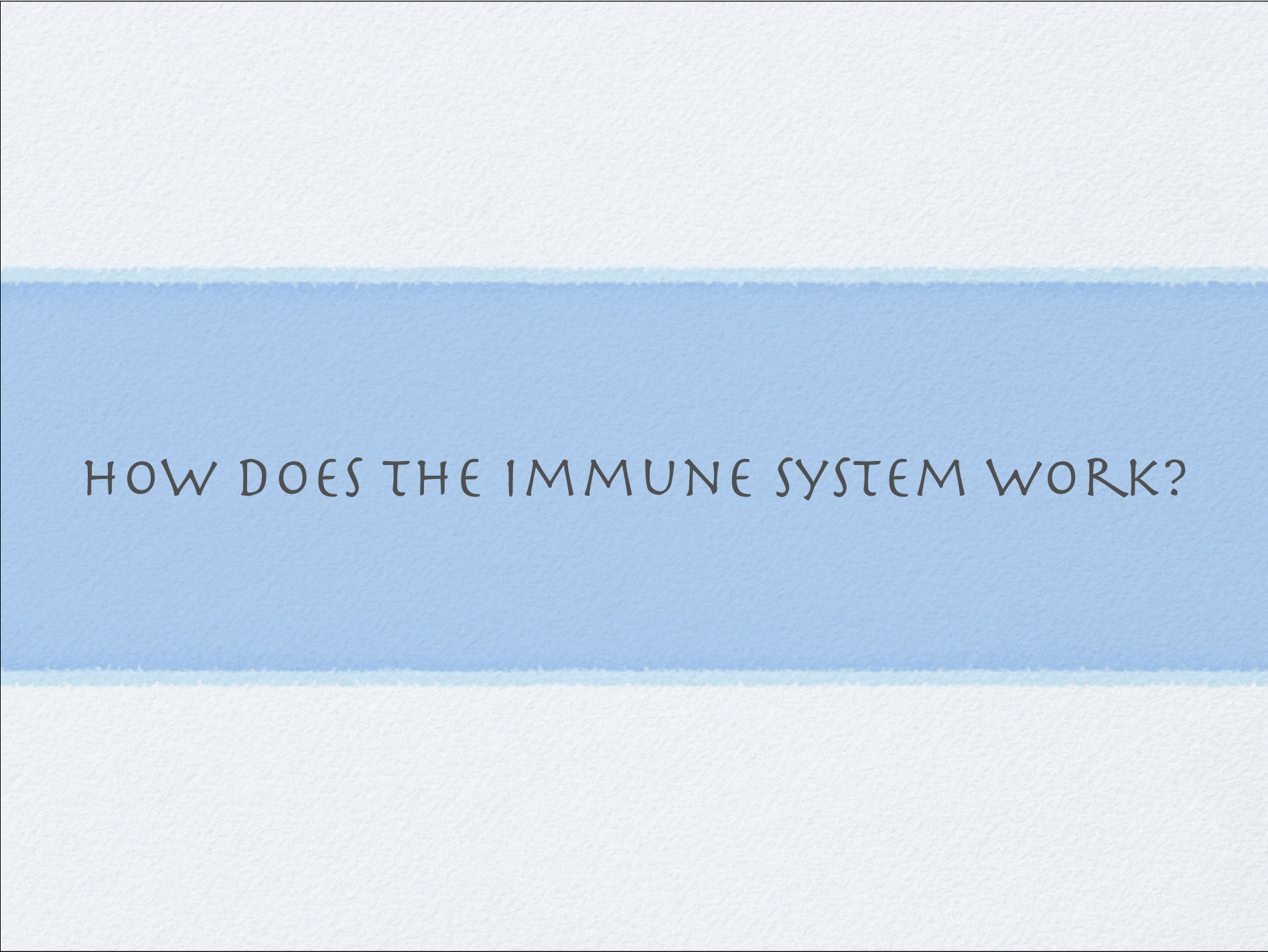


Figure 10-2 Immunobiology, 7ed. (© Garland Science 2008)



HOW DOES THE IMMUNE SYSTEM WORK?

