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Ira Mellman's Lecture Part 1:

The Cellular Basis of the Immune Response

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1. Keywords and Terms

Innate immune response, adaptive immune response, toll-like receptor, antigen, phagocytosis, antibody, major histocompatibility complex (MHC), T cell receptor (TCR), CD4 T cell, CD8 T cell.

2. Lecture Notes

The basic function and organization of the immune system is conserved among invertebrates and vertebrates, and is capable of distinguishing between self and non-self cells/tissues. The immune response is comprised of two distinct arms: the innate response and the adaptive response. While the innate response recognizes pathogens based on common components, the adaptive response recognizes pathogens on an individual basis.

The innate immune response was first observed by Elie Metchnikoff, who noted that inflammation was protective, not destructive, to hosts. Instead of injuring tissue, the

purpose of inflammation is to recruit other immune cells. Besides promoting inflammation by the release of cytokines, the innate immune response also initiates the killing of pathogens by cytotoxic agents, destruction of bacterial cell walls by lysozyme, and the destruction of everything by lysosomal enzymes.

Innate Immunity

The initiation of the innate immune response depends on the recognition, by toll-like receptors (TLRs), of components that are shared among a broad range of pathogens. TLRs are named after a *Drosophila* receptor, Toll, whose importance was demonstrated in both embryonic development and adult survival. Adult flies lacking this receptor were found to be susceptible to infections. Toll's immune function is mediated by its cytoplasmic domain, which resembles the cytoplasmic domain of the vertebrate IL-1 receptor, which, when activated, turns on the inflammatory response. Over a dozen human TLRs have been identified on the same basis (i.e. they possess the IL-1 receptor cytoplasmic domain). Although they all share a common cytoplasmic signalling domain, they differ in their extracellular regions, each of which binds to a specific, necessary, and shared pathogenic component. TLR4, for example, binds to a bacterial lipopolysaccharide, while TLR5 binds a bacterial flagellar component. Some TLRs (such as TLR7, TLR8, and TLR9) are found intracellularly and bind to virally-associated nucleic acid components. Upon TLR ligand binding, signalling through the cytoplasmic domain is initiated, ultimately activating pathways in the nucleus. Among these, the NF κ B is a simple, yet critical pathway that signals phagocytosis, an actin-dependent engulfing, of invading pathogens by macrophages and other immune cells.

Adaptive Immunity

The other arm of the immune response is known as the adaptive immune response, the discovery of which can largely be attributed to Paul Ehrlich, who showed that individuals made protective antibodies in the blood upon immunization by an infectious agent. Antibodies have a molecularly-based specificity to a particular antigen on a particular pathogen, contrary to the broader approach of the innate immune response. The structure of an antibody includes 4 chains – 2 heavy and 2 light – that create a “Y” shaped molecule. The base of the “Y” is termed the “Fc” region, while the two arms of the “Y” are each called “Fab.” It is the sequence variability in the Fab region that lends specificity to the antibody. Once an antibody recognizes and binds to its antigen, it recruits complement proteins that insert themselves into the plasma membrane of the pathogen, ensuring its lysis. The utility of an antibody lies not only in its Fab region, however. The Fc portion of an antibody can bind macrophages, thereby bringing a

phagocytic immune cell into closer proximity to a pathogen, illustrating one way in which the innate and adaptive responses cooperate for maximal effect.

B cell function

Antibodies are made by B lymphocytes, which are found throughout the lymphoid tissues. Not only do B lymphocytes produce and secrete antibodies, but they also have membrane-bound antibodies that are capable of recognizing and binding pathogenic antigens, initiating further B cell development and amplification of that antibody. Membrane antibody binding to an antigen also signals the B cell to internalize the pathogen by endocytosis. Once endocytosed, the pathogen is fragmented into peptides, which are loaded onto major histocompatibility complex class II (MHC II) molecules (a hallmark of antigen presenting cells, or APCs). On the surface of the B cell, the MHC II-peptide complex can be recognized and bound by a T cell receptor (TCR) on a T cell, which, in turn, releases cytokines that signal B cell development, division, and further antibody production.

T cell function

There are two types of T cells: CD4 and CD8. While CD4 T cells recognize the MHC II-peptide complex as described above, CD8 T cells recognize a different complex – MHC I-peptide, but both classes of T cells possess highly diverse and specific TCRs. This degree of specificity is conveyed by rearrangement of the TCR gene. While the TCR provides specificity, the CD4 and CD8 surface proteins recognize invariable portions of MHC II and MHC I, respectively, to facilitate the interaction between T cells and cognate MHC-peptide complexes.

Unlike CD4 T cells, which respond to extracellular antigens, CD8 T cells recognize intracellular pathogens, e.g. viruses that have entered host cells through the plasma membrane. Peptide antigens from these pathogens are loaded onto MHC I, and following recognition of this complex by a CD8 T cell, an immunological synapse is formed between the T cell and the infected host cell. At this synapse, CD8 T cells polarize intracellular granules that contain lysosomal and lytic enzymes, ligands that induce apoptosis, and perforating molecules, release of which spells certain death for target cells.

