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RHEUMATOLOGY ADVANCED
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Immunology Part 2 “Cytokinology”

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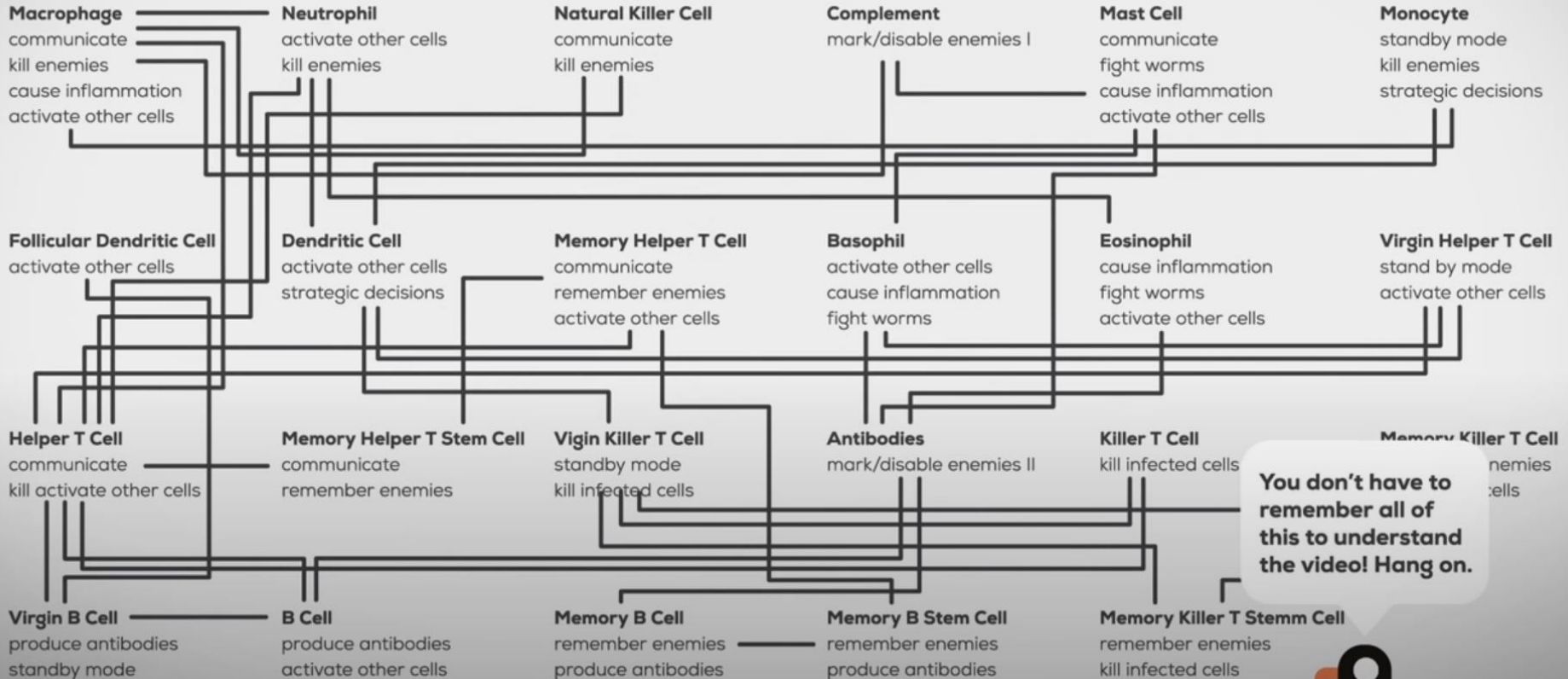
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- Betsy Kirchner, DNP:
 - Consultant: Janssen
- Amanda Mixon, PA-C:
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 - Speaker, Consultant: Abbvie, Janssen
 - Consultant: Sanofi, Novartis

Objectives

- Understand the basic functions of cytokines
- Become aware of the history of cytokine discovery
- Learn the different classes of cytokines

THE HUMAN IMMUNE SYSTEM



You don't have to remember all of this to understand the video! Hang on.



A diagram illustrating a macrophage's response to an external stimulus. On the left, a teal background contains numerous small, light-green, pill-shaped particles. A large, circular macrophage is positioned in the center, composed of a red core and a multi-colored outer ring (orange, yellow, and light orange). A white speech bubble with a tail pointing to the top of the macrophage contains the text "We need help!". To the right, a yellow horizontal bar extends from the macrophage, ending in a white circular vesicle filled with small, yellow, ring-shaped particles. A yellow rectangular label above this vesicle reads "MESSENGER PROTEIN".

