# OLLI SG 492
# Human Immune System

## Session 3 - March 23, 2022

# Today’s Meeting

- Recap of our last meeting.
- Additions, clarifications, modifications on some basic features of the immune system.
- A look at the inflammatory response, and the phases of an immune response.
- A look at two important actors in the innate immune system - macrophages and neutrophils.
- Review of the discovery of dendritic cells by Ralph Steinman, and how his lab pieced together the function of dendritic cells.

# Recap

- Janeway’s Puzzle:
  - Adjuvants are required for vaccines to be effective - “Dirty Little Secret.”
  - Asked: What triggers an immune response?
- Proposed that there must be immune cells with pattern-recognition receptors, indicating the presence of a “germ”, something that would harm the body.
- The pattern-recognition receptors would lock onto important features of pathogens that do not change over time.
- At the time he posed this theory, Janeway had no evidence, no experimental proof, of the existence of such receptors.

# Recap

- Jules Hoffmann's lab, working on Drosophila, discovered that some of its genes, toll genes, play an important role in fighting infections.
- These toll genes code for receptors that can detect pathogens, and initiate an immune response.
- Ruslan Medzhitov, working in Janeway's lab, found human genes that are similar to the insect toll gene; the human genes code for proteins that make a toll-like receptor (TLR).
- Bruce Beutler's lab discovered similar toll-like genes and receptors in mice. The TLRs locked onto LSP (lipopolysaccharide), an important molecule for bacterial cell walls.
- These discoveries provided the experimental evidence to support Janeway's theory, solidifying the role (existence?) of the innate immune system.

# Recap

## Puzzle Solved

“Finally the pieces came together to reveal the big picture: the TLR4 gene encodes for a protein molecule that is able to interlock with a component from the outer wall of bacteria (LPS). In other words, the TLR4 gene encodes for a **pattern-recognition receptor**, the very type of molecule that Janeway had predicted existed – one of the eyes of the immune system, as Beutler puts it – giving immune cells with this receptor protein protruding from their surface an innate ability to lock onto bacteria. When TLR4 locks onto the bacterial molecule LPS, this signifies that there is something in the body that may very well require an immune response.”

# Recap

- We also briefly covered:
  - Aspects of the lymphatic system and lymph nodes.
  - That all the cellular elements of the blood, including the cells of the immune system, arise from **pluripotent hematopoietic stem cells** in the bone marrow.
  - The origin of, and the relationship between, all the types of immune cells.

# Basics of the Immune System

## Additions, Clarifications, Modifications

- Receptors:
  - All receptors of immune cells are proteins and coded for by genes.
  - T cells and B cells can identify a near-infinite range of antigens because the genes involved in producing their receptors are segmented and, during their development, the segments are shuffled.
  - The genes producing pattern-recognition receptors are fixed.
  - The genes producing antigen-specific receptors are random.
  - Antigen-specific receptors lock onto antigens; pattern-recognition receptors lock onto a wide range of molecules.

# Basics of the Immune System

## Additions, Clarifications, Modifications

- Innate Immune System is our “First Line of Defense” (?):
  - Barriers to infection - skin; epithelial cells lining the gastro-intestinal pathways, and the air pathways (lungs, nose, etc.), secrete mucus that contains antimicrobial proteins.
  - Complement System - Liver cells produce around 30 different plasma proteins that have an antimicrobial effect.
    - These proteins make up around 10% of blood serum.
    - They can directly degrade and kill pathogens they encounter.
    - They can recruit antibodies to a pathogen.
    - They can make it easier to identify a pathogen, resulting in phagocytosis of the pathogen.

# Basics of the Immune System

## Additions, Clarifications, Modifications

- Kurzgesagt video on Complement.

# Basics of the Immune System

## Additions, Clarifications, Modifications

- “First Line of Defense” (?):
  - Other cells of the body produce enzymes with antimicrobial activity, e.g., cells that produce saliva, sweat and tears.
- Types of infections:
  - Pathogens may be present in the extracellular environment, outside cells.
  - Pathogens may be present in the intracellular environment, inside cells.
  - Eliminating intracellular pathogens (usually?) involves the destruction of the infected cell.