T cell activation occurs in two ways: binding of the TCR and co-stimulatory receptors. As mentioned above, binding of a TCR to its cognate MHC-peptide complex initiates signalling events within the T cell. Elsewhere on the T cell membrane, co-stimulatory receptors recognize co-stimulatory molecules on the surface of infected host cells, B cells, and other immune cells, resulting in further signalling that helps amplify that T cell.

And all the while, outside the T cell, cytokines are being secreted by APCs, which enhance the T cell response even further.

While the innate and adaptive responses differ in fundamental ways, they nevertheless are interconnected. In Part 2, we will see how the innate immune response's ability to detect common pathogenic components and the adaptive immune response's ability to launch an antigen-specific attack via antibodies are linked by a particular type of APC known as dendritic cells.

3. Review Questions

1. How many pathogens/toxins can the immune response potentially recognize?
2. What are the two arms of the immune response?
3. What does the innate response recognize?
4. What does the adaptive response recognize?
5. How is the toll receptor (and Toll-like receptors) similar to the IL-1 receptor?
6. What are examples of TLRs that recognize nucleic acids?
7. What cells make antibodies?
8. What does a T cell receptor recognize?
9. What does CD4/CD8 recognize?
10. What generates TCR variability?

4. Answers to Review Questions

1. The immune response's potential is limitless!
2. Innate and adaptive responses.

3. Shared or common components that are conserved among pathogens, and are necessary for their survival.
4. Individual antigens, specific to a particular pathogen.
5. They share homology in their cytoplasmic signalling domain, which turns on pathways such as NF κ B.
6. TLR7, TLR8, or TLR9
7. B lymphocytes.
8. An MHC-peptide complex. Specifically, CD4 T cells recognize MHC II-peptide complexes and CD8 T cells recognize MHC I-peptide complexes.
9. The T cell surface proteins recognize invariable portions of the MHC molecule.
10. Gene rearrangement.

5. Discussion Questions

1. How do B cells (and other antigen presenting cells) contribute to the immune response?
2. An antibody is a 150kD protein made up of two heavy chains and two light chains. Describe the two regions of an antibody.
3. What occurs at the immunological synapse?
4. T cell activation occurs at two levels. What are they?

6. Answers to Discussion Questions

1. B cells in particular make antibodies, the secreted versions of which mark infected cells or pathogens themselves for destruction by complement, macrophages, etc. But in the context of antigen presenting cells (APCs), B cells can recognize antigens via membrane-bound antibodies, internalize the pathogen (or infected cells) associated with the antigen, cleave the antigen into peptide fragments that can be loaded onto MHC II, *and transport the MHC II-peptide complex onto the cell surface for recognition by CD4 T cells.*
2. An antibody is roughly Y-shaped. The base is referred to as the Fc region, and can be recognized by macrophages. The arms are referred to as the Fab region, and it is this region that gives an antibody specificity. This is the part of the antibody that recognizes and binds to pathogenic antigens.
3. This describes the binding between an infected cell and the CD8 T cell that specifically recognizes it via its TCR. Here, the CD8 T cell polarizes intracellular granules towards the infected cell. These granules are released, unleashing a variety of lytic enzymes, apoptotic ligands, and perforating molecules at the infected cell.
4. Binding between a T cell and its target occurs via the T cell receptor and co-stimulatory receptors. The TCR is highly specific to a particular peptide loaded onto an MHC molecule. Once a TCR has bound its specific MHC-peptide complex, it initiates signalling events that further the immune response. At the same time, co-stimulatory receptors on the T cells are also binding to surface molecules on antigen-presenting cells, infected cells, and other cells, which signals further development and amplification, culminating in an even more enhanced response.

7. Explain or Teach These Concepts to a Friend

1. How does the innate immune response kill pathogens?
2. Describe the role that antibodies play in pathogen clearance.
3. How do CD4 and CD8 T cells vary?

8. Research the Literature on Your Own

1. A key element of the immune response is its ability to distinguish self from non-self antigens, but sometimes, this tightly regulated process goes awry. How is tolerance achieved, and in what ways can auto-immunity arise?
2. Along similar lines, cancer is a disease involving the hyperproliferation of the body's own cells, i.e. the antigens involved are all self. What are some therapies that show promise in manipulating our own immune system to target cancer cells?
3. Conventionally, CD4 T cells recognize extracellular antigenic peptides loaded onto MHC II molecules, while CD8 T cells recognize intracellular antigenic peptides loaded onto MHC I molecules. However, it has been shown that CD8 T cells can also respond to extracellular antigenic peptides loaded onto MHC I molecules via cross presentation. What are the mechanisms that drive cross presentation?