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Cytokines

M1 – Immunology Sequence

Winter 2009



Cytokines and Chemokines

1. Structure and function
2. Cytokines in septic shock
3. Cytokine modulation in therapy
4. How viruses exploit cytokines and chemokines

Cytokines and chemokines are the medium by which cells communicate with one another, without cell-to-cell contact. This includes communication between cells within innate immunity, between cells within adaptive immunity, and between cells within innate immunity and cells within adaptive immunity.



Original Image: <http://www.hyscience.com/cytokines.jpg>



PD-INEL

Source Undetermined

Autocrine—A cytokine that acts upon the cell that secreted it.

Paracrine—A cytokine that acts upon a cell neighboring the cell that secreted it.

Endocrine—a cytokine that acts at a distance from the cell secreting it.

We will or haved discuss(ed) the functions of several interleukins:

IL-2

IL-4

IL-7

IL-12

IL-13

interferon- γ

Dr. Fantone will discuss the role of cytokines in immunopathology next week.

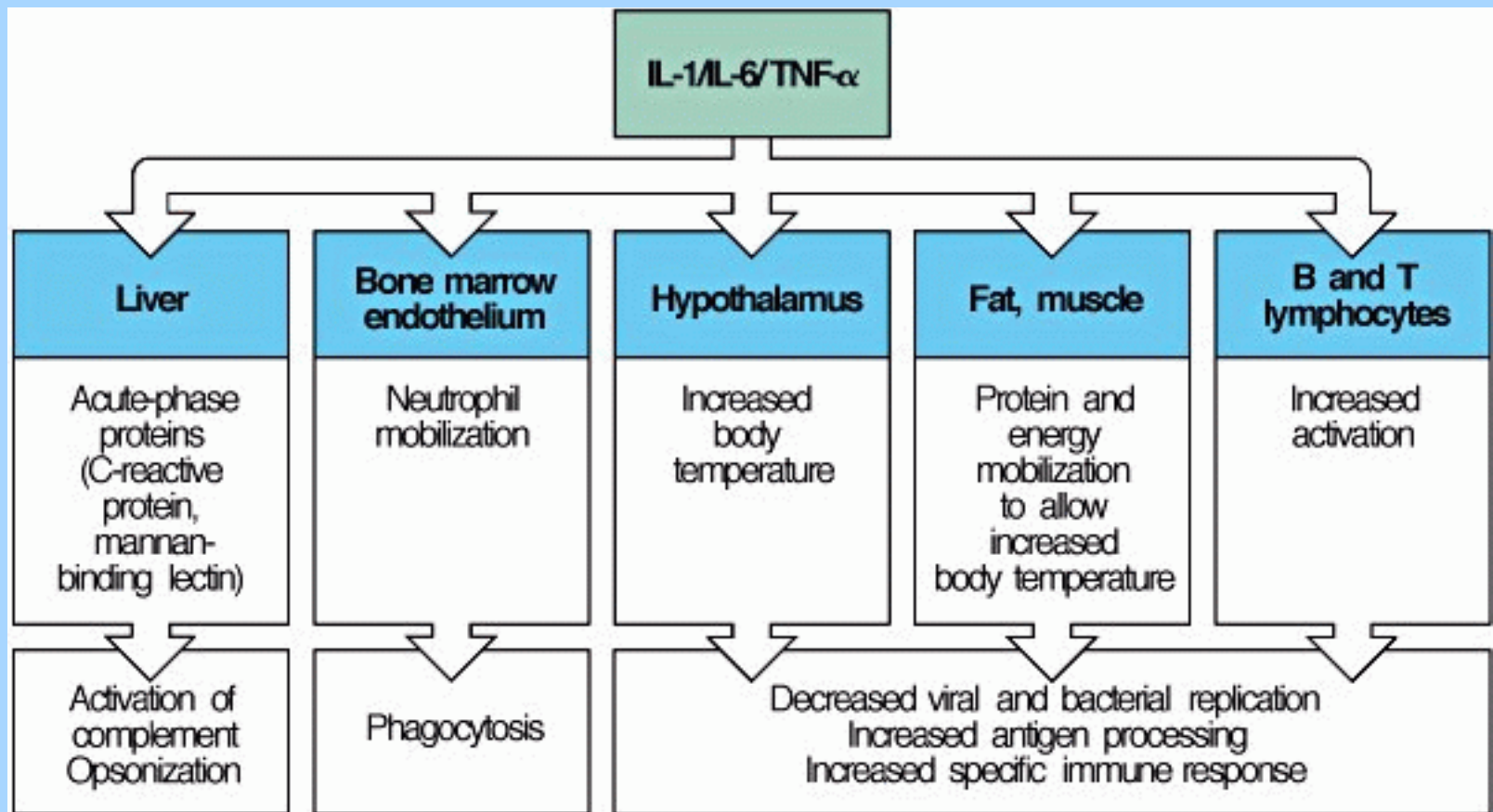
All cytokines have multiple functions and multiple target cells.

