Chapter X:

Evolution of the immune system

Task of the Immune sytem

Distinguish self from non-self

Mount a protective response

- The evolution of the immune system is studied by comparing the presence and absence of genes/traits in different species

- Evolution of the **innate** immune system

- Evolution of the adaptive immune system

Innate immunity

- Fast response with “no memory”.
- Pathogen recognition by an army of “fixed” receptors with the capacity to distinguish unique pathogen associated molecular patterns (PAMP)
- Some components are extremely old

Antimicrobial Peptides (Defensins)

- Host defense peptides active against bacteria, fungi and many viruses
- Small cysteine-rich cationic proteins. Two exon genes. First part encodes a leader, the second exon a 6 to 8 cysteine residue motif, engaging its target.
- Defensin family is highly polymorphic
- Most defensins function by binding to the microbial cell membrane, and, once embedded, forming pore-like membrane defects.

Defensins

- Most multicellular organisms make multiple defensins
  Arabidopsis thaliana 13
  Drosophila >15,
  one human gut cell > 21
- Specialization: some are active against gram-negative others are targetting gram-positive bacteria

Defensins are likely to be the most ancient part of the immune system

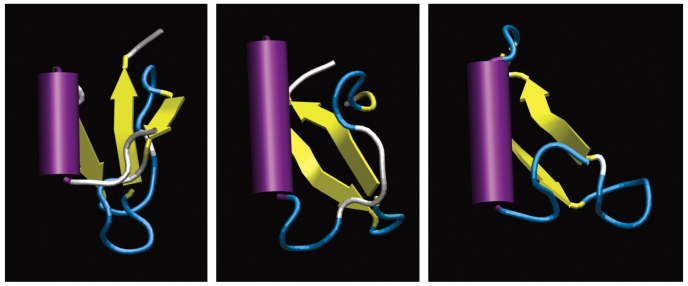


Figure 16-2 Immunobiology, 7ed. (© Garland Science 2008)

a b c

Antimicrobial defensins of a) plants, b) insects and c) mammals are structurally related and the progenitor gene may have been present in a common ancestor which lived approximately 2 a 3 billion years ago

Toll Receptors

- Alert the immune system to the presence of microbial infections
- First detected in fruitflies (embryonic development/immune defense), later in humans (Immune function).

- Also present in plants
- Subject to duplication/specialization

Toll-like receptors may represent the most ancient pathogen recognition system

activation results in production of cytokines and inflammation

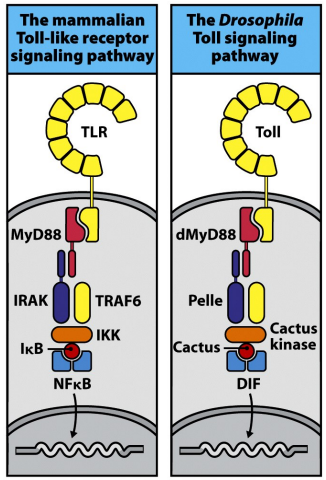


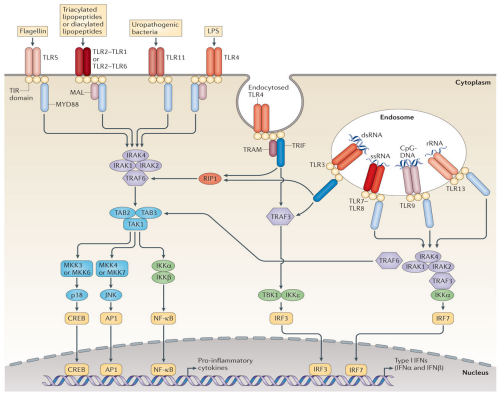
Figure 16-3 Immunobiology, 7ed. (© Garland Science 2008)

activation induces expression of antimicrobial peptides primarily acting on gram-positive bacteria and fungal pathogens

Toll-like receptors genes have undergone extensive diversification in some invertebrate species

- humans — 13 TLR (#11-13 pseudogenes)
- mice — 13 TLR (#10 pseudogene)
- sea urchin — 222 TLR (many pseudogenes but like other species a conserved signaling machinery)
- Drosophila — 1 TLR

Mammalian TLR signalling Pathways



Nature Reviews | Immunology

A second recognition system in Drosophila homologous to the mammalian TNF receptor pathway provides protection from gram negative bacteria

