15.4Q: Innate Immunity

The ability of a multicellular organism to defend itself against invasion by pathogens (bacteria, fungi, viruses, etc.) depends on its ability to mount immune responses. All metazoans (probably) have inborn defense mechanisms that constitute **innate immunity**. Vertebrates have not only innate immunity but also are able to mount defense mechanisms that constitute **adaptive immunity**. This table gives some of the distinguishing features of each type of immunity.

<table>
<thead>
<tr>
<th>Innate Immunity</th>
<th>Adaptive Immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogen recognized by receptors encoded in the germline</td>
<td>Pathogen recognized by receptors generated randomly</td>
</tr>
<tr>
<td>Receptors have broad specificity, i.e., recognize many related molecular</td>
<td>Receptors have very narrow specificity; i.e., recognize a particular epitope</td>
</tr>
<tr>
<td>structures called PAMPs (pathogen-associated molecular patterns)</td>
<td></td>
</tr>
<tr>
<td>PAMPs are essential <strong>polysaccharides</strong> and <strong>polynucleotides</strong> that differ</td>
<td>Most epitopes are derived from <strong>polypeptides</strong> (proteins) that reflect the</td>
</tr>
<tr>
<td>little from one pathogen to another but are not found in the host.</td>
<td>individuality of the pathogen.</td>
</tr>
<tr>
<td>Receptors are PRRs (pattern recognition receptors)</td>
<td>In jawed vertebrates, the receptors are B-cell (<strong>BCR</strong>) and T-cell (<strong>TCR</strong>)</td>
</tr>
<tr>
<td>Immediate response</td>
<td>receptors for antigen</td>
</tr>
<tr>
<td>Little or no memory of prior exposure</td>
<td>Slow (3–5 days) response (because of the need for clones of responding cells to</td>
</tr>
<tr>
<td></td>
<td>develop)</td>
</tr>
<tr>
<td></td>
<td>Memory of prior exposure</td>
</tr>
</tbody>
</table>

https://bio.libretexts.org/TextMaps/Introductory_and_General_Biology/Book%3A_Biology_(Kimball)/Unit_15%3A_The_Anatomy_
The Cells of the Innate Immune System

A variety of different types of cells participate in innate immunity. What they all have in common is that the receptors by which they recognize pathogens are limited in their specificity. This is in contrast to the B cells and T cells of the adaptive immune system that generate receptors — BCRs and TCRs respectively — that are exquisitely specific for the pathogen.

The players:

- The several granulocytes of the blood and tissues
  - neutrophils
  - eosinophils
  - basophils and mast cells
- monocytes and macrophages
- dendritic cells
- Innate Lymphoid Cells (ILCs). These are cells that look like lymphocytes but do not have the antigen receptors found on B lymphocytes (BCRs) and T lymphocytes (TCRs). They include cytotoxic Natural Killer (NK) cells and several subsets of non-cytotoxic cells (ILC1, ILC2, ILC3, etc.) each with its own pattern of cytokine secretion and favored targets.

Pathogen-Associated Molecular Patterns (PAMPs)

Pathogens, especially bacteria, have molecular structures that are not shared with their host and are shared by many related pathogens. They are relatively invariant; that is, do not evolve rapidly (in contrast, for example, to such pathogen molecules as the hemagglutinin and neuraminidase of influenza viruses).

Examples:

- the flagellin of bacterial flagella
- the peptidoglycan of Gram-positive bacteria
- the lipopolysaccharide (LPS, also called endotoxin) of Gram-negative bacteria
- double-stranded RNA. (Some viruses of both plants and animals have a genome of dsRNA. And many other viruses of both plants and animals have an RNA genome that in the host cell is briefly converted into dsRNA).
- unmethylated DNA (eukaryotes have many times more cytosines, in the dinucleotide CpG, with methyl groups attached).

Pattern Recognition Receptors (PRRs)

There are three groups:

1. secreted molecules that circulate in blood and lymph;
2. surface receptors on phagocytic cells like macrophages that bind the pathogen for engulfment;
3. cell-surface receptors that bind the pathogen initiating a signal leading to the release of effector molecules (cytokines).

**Secreted PRRs**

Example: Circulating proteins (e.g., C-reactive protein) that bind to PAMPs on the surface of many pathogens. This interaction triggers the complement cascade leading to the opsonization of the pathogen and its speedy phagocytosis.

**Phagocytosis Receptors**

*Macrophages* have cell-surface receptors that recognize certain PAMPs, e.g., those containing mannose. When a pathogen covered with polysaccharide with mannose at its tips binds to these, it is engulfed into a phagosome.