TWO LEVEL ARCHITECTURE

- Innate Immune System (IIS)
 - border guards, troops on patrol
 - early defense, non specific
 - alert and control adaptive IS
- Adaptive Immune System (AIS)
 - highly specific
 - aggressive
 - needs control / safety mechanisms
- Basic interaction mechanism is pattern matching (binding)
 - many patterns, combinations
- Location is important

PRESENTATION

- MHCs are used by cells to display peptides (protein fragments) on their surface
- MHC I samples/presents internal protein fragments
 - CTLs scan MHC I -- looking for cells that have virus inside
- MHC II samples/presents environment protein fragments
 - Helper T Cells use MHC II as signal to activate troops

HOW DO MHC'S DISTINGUISH?

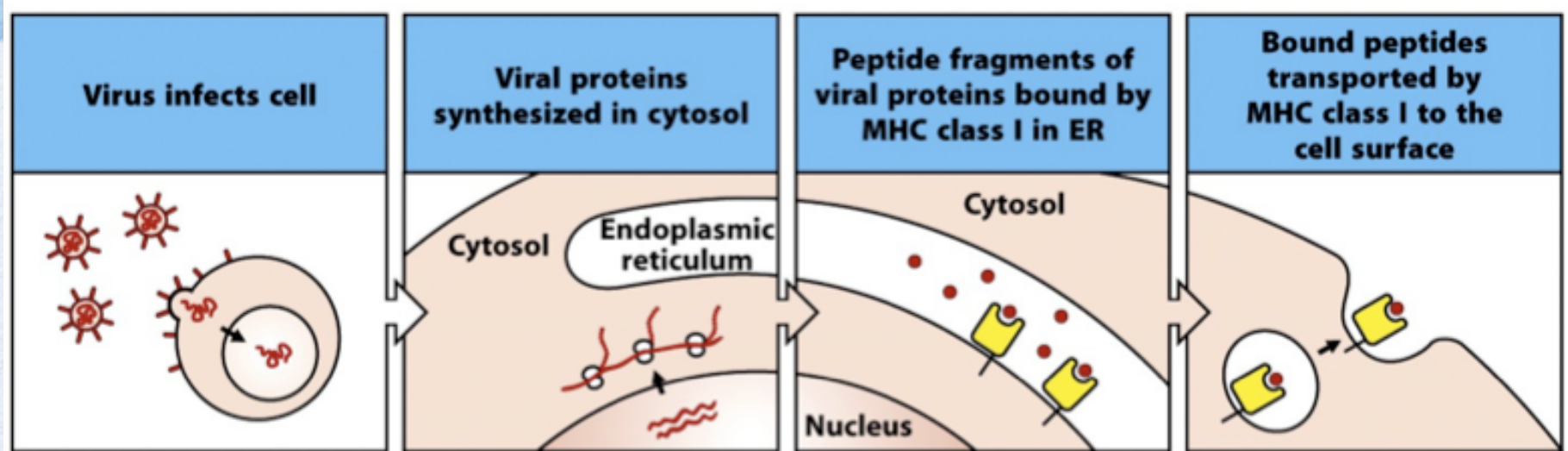
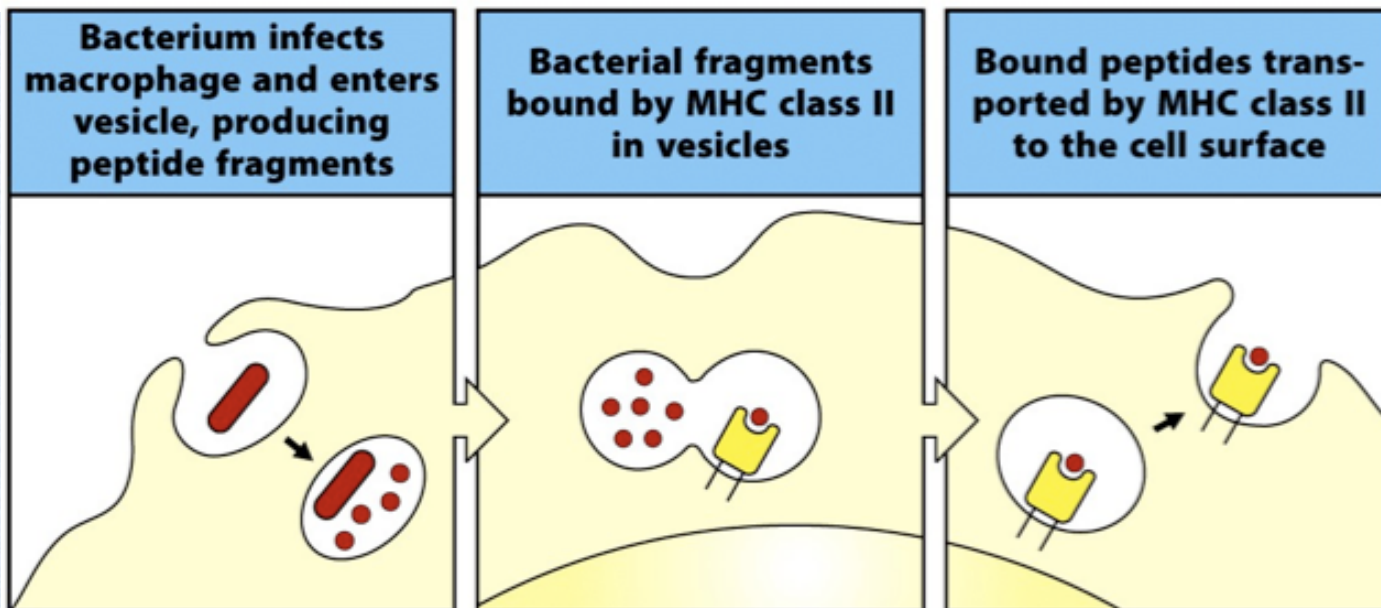


