

HHMI's 1996 Holiday Lectures on Science

The Immune System: Friend and Foe

Lecture One

How Immune Cells Create Trillions of Receptors from a Few Hundred Parts

John W. Kappler, Ph.D.

White blood cells of the type called lymphocytes are able to recognize almost any kind of foreign material that enters the body, including bacteria, viruses (such as HIV), and human-made chemicals that did not exist when the immune system was evolving. Lymphocytes are divided into two principal groups, termed B cells and T cells. Both have the ability to identify a wide array of intruders because each bears on its surface a unique receptor, one created by random combinations of relatively few components. Much as random choices from a restaurant menu can lead to meals with a huge number of variations, random combinations of components can lead, to trillions of different receptors. The human body thus has at least a trillion ways of recognizing that something foreign has invaded.

Key Concepts

- Two types of lymphocytes are involved: B cells and T cells. B cells have antibodies as their cell-surface receptors, whereas T cells have T cell receptors (TCRs). Trillions of different antibodies and receptors can be formed.
- Each cell carries thousands of copies of a single, specific receptor. Diversity results from the random assembly of gene components that encode antibodies (in B cells) and TCRs (in T cells).
- Stimulation of the cell-surface receptor is the first step in activating each type of cell.
- Antibodies consist of a light chain and a heavy chain. The light chain is formed when the lymphocyte selects one constant gene region, one

variable region, and one joining region from among many. The heavy chain is formed from an independent selection of these regions plus another—a diversity region.

- The cell links the components, and the information the components convey is translated to form a specific protein.

References

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Understanding the Immune System. A guide that includes "The Immune System—How It Works" (L.W. Schindler. Bethesda, Md.: National Institutes of Health, 1993. NIH Publication No. 94-3229), a set of 40 slides based on the illustrations from this publication, and prepared remarks to accompany the slide presentation.

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Lecture Two

How the Immune System Detects Invaders

Philippa Marrack, Ph.D.

The immune system recognizes invaders in a complex way. The two lymphocyte groups use different strategies. B cells can attack the intruder directly. T cells require assistance from B cells or other white blood cells that ingest and digest foreign invaders. Protein fragments from the processed invader reappear on the surface of these cells bound in specialized grooves of a complex of proteins. This complex, known as MHC (major histocompatibility complex) proteins, presents the invader fragments to T cells. The T cell receptors recognize the bound protein complex and initiate a cascade of events, enlisting the B cell army as well as other T cells. This system allows lymphocytes to identify and destroy cells in which viruses or bacteria are hidden and multiplying.

Key Concepts

- B cells produce antibodies that attack antigens. T cells kill infected cells directly and regulate B cell function.
- Antibodies bind directly to intact antigens that are part of larger structures, such as viruses. T cells bind processed antigen fragments when they are properly presented.
- TCRs are stimulated when they are presented with peptide fragments from the appropriate antigen correctly displayed in the major histocompatibility complex (MHC).
- MHC proteins play a special role in distinguishing self from nonself. This was first recognized when transplants between individuals of the same MHC type succeeded without immunosuppression of the recipient.
- Each individual has a distinctive set of MHC genes that code for the synthesis of MHC proteins. Some MHC proteins display antigens more

effectively than do others, in part contributing to the varied resistance of individuals to different pathogens.

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Lecture Three

How the Host Avoids "Friendly Fire"

John W. Kappler, Ph.D.

Normally, the trillion of lymphocytes do not attack their host. To prevent such attacks, lymphocytes bearing receptors that might react with host tissues are selectively destroyed during their development. Cells that escape this screen treat host molecules as invaders, causing serious autoimmune (self-destructive) diseases such as juvenile diabetes, rheumatoid arthritis, and lupus erythematosus.

Key Concepts

- After producing a varied repertoire of T and B cell receptor specificities, the body systematically eliminates any cells that are activated by antigens normally present in the body.
- Almost all self-reactive T cells are eliminated in the thymus. Those that escape are prevented from attacking the host by mechanisms only now being elucidated.
- Failure to eliminate self-reactive immune cells results in autoimmune diseases such as multiple sclerosis, lupus erythematosus, and certain forms of arthritis.

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Lecture Four

Stalking the Elusive Pathogen

Philippa Marrack, Ph.D.

Some organisms have evolved ways of evading or subverting the body's defenses. The malaria parasite, for example, changes its coat proteins to stay one step ahead of the host's immune cells. Herpes viruses become almost undetectable to lymphocytes. The AIDS virus destroys a subset of T cells that are essential for a successful immune response. Thus, the immune system fights off many but not all infections. By learning more about how such pathogens work, scientists may find new ways to thwart them.

Key Concepts

- No defense is perfect, and many pathogens have evolved novel ways to defeat the body's immune system.
- Pathogen strategies involve hiding from the immune system, changing structure to avoid recognition by the body's defenses, and preempting surveillance by directly attacking immune cells.
- A better understanding of how pathogens circumvent the immune system is necessary to develop more effective diagnosis and treatments for autoimmune infections.

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