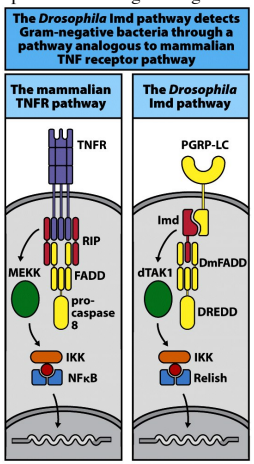


Figure 16-4 Immunobiology, 7ed. (© Garland Science 2008)

Both Toll and Imd pathways activate gene transcription to eliminate infections

First signs of a complement-like system

Echinoderms (stekelhuidigen)

The "primitive" complement system of echinoderms resembles the alternative pathway of complement activation in mammals

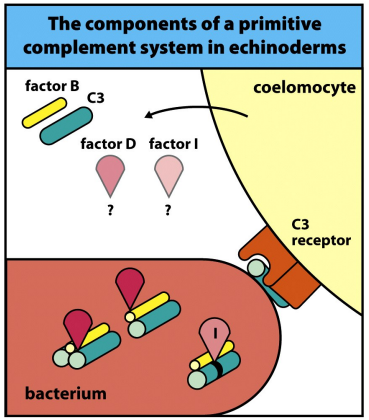


Figure 16-5 Immunobiology, 7ed. (© Garland Science 2008)

most primitive function is opsonization (increasing the efficiency of pathogen uptake)

Tunicates; sea squirts

The lectin pathway of complement-activation evolved in invertebrates

The lectin pathway of complement activation evolved in invertebrates

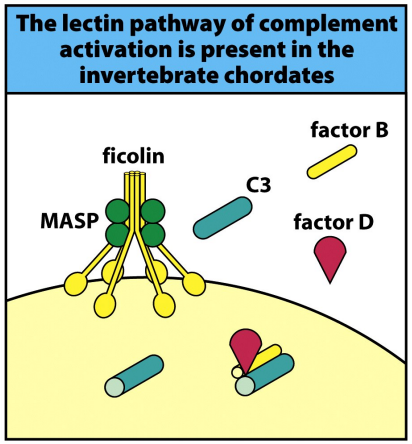


Figure 16-6 Immunobiology, 7ed. (© Garland Science 2008)

MASP MBL-associated serine protease

MBL=Mannose binding lectin

Some invertebrates generate extensive diversity in a repertoire of immunoglobulin-like genes (a non-rearranging system)
Function: opsonization of invading bacteria

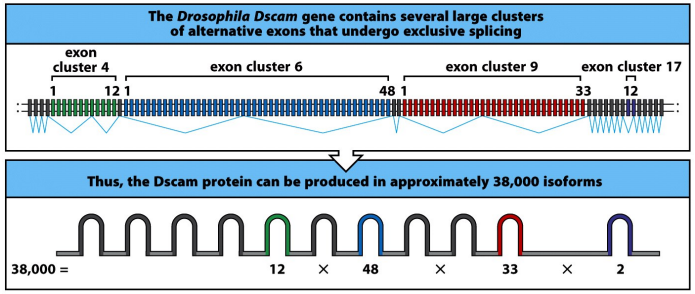


Figure 16-7 Immunobiology, 7ed. (© Garland Science 2008)

Dscam Down syndrome adhesion molecule (opsonizes invading bacteria)

Chapter ? | Evolution of the immune system

- The evolution of the immune system can be studied by comparing the genes expressed by different species

  - Evolution of the innate immune system

  - Evolution of the **adaptive** immune system(s)

Adaptive Immune System

- Mounting a response takes time
- Highly specific receptors
- Gene rearrangement
- Memory
- Some key genes: TcR, Ig, RAG and MHC or are there other possibilities?

First evidence for an adaptive immune system

Agnathans: Jawless fish

Lamprey

Hagfish

Agnathans

- Diverse haematological cells – heterogenous leukocytes
- Produce opsonins and agglutinins
- Allograft rejection
- DO NOT have MHC, Ig, TcR or RAG-1/RAG-2 genes
- Have their own adaptive immune receptors VLR-A (T cell like) and VLR-B (B-cell like).
- LRR receptors that can rearrange somatically.
- Mechanism is unknown, but probably a transposase.
- 35 VLR-A molecules and 38 VLR-B molecules

Agnathans possess an adaptive immune system that uses somatic gene rearrangement to diversify receptors built from LRR (Leucine Rich Repeat) domains