For example, all nucleated cells have an IL-1 receptor. IL-1...

- induces fever—originally called “endogenous pyrogen”.
- mobilizes leukocytes from the bone marrow.
- mobilizes insulin and glucagon.
- activates endothelial cells for increased adhesion to circulating leukocytes.
- activates lymphocytes to produce more IL-2.

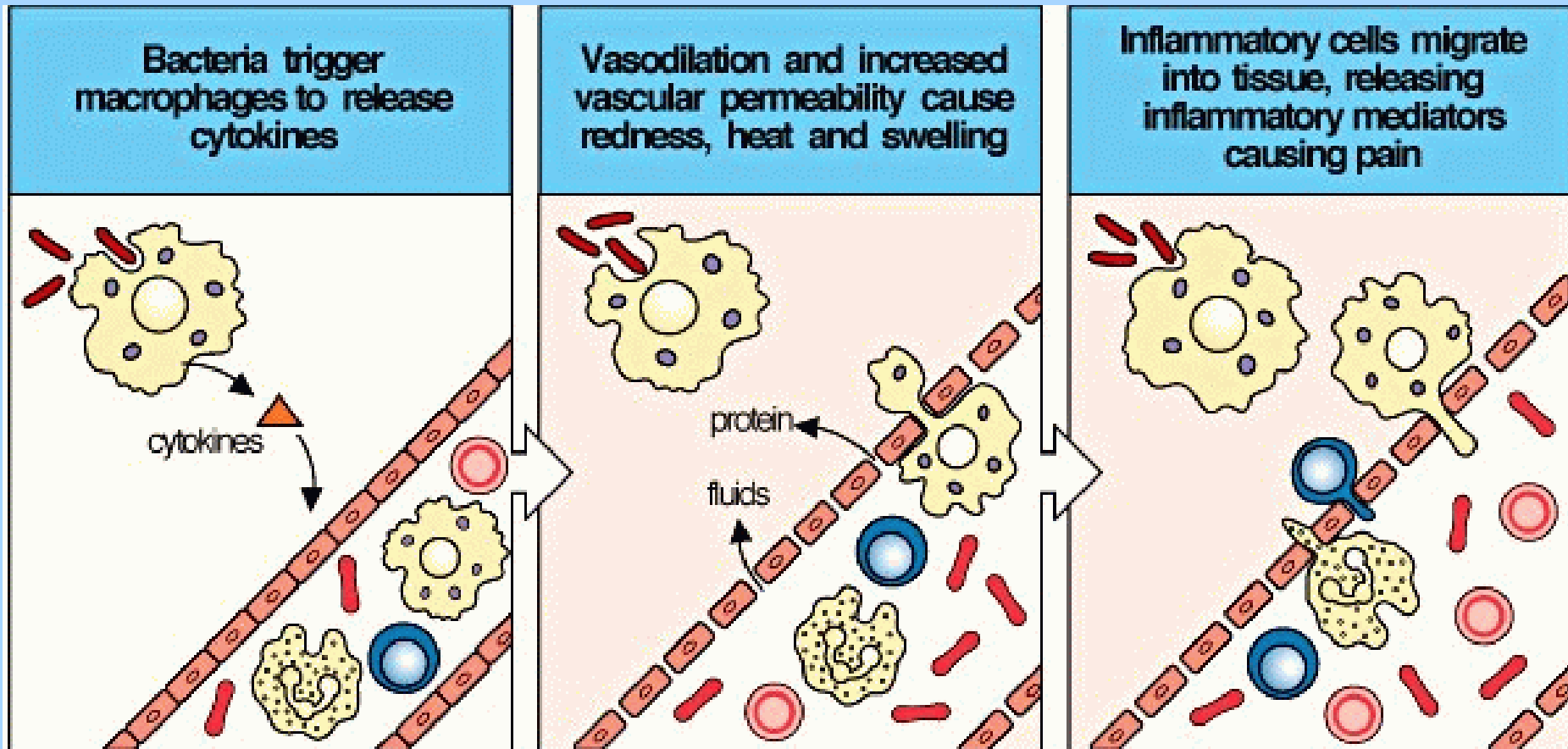
Cytokines have shared activities

IL-1, IL-6, and tumor necrosis factor (TNF) share some pro-inflammatory activities.