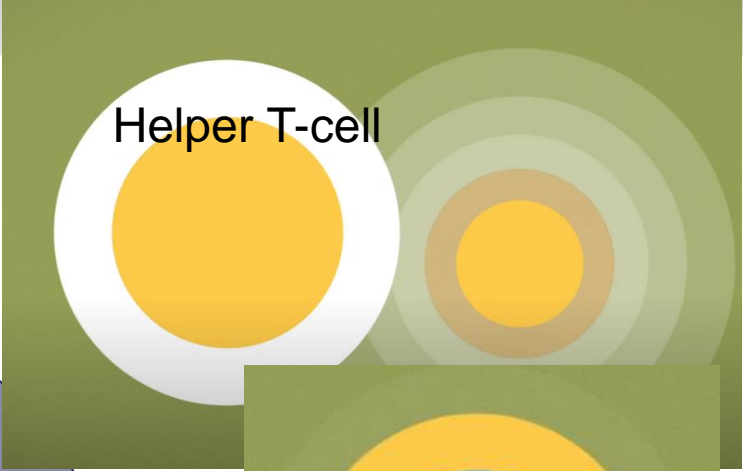
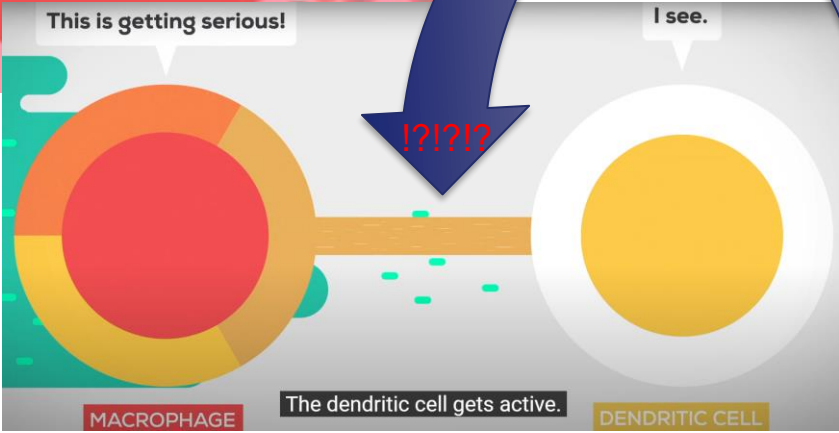
We need help!

MESSENGER PROTEIN

MACROPHAGE



Neutrophil



Helper T-cell





In a team effort, the infection is wiped out.

A cartoon illustration of a cell with a face, set against a background of a large blue cell and a purple cell. The cell has a black body with two white eyes and a black mouth. It is surrounded by various colored circles and shapes, representing organelles or molecules. The background features a large blue cell with a bright yellow center and a purple cell with a dark purple center. The overall style is colorful and playful.

Cells have neither ears nor eyes.

A stylized illustration of a cell with concentric layers in shades of blue and cyan. A callout box labeled 'Cytokines' points to a smaller, multi-layered circular structure with a yellow center, representing a cytokine molecule. The background is a dark purple with faint, abstract shapes and small white and blue dots.

Cytokines

They communicate mostly via tiny information proteins called cytokines.



Nearly every important immune reaction is controlled by them.

History of Cytokine Discovery

- Valy Menkin 1944: suggested that soluble factors drive host reactions.
 - “Pyrexin” (contaminant – bacterial endotoxin).
- Bennett & Paul Beeson 1953: fixed Menkin’s contaminants.
 - Identified endogenous pyrogen (EP)
- Rita Levi-Montalcini & Viktor Hamburger 1953: discovered NGF (intercellular signal)
- Alick Isaacs & Jean Lindenmann 1957: discovered interferons

History of Cytokine Discovery

- Kasakura and Lowenstein (1965)
 - Leukocyte mitogenic or blastogenic factors (LMF/BF)
- David (1966); Bloom & Bennett (1966)
 - Macrophage migration inhibitory factors (MIFs)
- Ruddle & Waksman (1967); Granger & Williams (1967)
 - Lymphotoxin

Functions of Cytokines: What are they?

- Very small proteins used to convey information
 - Activate and guide the immune system
- 100s of different cytokines
- Four major functional classes
 - Interferons
 - Interleukins
 - Colony stimulating factors
 - Tumor necrosis factors

Functions of Cytokines: What are they?

- Have roles in diagnosis, prognosis, and therapies
- Soluble factors, membrane proteins, intracellular
- Every cell (except RBC) is capable of producing and responding to a cytokine

Functions of Cytokines



Functions of cytokines: Interferons

- One strategy to slow down viral replication: slow down all protein synthesis.
 - Some interferons send out a general “slow down” order at the first sign of danger; at that point the immune system doesn’t know how big the threat is.
- Plasmacytoid dendritic cells exist solely to detect viruses (or interferons) and release massive amounts of interferon.