# Basics of the Immune System

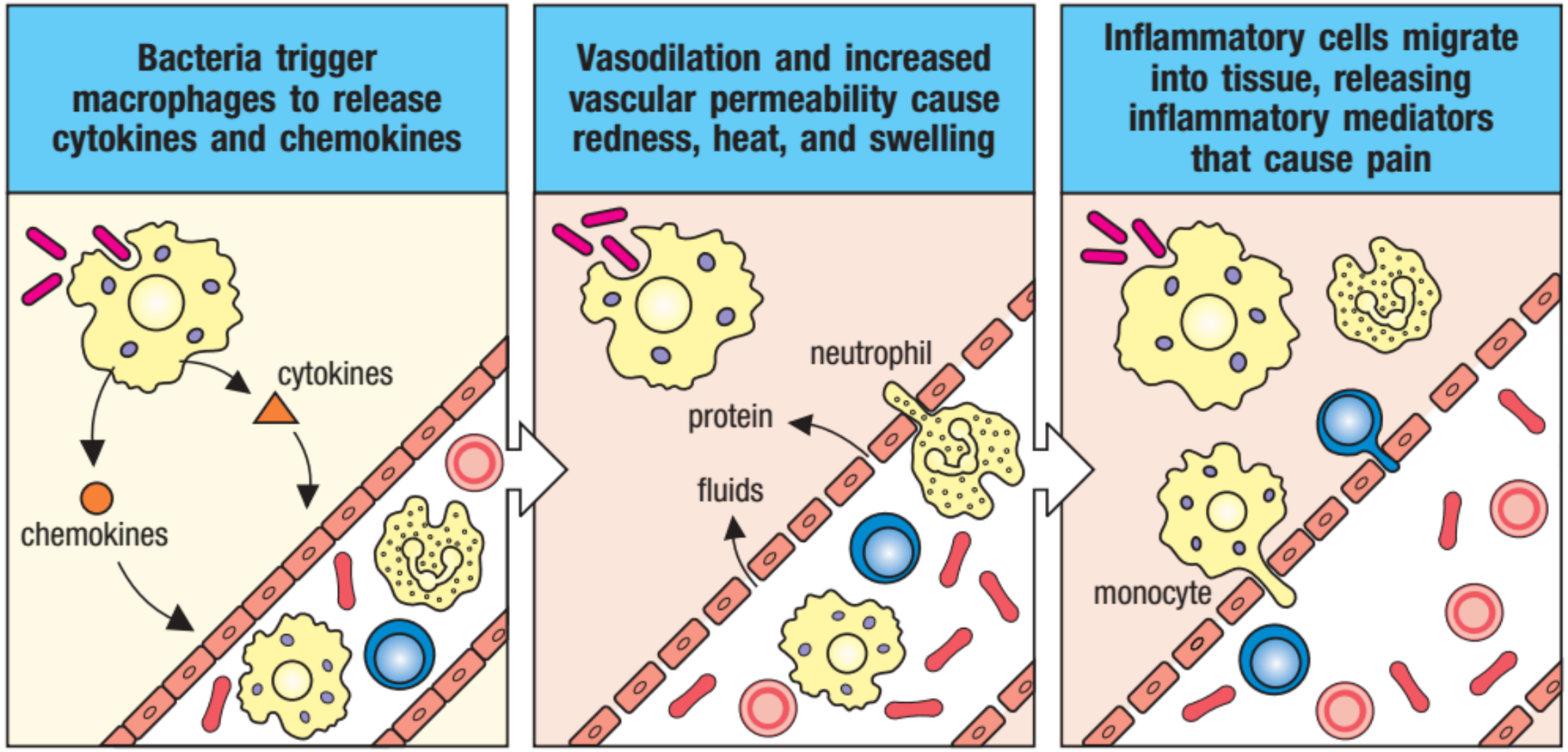
## Additions, Clarifications, Modifications

- Pattern-recognition Receptors (PRRs):
  - In addition to TLRs, there are many more PRRs.
  - Each PRR can detect a specific (attribute/component of a…?) germ.
  - PRRs are positioned strategically in different parts of the body, where their specific germ might be found.
- New Era for Vaccines:
  - Instead of using dead or deactivated pathogens, use the molecules that are the specific targets of pattern-recognition receptors, switching on the innate immune system.