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Action of macrophage-derived IL-1, IL-6, and TNF



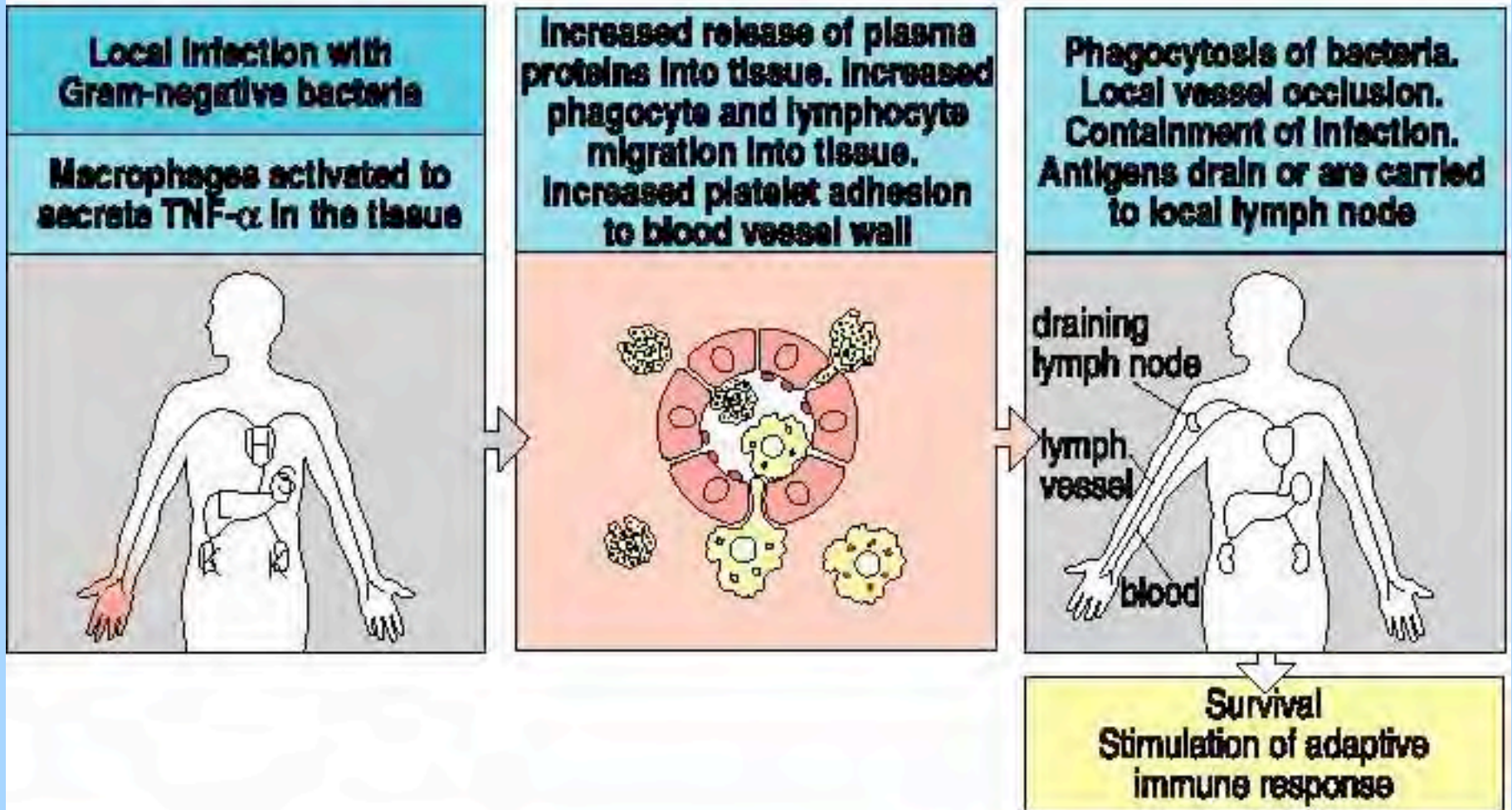
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When secreted in normal amounts, cytokines are important in normal homeostasis, for example, circadian rhythm.

When secreted in larger amounts, cytokines are important in cell recruitment, cell differentiation, and inflammation important in fighting infections.