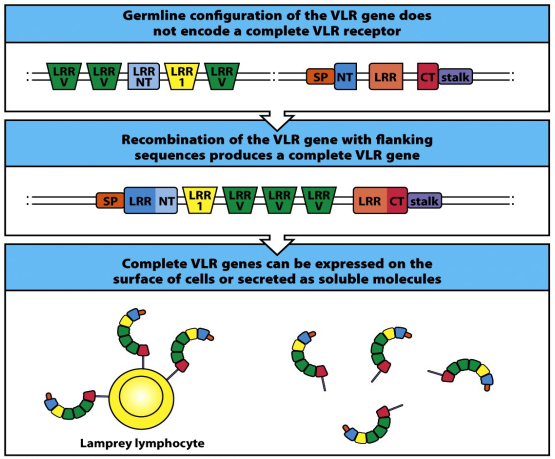


Figure 16-8 Immunobiology, 7ed. (© Garland Science 2008)

VLR = variable lymphocyte receptors

mechanism?

Memory?

Adaptive immunity based on a diversified repertoire of Ig-like genes appeared "abruptly" in the jawed-vertebrate lineage

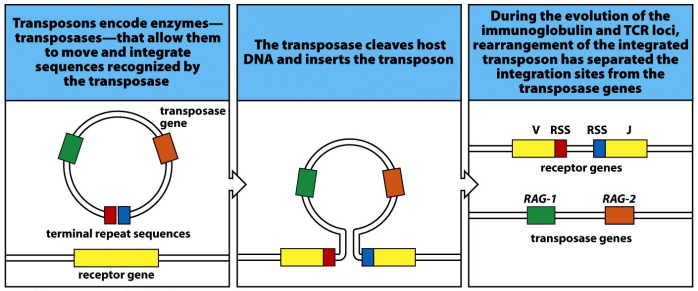
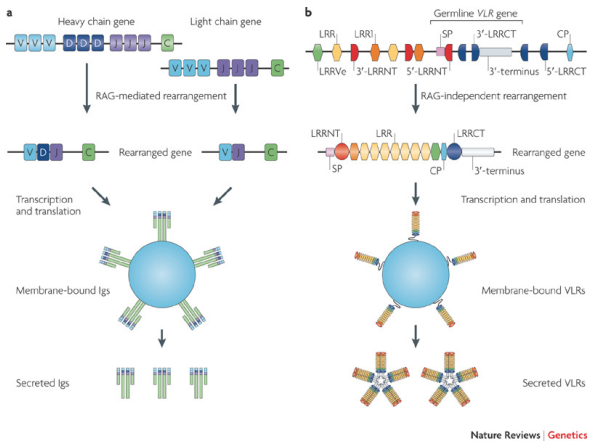


Figure 16-9 Immunobiology, 7ed. (© Garland Science 2008)

Two distinct forms of adaptive immunity in vertebrates



- MHC class I and II molecules are first found in the cartilaginous fish
- Both alpha/beta and gamma/delta T cell receptors are present in cartilaginous fish
- Adaptive Immune system in jawed vertebrates is approximately 450 million years old

Antigen receptors: about cross talk

- Innate immunity
  - TLR, C-type lectins, and NOD-like (NLR) receptors
  - Invariant TcR (NK recognition) (Rapid)
  - Non-polymorphic MHC-like molecules (i.e. CD1, MR1)
  - Non-classical MHC such as HLA-E
- Adaptive immunity
  - T cell Receptor (α/β and γ/δ)
  - Immunoglobulins
  - MHC I and II – pathogen fragment presentation

Different species generate immunoglobulin diversity in different ways

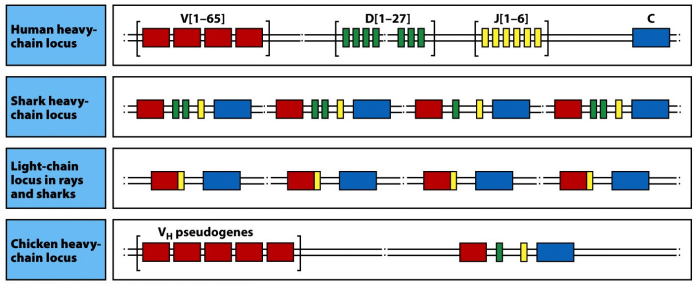


Figure 16-10 Immunobiology, 7ed. (© Garland Science 2008)

Key events in adaptive immunity

- Agnatha have a rudimentary GALT system
- Teleosti (bony fish) possess thymus and spleen
- Amphibians show emergence of bone marrow
- Aves*/Reptilia/mammalia possess lymph nodes and germinal centers.

***bursa of fabricius** a lymphoid organ in young chickens where B cells mature