# Basics of the Immune System

## Inflammatory Response

**Fig. 1.10 Infection triggers an inflammatory response.** Macrophages encountering bacteria or other types of microorganisms in tissues are triggered to release cytokines (left panel) that increase the permeability of blood vessels, allowing fluid and proteins to pass into the tissues (center panel). Macrophages also produce chemokines, which direct the migration of neutrophils to the site of infection. The stickiness of the endothelial cells of the blood vessel wall is also changed, so that circulating cells of the immune system adhere to the wall and are able to crawl through it; first neutrophils and then monocytes are shown entering the tissue from a blood vessel (right panel). The accumulation of fluid and cells at the site of infection causes the redness, swelling, heat, and pain known collectively as inflammation. Neutrophils and macrophages are the principal inflammatory cells. Later in an immune response, activated lymphocytes can also contribute to inflammation.



# Basics of the Immune System

## Phases of the Immune Response

| Phases of the immune response | | | |
|---|---|---|---|
| **Response** | | **Typical time after infection to start of response** | **Duration of response** |
| Innate immune response | Inflammation, complement activation, phagocytosis, and destruction of pathogen | Minutes | Days |
| Adaptive immune response | Interaction between antigen-presenting dendritic cells and antigen-specific T cells: recognition of antigen, adhesion, co-stimulation, T-cell proliferation and differentiation | Hours | Days |
| | Activation of antigen-specific B cells | Hours | Days |
| | Formation of effector and memory T cells | Days | Weeks |
| | Interaction of T cells with B cells, formation of germinal centers. Formation of effector B cells (plasma cells) and memory B cells. Production of antibody | Days | Weeks |
| | Emigration of effector lymphocytes from peripheral lymphoid organs | A few days | Weeks |
| | Elimination of pathogen by effector cells and antibody | A few days | Weeks |
| Immunological memory | Maintenance of memory B cells and T cells and high serum or mucosal antibody levels. Protection against reinfection | Days to weeks | Can be lifelong |