Functions of cytokines: Interleukins

- Human genome encodes for >50
- IL-1 to IL-17
 - IL-1 and IL-2 activate T and B cells
 - IL-1 mediates inflammation
 - IL-2 also stimulates T- and B-cell growth and maturation
 - IL-4 often increases antibody secretion by B cells
 - IL-6 also mediates inflammation
 - IL-12 stimulates production of cytotoxic T cells and natural killer cells

Functions of Cytokines: Colony stimulating factors

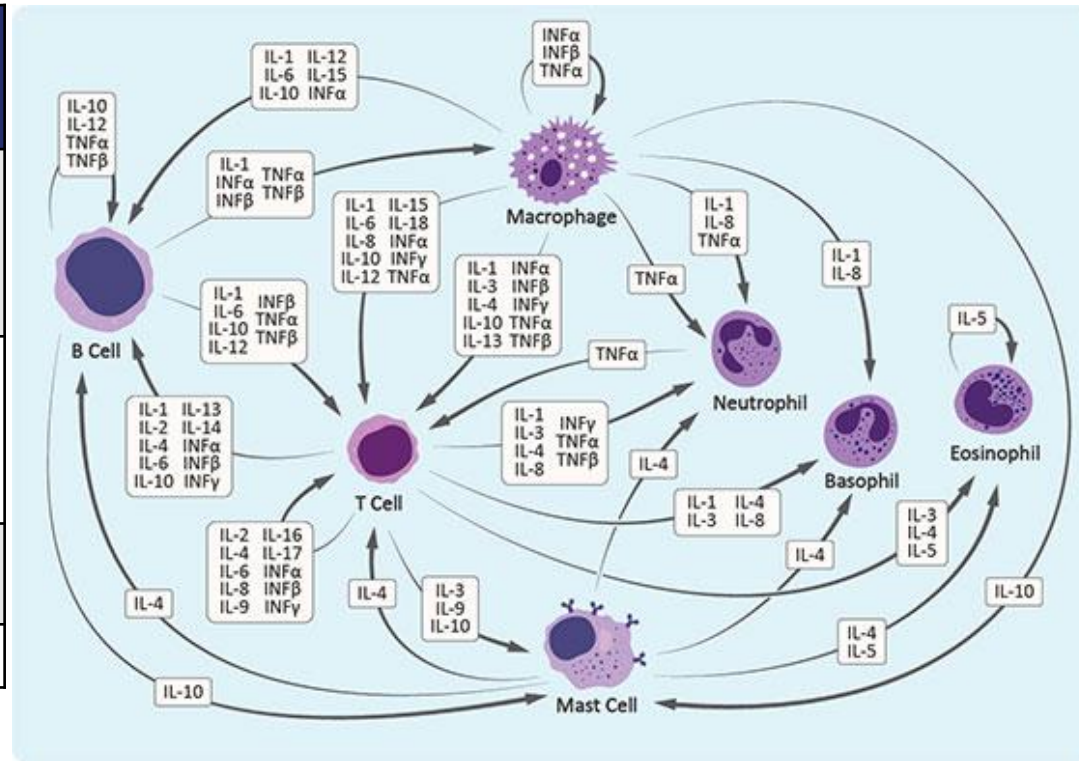
- Bind to receptor proteins on the surfaces of hemopoietic stem cells
- Activate intracellular signaling pathways
- Cause the cells to proliferate and differentiate into a specific kind of blood cell
- CSF2 overlaps in structure, function, and receptors with IL-3 and IL-5

Functions of cytokines: Tumor necrosis factor

- Primary role is regulation of immune cells
- Pro-inflammatory
- 2 receptors
 - TNFR-1: ubiquitously expressed
 - TNFR-2: expressed mainly on immune cells

Functions of Cytokines

| Pro-inflammatory | Anti-inflammatory | Death receptor ligands |
|--|---|--------------------------------------|
| (IL)-1 α/β | Transforming Growth Factor (TGF)- β | Tumor Necrosis Factor (TNF) α |
| Tumor Necrosis Factor (TNF) α/β , | IL-10 | FasL |
| Interferon (IFN)- γ | IL-4 | TRAIL |
| IL-6 | IL-6 | |



Important cytokines in rheumatology

| | Action/local effects | Clinical effects |
|------------------|--|--|
| IL-1 | Activates vascular endothelium, lymphocytes | Fever IL-6 |
| IL-6 | Lymphocyte activation, increased antibody production | Fever APRs |
| CXCL8 (IL-8) | Recruits basophils/ neutrophils /T-cells, stimulates phagocytosis | Airway remodeling |
| IL-12 (IL-23) | Stimulates T cells, production of TNFa & IL-17, activates NK cells | * |
| IL-17 | Recruits monocytes, neutrophils | Epidermal hyperplasia Airway remodeling |
| TNFa | Activates vascular endothelium, increases vascular permeability | Fever Shock |

References

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