Figure 1-30 Immunobiology, 7ed. (© Garland Science 2008)



WHY PRESENTATION?

- Some cells recognize invaders `raw' -- Mph, NK,
- Some just attack when active
- Some need more information/restraint
- Presentation provides
 - Provenance
 - MHCI guarantees peptide from inside cell,
 - MHCII guarantees from environment
 - Presenter and receiver must authenticate
 - MHCI focus CTL (expensive) on infected cells (groups of viruses). Antibodies (plentiful, cheap) take care of single free viruses

THE COMPLEMENT SYSTEM

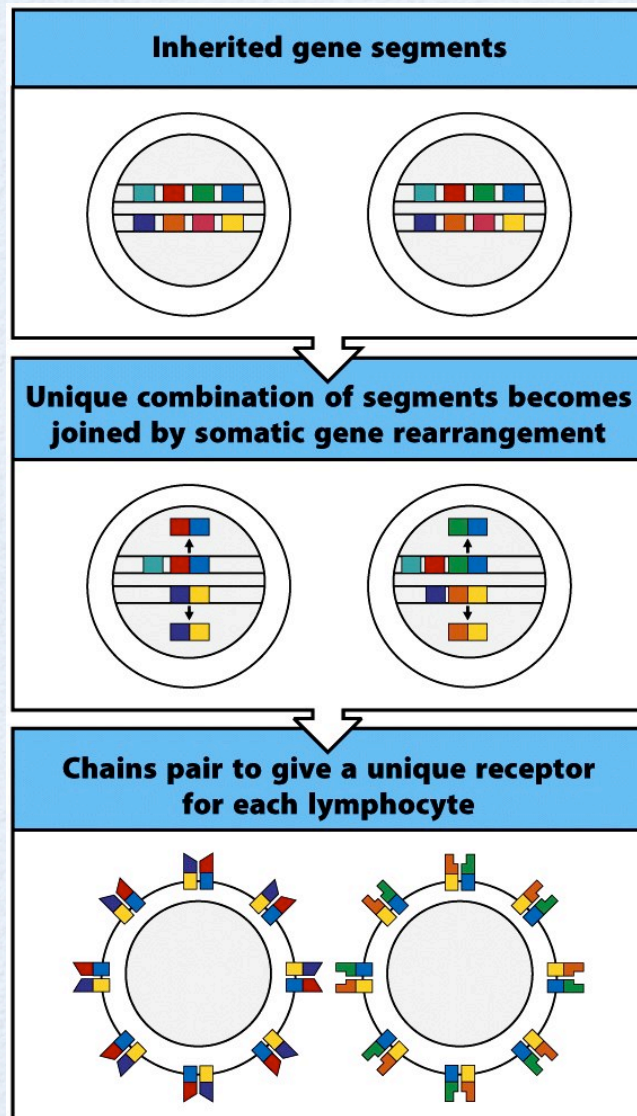
A FIRST LINE OF DEFENSE

- A collection of proteins that, when activated form complexes on cell surfaces
 - attract phagocytes
 - drill holes and kill
- Why don't they kill self cells? 3 level protection mechanism
 - DAF on surface accelerates breakdown of CS complex
 - Surface proteins can clip complex elements inactivate
 - CD59 (aka protectin) kicks complex off surface before hole drilled
- Bio caveat DAF/CD59 name protein classes.
 - May differ in detail across organisms
 - DAF of foreign cells may not be effective against host CS (transplant problems).

DIVERSITY

- There is a unique antibody type for each organic compound
- Each B Cell (and its progeny) produces exactly one type.
- Similarly for T Cells and T Cell receptors.
- How can this be? It would take all of the genes and more.

DIVERSITY



- Solution: Edit the DNA!
- Immature B and T cells have genes with multiple instances of several modules.
- These genes are edited in a series of clip/rejoin operations to mix 'n match

Figure 1-14 Immunobiology, 7ed. (© Garland Science 2008)

DIVERSITY -- BUT

- Not all combinations are desired.
 - Competence tests -- does the resulting gene produce functioning proteins? Many cells die because mix n match fails at this level
- Tolerance tests
 - TCRs must recognize presentation mechanism and not recognize self
 - ow it commits suicide

SECURE ACTIVATION

- Innate system components, non specific, always alert
 - Macrophage, DC activated by generic pathogen recognition
- Adaptive components are specific and aggressive, should not be activated if not needed
 - TCell 2key match
 - peptide and presenter, and co-stimulation
 - B Cell has 2 phase activation:
 - recognize and present its pathogen
 - connect with Tc that has seen the same pathogen