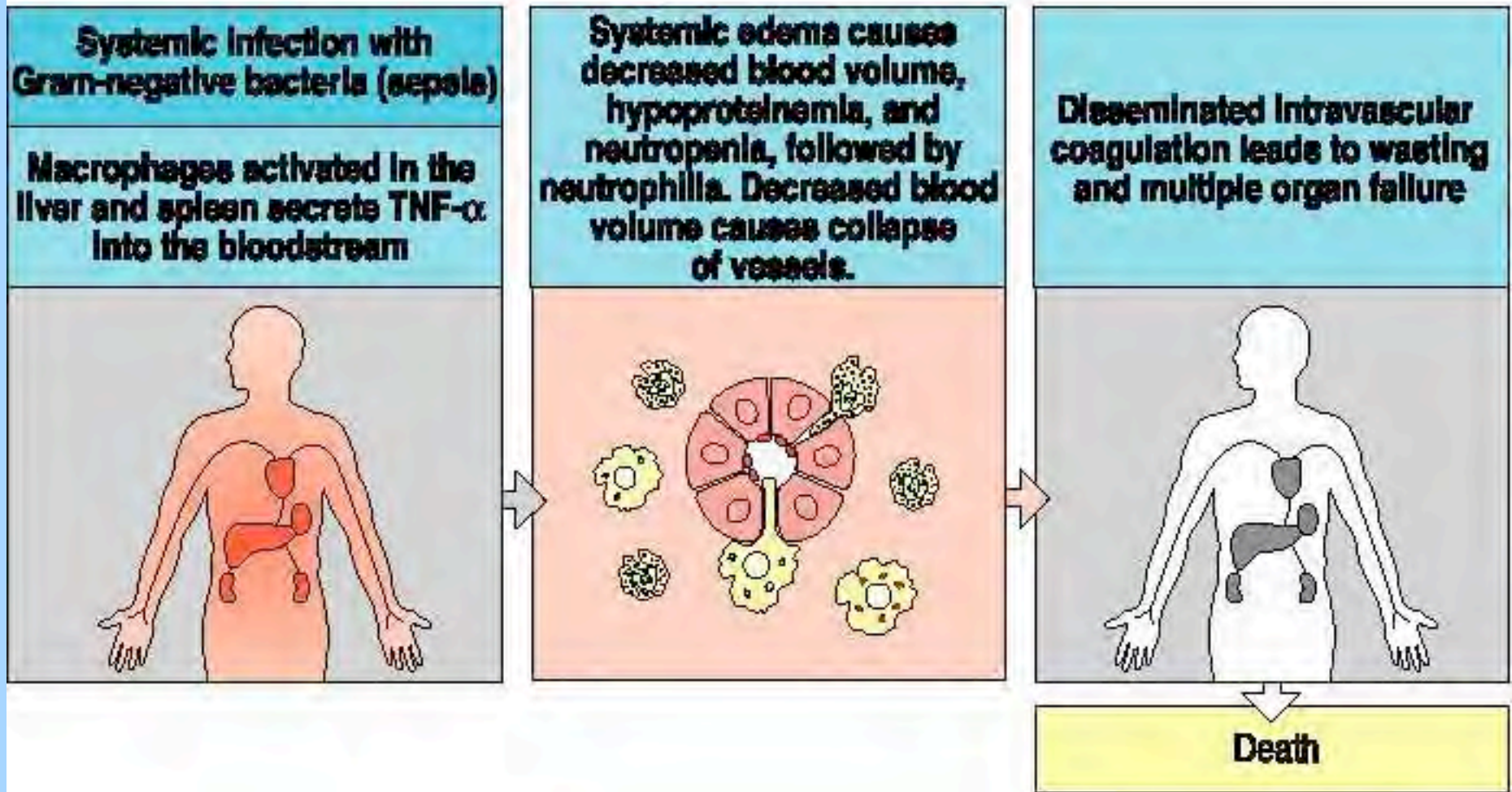
When secreted in excessive amounts, cytokines can lead to pathology.

Figure 8.12a



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Figure 8.12b



The cytokine “storm”

For example, septic shock results from systemic production of cytokines in massive amounts. This leads to multi-organ failure, a problem in medical intensive care units with no good solution. It is thought that production of IL-1, TNF, and IFN γ (after recognition of bacterial toxins) are the initiating cytokines for septic shock.