# Basics of the Immune System

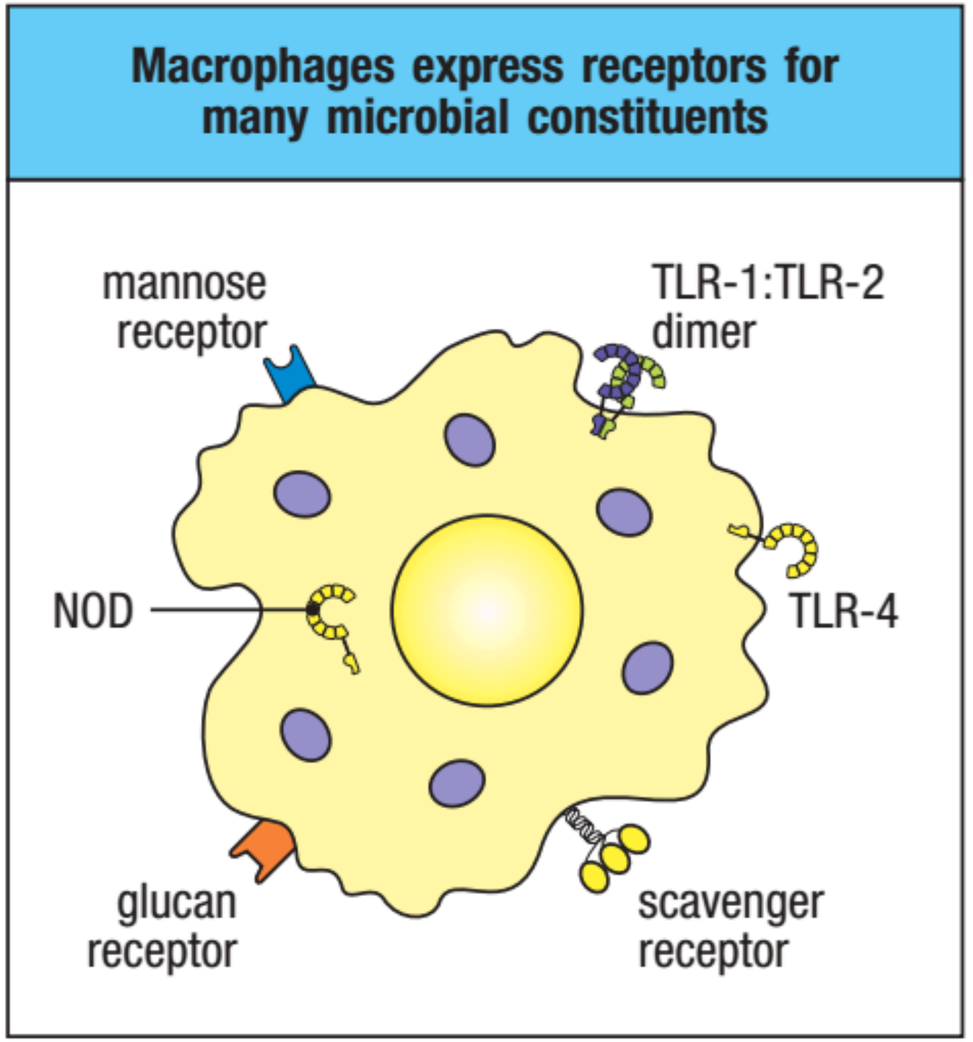
## Macrophages

- Resident in almost all tissues of the body.
- Many arise in tissue during embryonic development, but some that arise in adult bone marrow are the mature form of monocytes.
- Relatively long-lived cells.
- Engulf and kill pathogens through phagocytosis; sift through lymph by macropinocytosis.
- Also dispose of infected cells targeted by an adaptive immune response.
- Orchestrate immune responses by inducing inflammation and recruiting other immune system cells.
- Scavenger cells.

# Basics of the Immune System

## Macrophage Receptors

**Fig. 1.9 Macrophages express a number of receptors that allow them to recognize different pathogens.** Macrophages express a variety of receptors, each of which is able to recognize specific components of microbes. Some, like the mannose and glucan receptors and the scavenger receptor, bind cell-wall carbohydrates of bacteria, yeast, and fungi. The Toll-like receptors (TLRs) are an important family of pattern recognition receptors present on macrophages, dendritic cells, and other immune cells. TLRs recognize different microbial components; for example, a heterodimer of TLR-1 and TLR-2 binds certain lipopeptides from pathogens such as Gram-positive bacteria, while TLR-4 binds both lipopolysaccharides from Gram-negative and lipoteichoic acids from Gram-positive bacteria.