T-cell activation requires both antigen and co-stimulatory signals

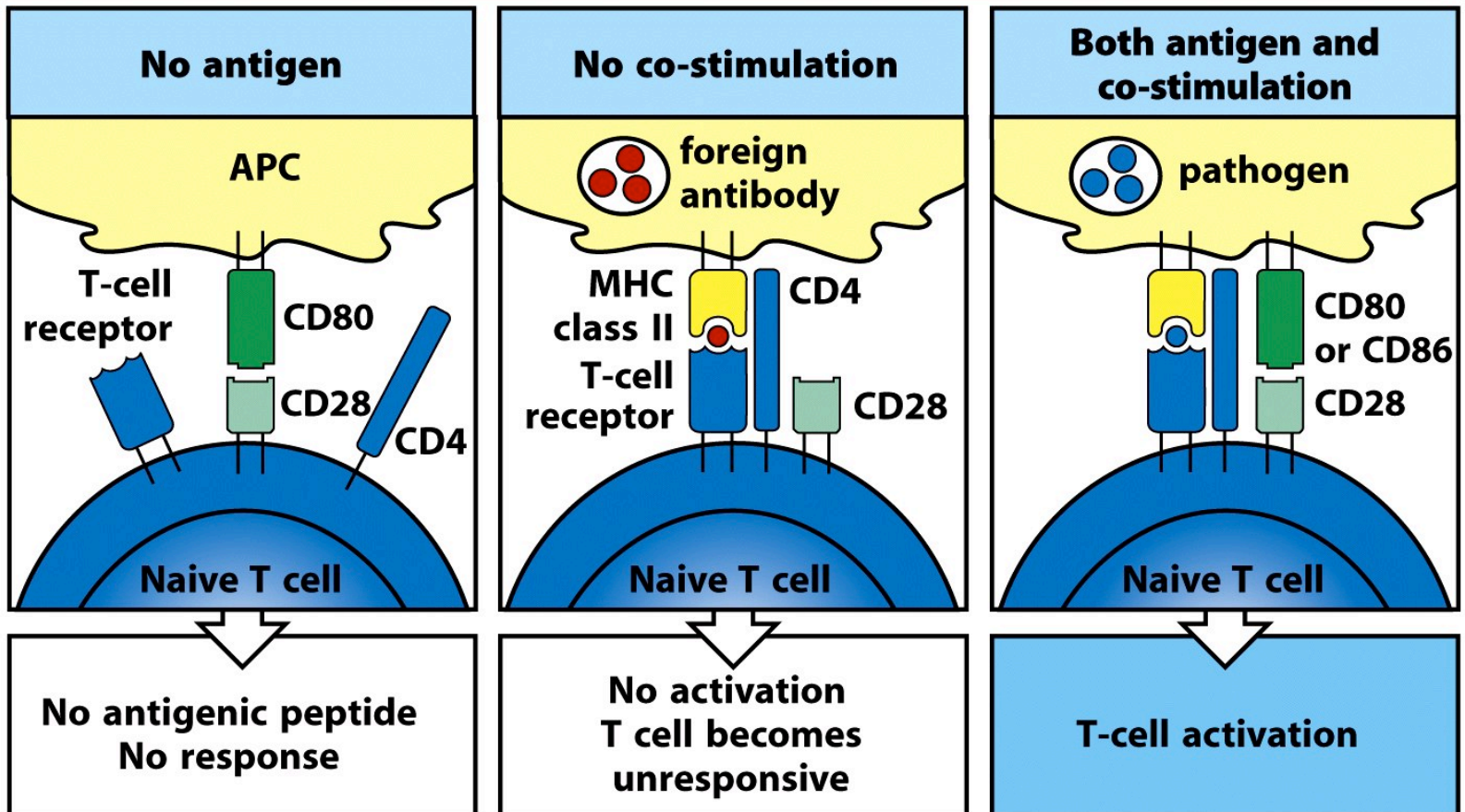


Figure 2-23 Immunobiology, 7ed. (© Garland Science 2008)