**Toll-Like Receptors (TLRs)**

Macrophages, dendritic cells, and epithelial cells have a set of transmembrane receptors that recognize different types of PAMPs. These are called Toll-like receptors (TLRs) because of their homology to receptors first discovered and named in *Drosophila*. Mammals have 12 different TLRs each of which specializes — often with the aid of accessory molecules — in a subset of PAMPs. In this way, the TLRs identify the nature of the pathogen and turn on an effector response appropriate for dealing with it. These signaling cascades lead to the expression of various **cytokine genes**. Examples:

- **TLR-1**: Forms a heterodimer with TLR-2 at the cell surface which binds to the peptidoglycan of Gram-positive bacteria like *Streptococci* and *Staphylococci*.
- **TLR-2**: With TLR-1, binds cell-wall components of Gram-positive bacteria.
- **TLR-3**: Binds to the double-stranded RNA of viruses engulfed in endosomes.
- **TLR-4**: Activated by the lipopolysaccharide (endotoxin) in the outer membrane of Gram-negative bacteria like *Salmonella* and *E. coli O157:H7*.
- **TLR-5**: Binds to the flagellin of motile bacteria like *Listeria*.
- **TLR-6**: Forms a heterodimer with TLR-2 and responds to peptidoglycan and certain lipoproteins.
- **TLR-7 and TLR-8**: Form a heterodimer that binds to the single-stranded RNA (ssRNA) genomes of such viruses as influenza, measles, and mumps that have been engulfed in endosomes.
- **TLR-9**: Binds to the unmethylated CpG of the DNA of bacteria that have been engulfed in endosomes. (The cytosines in the host's CpG dinucleotides often have methyl groups attached.)
- **TLR-11**: In mice, it binds proteins expressed by several infectious protozoans (Apicomplexa) as well as, like TLR-5, to flagellin. Humans do not have TLR-11.

In all these cases, binding of the pathogen to the TLR initiates a signaling pathway leading to the activation of NF-κB. This transcription factor turns on many cytokine genes such as those for tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and chemokines, which attract white blood cells to the site. All of these effector molecules lead to **inflammation** at the site. And even before these late events occur, the binding of Gram-positive bacteria to TLR-2 and Gram-negative bacteria to TLR-4 enhances phagocytosis and the fusion of the phagosomes with lysosomes.
Innate Immunity can trigger Adaptive Immunity

This can occur in several ways:

**Macrophages** and **dendritic cells** are phagocytes and are also responsible for "presenting" antigens to T cells to initiate both cell-mediated and antibody-mediated adaptive immune responses.

- Digested fragments of the engulfed pathogen are returned to the cell surface nestled in the cavity of class II histocompatibility molecules.
- Gene transcription turned on by the interaction of PAMPs and TLRs causes transmembrane molecules called **B7** to appear at the cell surface.
- T cells have a receptor for B7 called CD28.
- Simultaneous binding of
  - CD28 to B7 and
  - the antigen/class II complex to TCRs specific for it
- activates the T cell.
- This leads to repeated mitotic divisions producing **clones** of CD4+ T cells that can carry out cell-mediated immune responses and/or stimulate B cells to secrete antibodies of the appropriate specificity.

Dendritic cells also engulf self-antigens, e.g., body cells that have died by apoptosis, but because these have no PAMPs associated with them, there is no second signal to activate the T cells.

The interaction of PAMPs and TLRs on **dendritic cells** causes them to secrete cytokines, including

- **interleukin 12** (IL-12) which stimulates the production of Th1 cells
- **interleukin 23** (IL-23) which stimulates the production of Th17 cells
- **interleukin 6** (IL-6), which interferes with the ability of **regulatory** T cells to suppress the responses of **effector** T cells to antigen. A double-negative is a positive.

**B cells** are also antigen-presenting cells. They bind antigen with their BCRs and engulf it into lysosomes. They then transport the digested fragments to the cell surface incorporated in class II histocompatibility molecules just as macrophages and dendritic cells do. B cells also have TLRs. When a PAMP such as LPS binds the TLR, it enhances the response of the B cell to the antigen.