The septic shock cascade

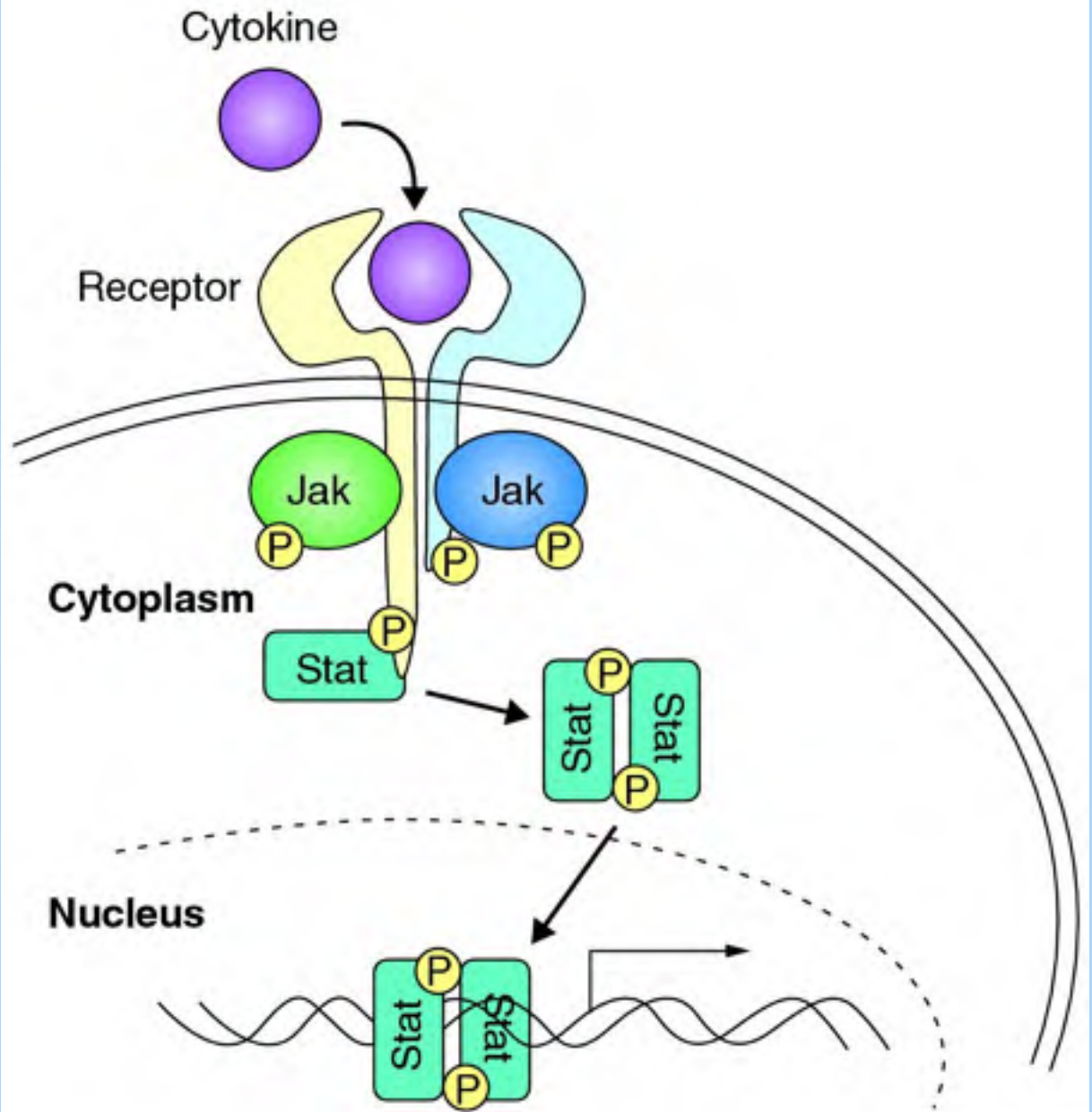
1. Bacterial toxins or LPS from gram-negative bacteria bind to TLRs on monocytes, *systemically*.
2. This results in the production of TNF, IL-1, and other pro-inflammatory cytokines. Fever results.
3. Neutrophils are recruited to the blood stream; the number of circulating lymphocytes and monocytes decreases.
4. Endothelial cells respond to the TNF, IL-1, etc., lowering blood pressure and resulting in the expression of chemokines by the endothelial cells. Activation and egress of neutrophils from the vessels leads to an oxidative response and more vascular leakage, lowering blood pressure even more.

5. The kinin proteolytic cascade is induced, resulting in production of bradykinin and increased vascular permeability.
6. The coagulation cascade is initiated. Disseminated intravascular clotting occludes small vessels, reducing perfusion of all major organs. Eventually, this contributes to organ failure.
7. Other organs (especially the liver) are acted upon by the pro-inflammatory cytokines, and begin to produce inflammatory molecules themselves.
8. Myocardial function is reduced by TNF and IL-1, exacerbating the problems with vascular leakage.
9. Death in 50-90% of cases.

Dr. Chang will discuss shock induced by T cell recognition of superantigens, which has a similar effector phase and outcome.