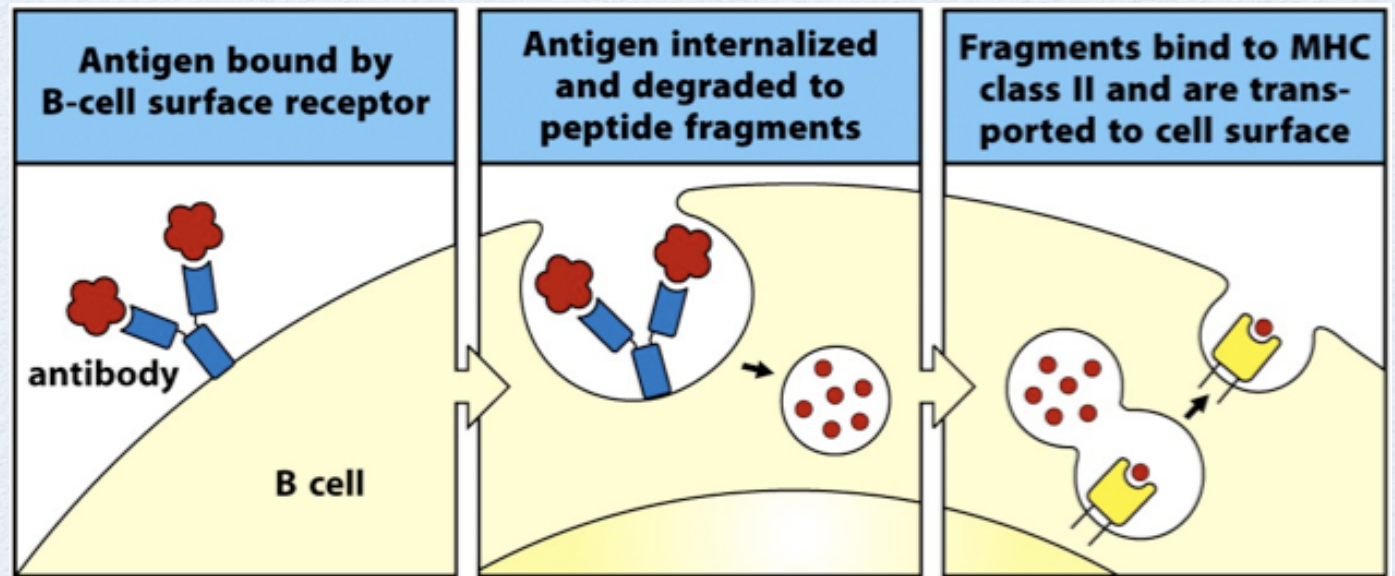
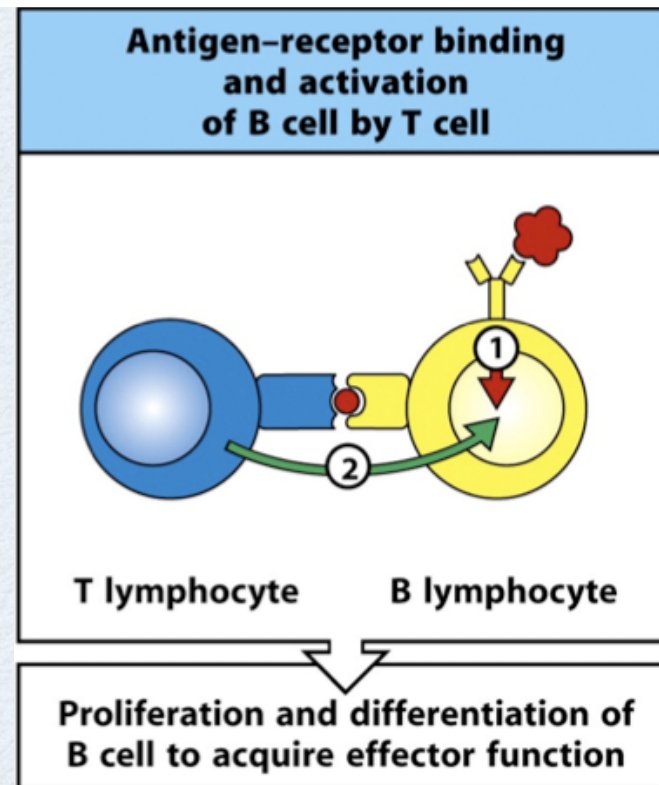


Figure 1-31 Immunobiology, 7ed. (© Garland Science 2008)

B Cell activation



RELIABLE TRANSPORT/DELIVERY

- Cells circulate / patrol / move from birth place to job site
- Need to exit vessels at the right spot and right time.
- Content/Interest driven addressing (aka zipcode)
 - cell expresses Selector Ligand
 - exit point expresses selector when interested (infection present)
 - if cell is attracted it expresses a hook (receptor) that grabs an intercellular adhesion molecule at the exit
 - attractants could be cytokines, bug bits (C5a, f-met)