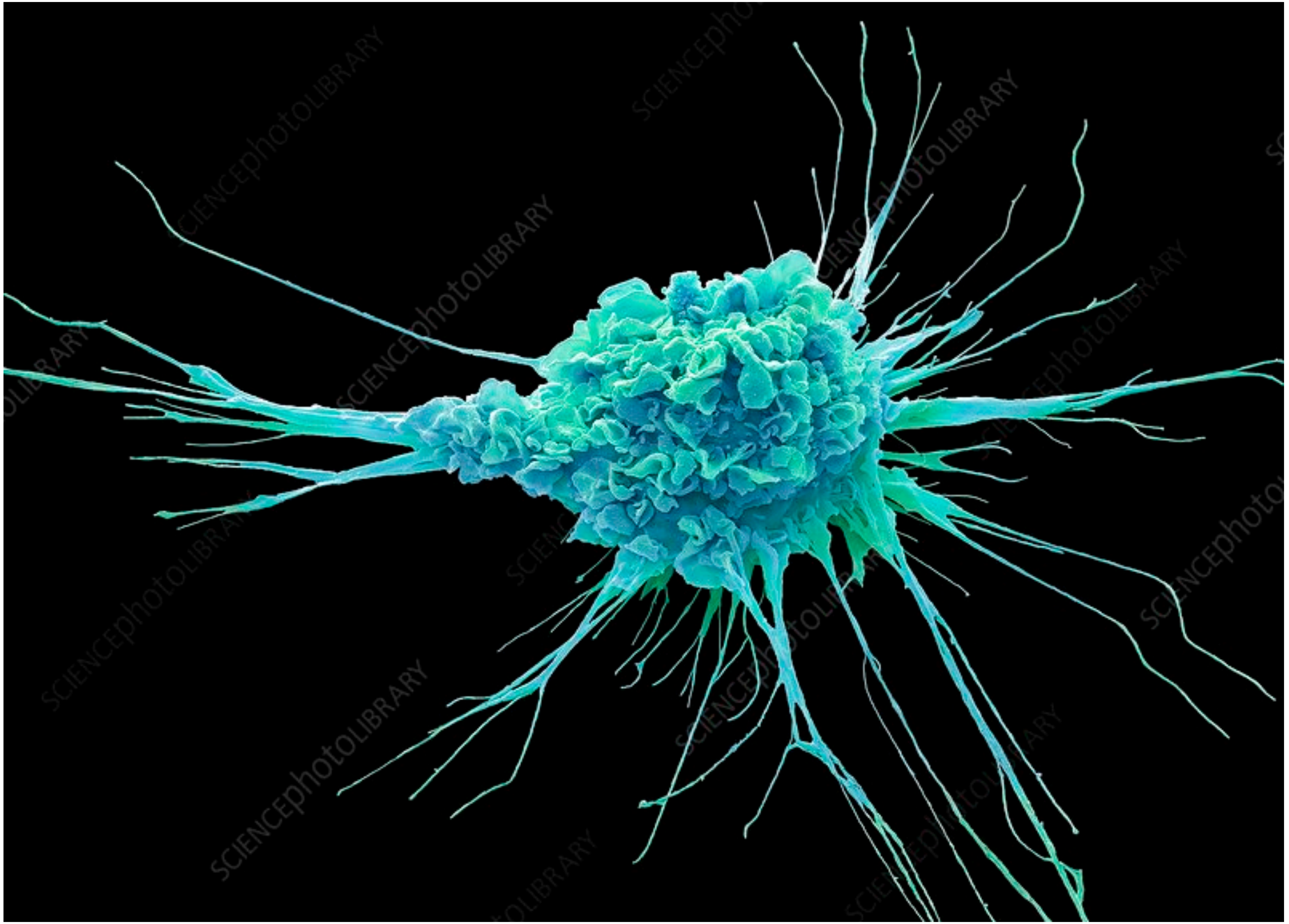
# Basics of the Immune System

## Neutrophils

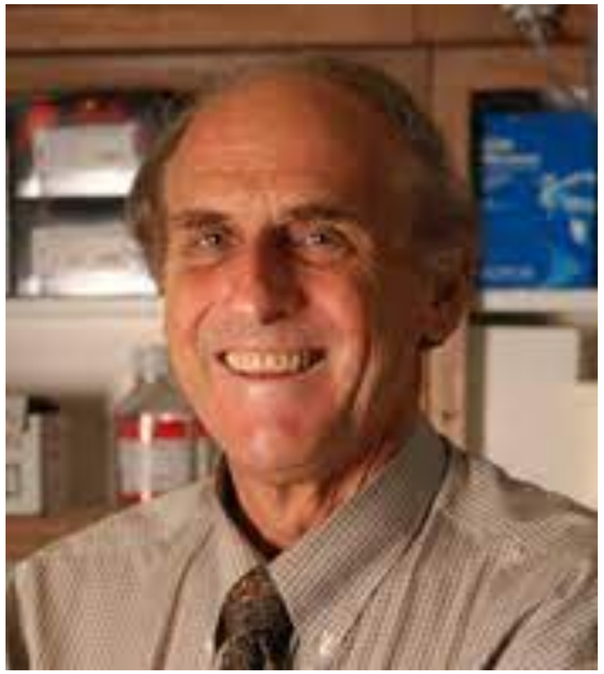
- Mature in the bone marrow; circulate in the blood system.
- Production increases during an immune response.
- Are the most numerous and important cells in innate immune responses.
- Destroy pathogens by phagocytosis; granules in the cytoplasm contain degradative enzymes and antimicrobial substances.