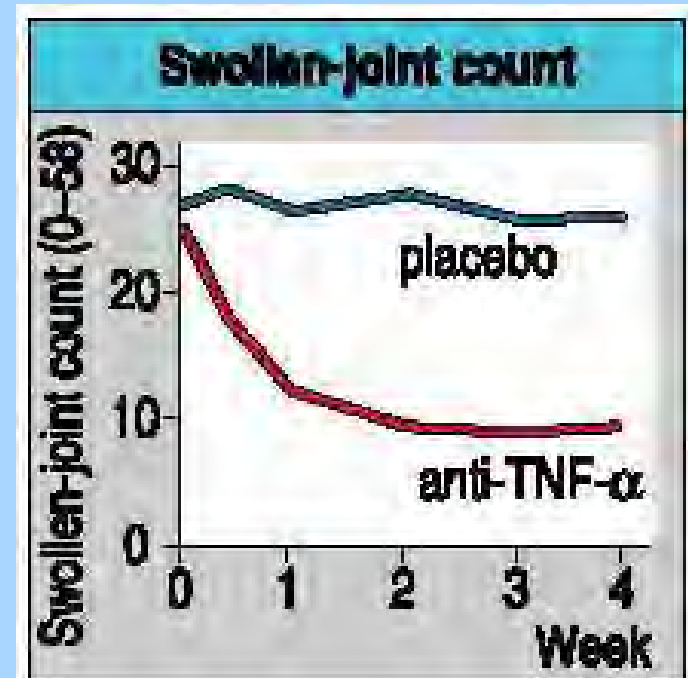
Cytokine
Signaling
via Stats

(recall IFN α
signaling
from September)



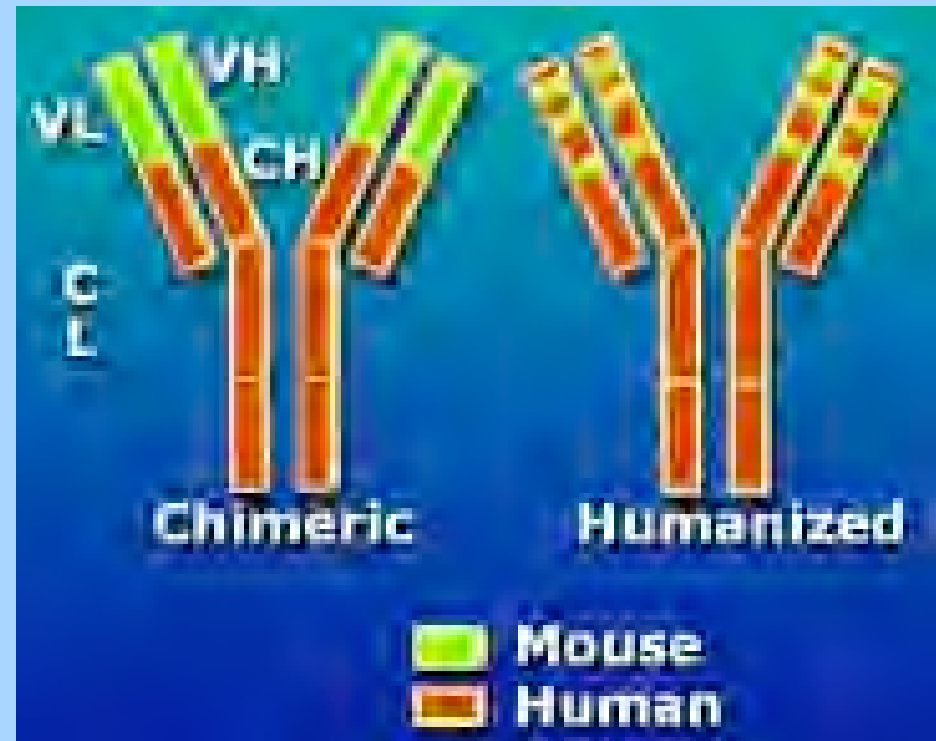
Therapeutics based on knowledge of cytokine action.

Tumor necrosis factor (TNF) is a pro-inflammatory cytokine produced by monocytes and lymphocytes. It activates endothelial cells for cell adhesion. Since it activates lymphocytes for cytokine production, it initiates a cytokine cascade and thus inflammation. Therapy with anti-TNF antibodies (made by hybridoma technology) has been remarkably successful for improving the symptoms of rheumatoid arthritis, Crohn's disease, and psoriasis--three autoimmune, inflammatory diseases.



In order to prevent immune responses to the mouse constant region parts of a hybridoma protein, therapeutic anti-TNF monoclonal antibodies have been “humanized”. Using recombinant DNA technology, the murine constant regions (and sometimes even the murine V framework regions), have been replaced by human constant regions.