TRANSPORT SYSTEM

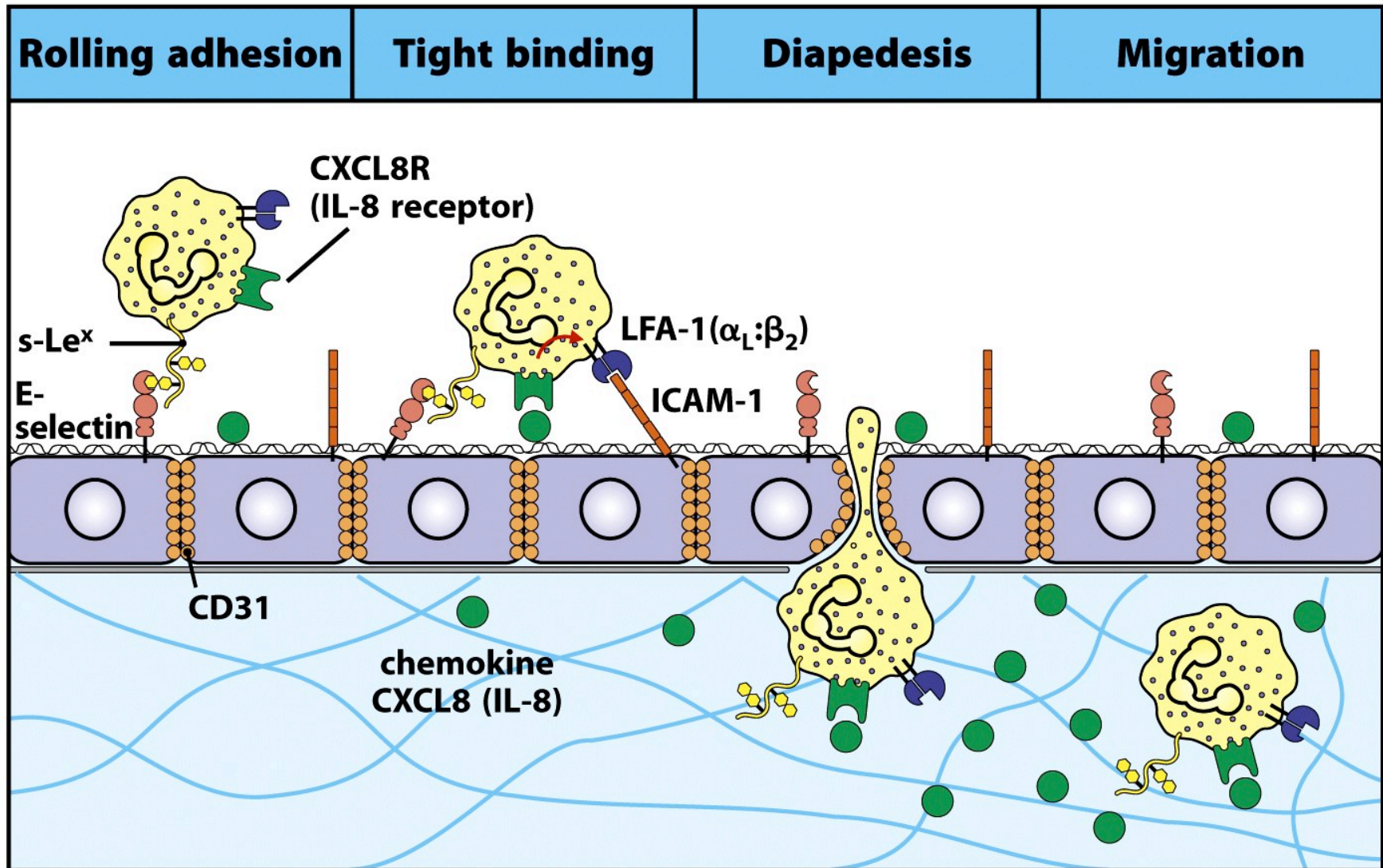


Figure 2-49 part 2 of 3 Immunobiology, 7ed. (© Garland Science 2008)

IMMUNE SYSTEM LOGIC?

- Key attributes
 - hierarchical organization: proteins, cells, locations
 - component state,
 - space
 - time/delay
- Key mechanism: pattern matching
- Diversity:
 - Multiple roles
 - Specialists ready for (almost) any need
 - counter attack, signal

IMMUNE SYSTEM LOGIC? II

- Activities:
 - eating, circulating, forming modules/complexes,
 - listening/expressing interest,
 - advertising
 - replicating
 - differentiating/refining specialty
 - continuous renewal of supply
 - supply reduction: cells dying, proteins degrading
 - junk elimination: wrong, not needed, worn out,
 - dangerous: self attack, virus nursery (tumors...)

IMMUNE SYSTEM LOGIC? III

- Control/safety mechanisms
 - battle alert system
 - initiate/continue response
 - 3 key activation of T cells
 - 2 phase activation of B cells
 - competence/tolerance tests
 - protection -- degrade, dislodge attacker

CONCLUDING QUESTION

What is the mathematics of immune system control?

- There are many trade offs, effects to balance
- Need rapid response and adaptation
- A very open system!

PATHWAY LOGIC TEAM

- Keith Laderoute
- Patrick Lincoln
- Carolyn Talcott

- Steven Eker
- Merrill Knapp
- Aneil Malavaparau
- Ian Mason
- Sylvan Pinsky
- Andy Poggio
- Malabika Sarker
- Mark-Oliver Stehr
- Frederic Vigneault

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