# Basics of the Immune System

## Dendritic Cell



# Ralph Steinman



- Born - January, 1943, Montreal; Died - September, 2011, New York City
- Professor, Rockefeller University, New York City
- Awarded Nobel Prize in Physiology or Medicine, 2011
- Recipient of numerous other awards, incl. the Albert Lasker Award for Basic Medical Research, 2007
- Discoverer of dendritic cells
- Died of pancreatic cancer

# Dendritic Cells

## Discovery

- An **unknown cell** was observed by Steinman in 1972 while working in Zanvil Cohn’s lab at Rockefeller University.
- It had a “stellate” shape with mobile branching; Steinman named it a “dendritic cell.”
- Using resources at Rockefeller, he was able to isolate and concentrate the dendritic cells for observation and experiment.
- When he published his findings, he was met with skepticism (and hostility); questions were raised about the uniqueness of dendritic cells.

# Dendritic Cells

## Discovery

- Further experimentation showed that dendritic cells could stimulate an immune response much better than any other immune cell.
- However, research also showed that dendritic cells sometimes failed to initiate an immune response.
- This result led to the finding that dendritic cells exist in two states - immature and mature.
- Taking all the experimental results under consideration, Steinman was able to construct a narrative of the functioning of dendritic cells.

# Dendritic Cells

## Function of Dendritic Cells

“From this, a narrative for what dendritic cells do in the body finally took shape. Immature dendritic cells patrol almost all of our organs and tissues but especially places exposed to the outside environment, such as our skin, stomach and lungs. These dendritic cells specialise in detecting germs, using the multitude of pattern-recognition receptors they carry. When an immature dendritic comes across a germ, it engulfs and destroys it. Having done so, it then switches into a different state: it matures. The mature dendritic cell makes a beeline to a nearby lymph node or the spleen, a depot jam-packed with other immune cells. There, in the lymph node, other immune cells are presented with fragments of the germs that the dendritic cells have engulfed. The right type of immune cells to deal with the problem then travel out from the lymph node to the site of trouble.”

# Dendritic Cells

## Function of Dendritic Cells

- Dendritic cells connect the innate and adaptive immune systems.
- A major complication arose when it was discovered that dendritic cells can actually stop an immune response.
- Dendritic cells use a protein coded for by the Major Histocompatibility Complex (MHC) genes to “present” peptides to lymphocytes, looking for a match with their antigen-specific receptors.
- In order for a lymphocyte to become activated if a match occurs, it also requires a signal from a second protein on the dendritic cell.

# Dendritic Cells

## Function of Dendritic Cells

- This second protein is called the “co-stimulatory” protein.
- When a dendritic cell actually engulfs and destroys a pathogen, it expresses the genes to produce the co-stimulatory protein.
- Absent the co-stimulatory protein signal, the lymphocytes ignore the peptide presented by the dendritic cell.
- Steinman also attempted to develop a dendritic cell based vaccine.  Research in this area is still ongoing.

# Preview of T and B Cells and Their Interaction With Dendritic Cells

- Lymphocytes and Dendritic Cells Video

# Up Next

- More on lymphocytes - the development and functions of T cells and B cells.
- More on dendritic cells interaction with, and activation of, lymphocytes.
- Control mechanisms of the immune system - interferon, cytokines, and chemokines.
- Read Chapter 3, Restraint and Control.