The resulting chimeric immunoglobulin genes are reinserted back into myeloma cells, where cell clones can be selected for high-level expression of anti-TNF antibodies.



Chemokines

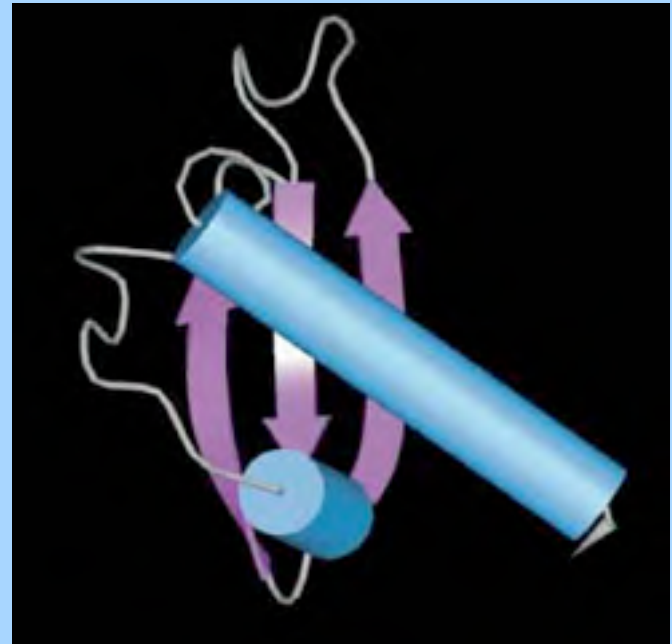
Chemokines are a family of more than 40 small polypeptides secreted by many cells, including lymphoid cells. One of their primary activities in the immune system is act on inflammatory cells (neutrophils) and cause their chemotaxis and activation (Dr. Stoolman will lecture on this next week). “Chemokine” is a shortened version of “chemotaxic cytokine”. Chemokines also have important roles in angiogenesis, hematopoiesis, cell growth, and cell metabolism.

Chemokines are classified according to the number and spacing of cysteines:

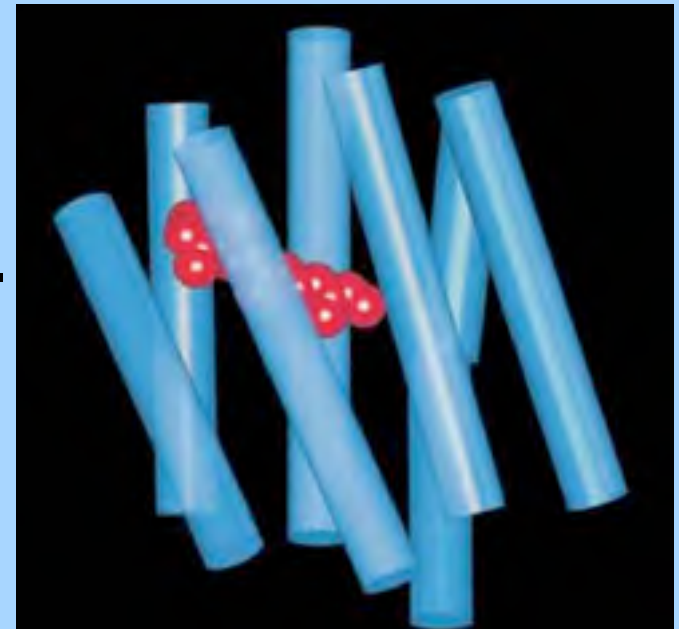
CC—adjacent, disulfide linked cysteines

CXC—disulfide linked cysteines separated by one amino acid.

Two minor groups: “XC” or “C” class of chemokines with only one cysteine and the “CX₃C” class with a three amino acid spacing.



Chemokine receptors are usually named by the chemokine they bind. CXCR4 is a co-receptor, along with CD4, for HIV on T lymphocytes. CCR5 is a co-receptor for HIV on monocytes/macrophages. Individuals who are homozygous for a mutation in CCR5 do not progress to AIDS, even after an HIV infection.



Type I interferons (alpha and beta) can be produced by most cells, and are important in innate immunity against viruses.