It has been known for many years that for vaccines to be effective, the preparation must contain not only the antigen but also materials called **adjuvants**. Several adjuvants contain PAMPs, and their stimulus to the innate immune system enhances the response of the adaptive immune system to the antigen in the vaccine. Pathogens coated with fragments of the complement protein C3 are not only opsonized for phagocytosis but also bind more strongly to B cells that have bound the pathogen through their BCR. This synergistic effect enables antibody production to occur at doses of antigen far lower than would otherwise be needed. Some workers feel that, in fact, adaptive immunity is not possible without the assistance of the mechanisms of innate immunity.
Antimicrobial Peptides

In addition to their innate pathogen-recognition systems, vertebrates (including ourselves), invertebrates (e.g., Drosophila), even plants and fungi secrete antimicrobial peptides that protect them from invasion by bacteria and other pathogens. In fact, probably all multicellular organisms benefit from this form of innate immunity. For humans, the best-studied antimicrobial peptides are the defensins, hepcidin and the cathelicidins.

Defensins

All our epithelial surfaces

- skin
- lining of the GI tract
- lining of the genitourinary tracts
- lining of the nasal passages and lungs

are protected by defensins.

- Some defensins are secreted by the epithelial cells themselves; others by Th17 cells and neutrophils.
- Some are secreted all the time; others only in response to attack by pathogens. (In some cases their genes are turned on by activated TLRs.)
- They are synthesized from larger gene-encoded precursors which are cut to produce the active peptide.
- These range in length from 25 to 45 amino acids.
- In humans, they contain 6 invariant cysteines that form 3 disulfide bonds that assist in producing a secondary structure that consists of 3 strands of anti-parallel beta sheet.
- They attack the outer surface of the cell membrane surrounding the pathogen eventually punching lethal holes in it. (Unlike eukaryotes, the phospholipids in the outer membrane of bacteria carry a surplus of negative charges, and the positive charges on the defensins probably enable them to penetrate the bacterial membranes while sparing host membranes.)

Curiously, some defensins (β-defensin) also affect coat color (in dogs and mice) and in other ways mimic the effects of melanocyte-stimulating hormone (MSH).

Hepcidin

Hepcidin is a peptide of 25 amino acids with a secondary structure (beta sheet) like that of the defensins. It is secreted by the liver and controls the level of iron in the blood and ECF by regulating its release from intracellular stores. Hepcidin secretion is increased in response to invasion by pathogens (fungi and bacteria). Many of these require iron for their virulence and by blocking the release of iron into the blood, hepcidin starves them of this essential factor.

Cathelicidins

The best known human cathelicidin is LL37, a peptide of 37 amino acids synthesized by macrophages, neutrophils, adipocytes, and epithelial cells (providing antimicrobial protection to our skin and the lining of our urinary tract). Unlike the defensins, its secondary structure is alpha helix.
Like defensins, the gene for LL37 can be turned on by activated TLRs. In macrophages, for example, cathelicidin synthesis within the cell promotes killing of engulfed bacteria like M. tuberculosis, the agent of TB. Activation of the cathelicidin gene requires the presence of the active form of vitamin D (1,25(OH)₂ vitamin D₃). This may explain:

- why people with a deficiency of vitamin D are more susceptible to tuberculosis;
- the physiological basis for the practice of exposing patients to sunlight in TB sanitariums (before the days of antibiotics).

### Antimicrobial Peptides and the GI Tract

The contents of the GI tract (especially the colon) are loaded with bacteria. But most of these cause no trouble thanks to a variety of defenses. Among these is the barrier of antimicrobial peptides that exists from mouth to anus.

- The epithelium of the mouth and tongue is protected by a layer of antimicrobial peptides as well as those secreted in the saliva.
- The stomach is also protected by antimicrobial peptides (cut by pepsin from a larger precursor) as well as by the low pH of gastric juice.
- The liquefied contents that leave the stomach are quickly neutralized by the bicarbonate ions in the pancreatic fluid. However, any bacteria that survived the trip through the stomach (e.g., *E. coli* has a proton pump that enables it to survive the strong acid of the gastric juice) are kept in check by the antimicrobial peptides secreted by the Paneth cells of the small intestine. So, the contents of the small intestine normally contain only a small population of microbes.
- Not so for the large intestine (colon). The colon supports an enormous population (>10¹³) of microorganisms, but these seldom invade its lining thanks to
  - a protective barrier of antimicrobial peptides as well as
  - the protective actions of continuous stimulation of
    - TLR-2s by Gram-positive commensals and
    - TLR-4s by Gram-negative commensals
- The rectum is also protected by an epithelial barrier of antimicrobial peptides.

### Contributors

- **John W. Kimball.** This content is distributed under a Creative Commons Attribution 3.0 Unported (CC BY 3.0) license and made possible by funding from The Saylor Foundation.