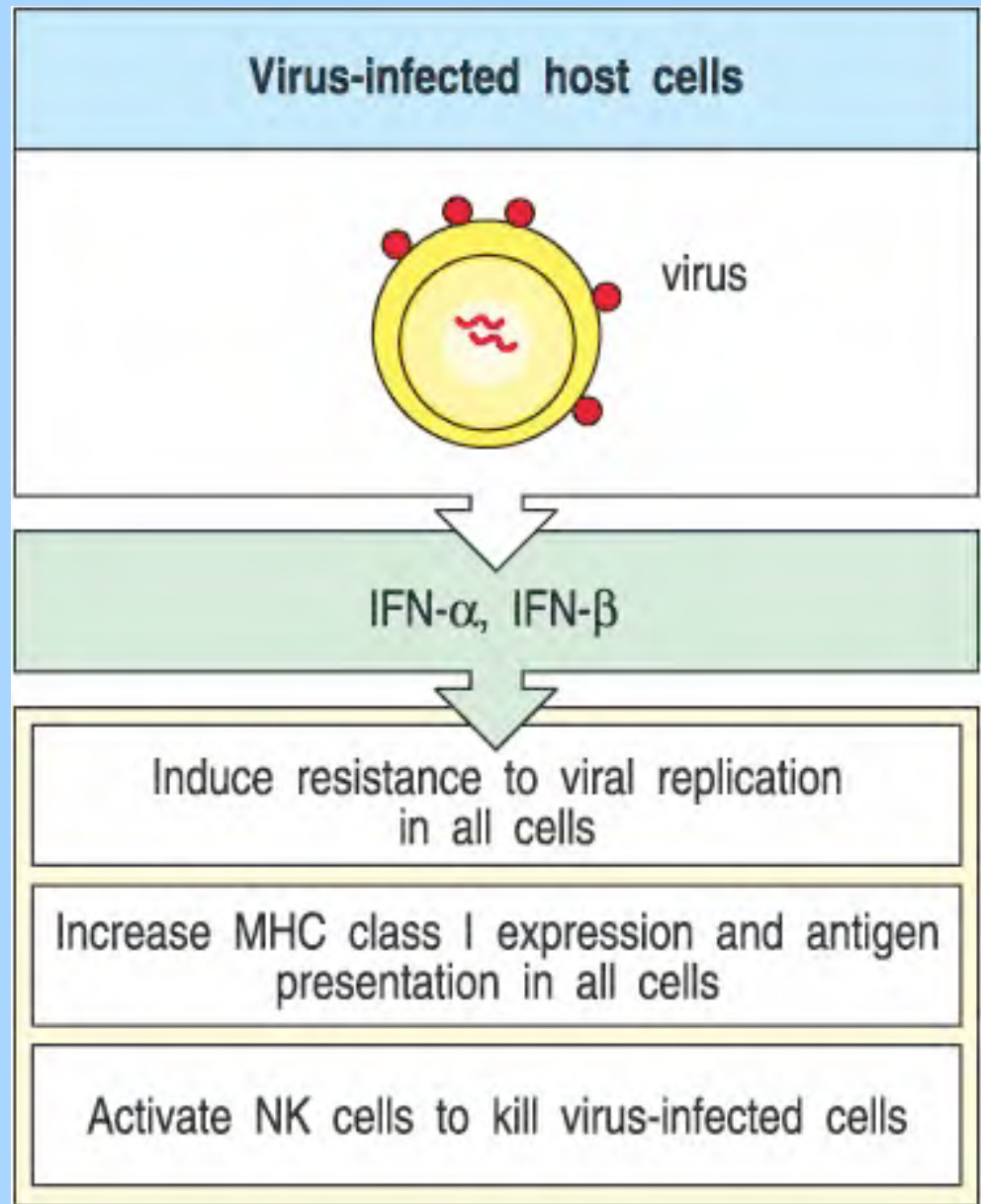


Fig 2.40 © 2001 Garland Science

Viruses must adjust to cytokines, or have exploited their activities.

IL-10 is generally anti-inflammatory by suppressing the expression of other cytokines by T lymphocytes. IL-10 can also stimulate the cell division and differentiation of B cells. Epstein Barr virus encodes its own version of IL-10 that confers upon B cells harboring the virus increased lifespan, with some cell division. At the same time the viral IL-10 blunts any inflammatory responses against the Epstein Barr virus.

Viruses also express soluble cytokine receptors that effectively neutralize the activity of pro-inflammatory cytokines.

Summary

1. Cytokines and chemokines are the medium by which cells communicate with one another, without cell-to-cell contact.
2. All cytokines have multiple functions and multiple target cells.
3. Cytokines have shared activities.
4. When secreted in larger amounts, cytokines are important in cell recruitment, cell differentiation, and inflammation important in fighting infections.

5. When secreted in excessive amounts, cytokines can lead to pathology.
6. In a small number of examples, therapies designed using knowledge of cytokine activities have been remarkably successful.
7. Viruses have exploited the activities of cytokines and chemokines by (i) producing viral versions of cytokines, (ii) producing inhibitors of cytokines, and (iii) by using chemokine receptors as co-receptors for cell entry.

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