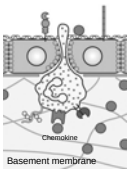
A Day in the Life of a Phagocytic Leukocyte

Diapedesis: Crawling Through Endothelial Junctions and Into the Tissue

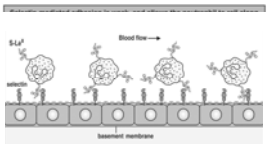
QuickTime™ and a
Sorenson Video decompressor
are needed to see this picture.



Movie, courtesy T. Springer

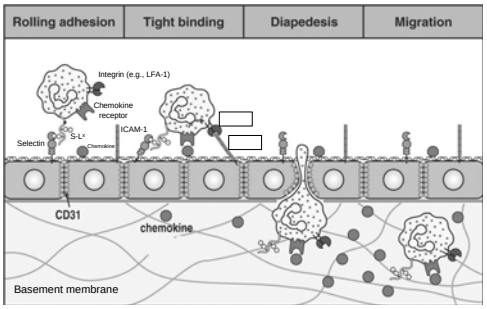
Selectin-mediated Adhesion is Weak and Promotes "Rolling" of Leukocyte Along Endothelia

QuickTime™ and a
Sorenson Video decompressor
are needed to see this picture.



Movie, courtesy T. Springer

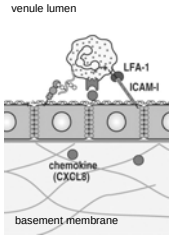
Leukocyte Migration, Start to Finish



Modified from: Parham, *The Immune System, 2nd ed.* (Garland: New York), 2005

Firm Adhesion is Triggered by Chemokine Activation of Leukocyte Integrins

QuickTime™ and a
Sorenson Video decompressor
are needed to see this picture.



Movie, courtesy T. Springer

The Innate Immune Response to Bacterial and Fungal Infections

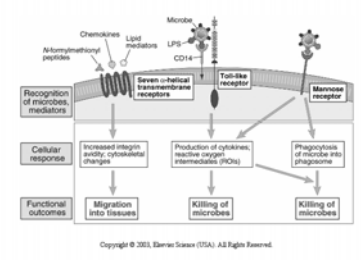
Relative Risk of Death Associated With Death of a Biological Parent Before the Age of 50

Cause of Death	Relative Risk
All causes	1.7
"Natural causes"	2.0
Infectious	5.8
Cardiovascular	4.5
Cancer	1.2

Conclusion: Genes that determine responses to infectious agents have a disproportionate effect on mortality

Source: Sorensen et al., *New Engl. J. Med.*, 318:727, 1988

Receptors Important in Innate Immunity

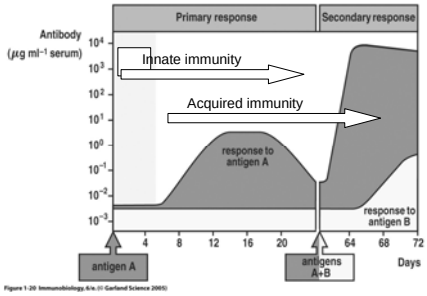


Distinctions Between Innate and Adaptive Immunity

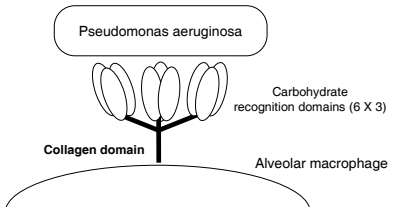
	Innate immune system	Adaptive immune system
Receptors	Germline-encoded	Somatically engineered
Distribution	Non-clonal	Clonal
Kinetics	Rapid	Slow (requires clonal expansion)
Specificity	Recognizes non-self "pattern recognition"	Recognizes "altered self" Primary structure (TCR) Higher order structure (Immunoglobulin; BCR)
Effector Cells	All	Primarily lymphocytes, DCs, Mϕ

Soluble "Defense Collagens" Participate in Innate Immunity

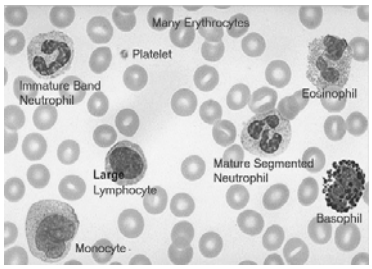
What Really Happens During the Lag Period Before the Acquired Immune Response?



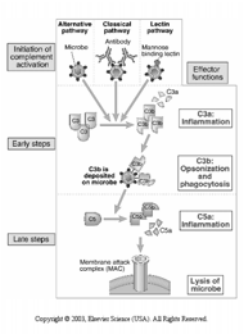
Domain Structure of Surfactant Protein A (SP-A), a Lung Soluble Defense Collagen (Collectin)



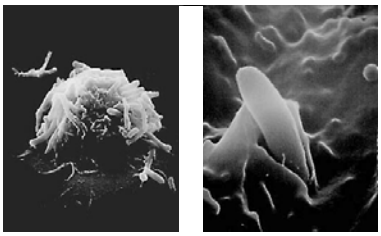
The Complement System is Critical for Innate Immunity and is Triggered by Multiple Ligands



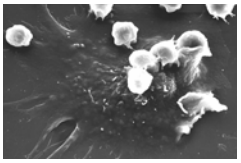
Complement is a Group of Proteins that Deposit On Microbial Pathogens and Help Kill Them



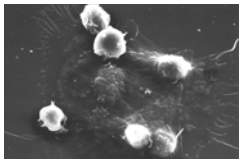
Mast Cells Can Phagocytose Too!



Phagocytosis of IgG-coated Targets by Macrophages

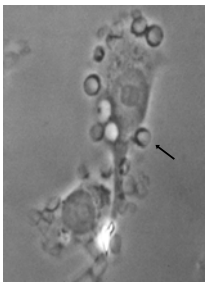


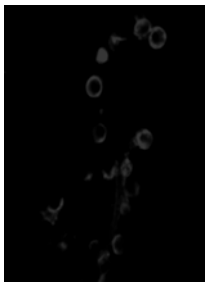
3 min



10 min

Extension of an F-actin-rich "Phagocytic Cup" Around Phagocytic Targets



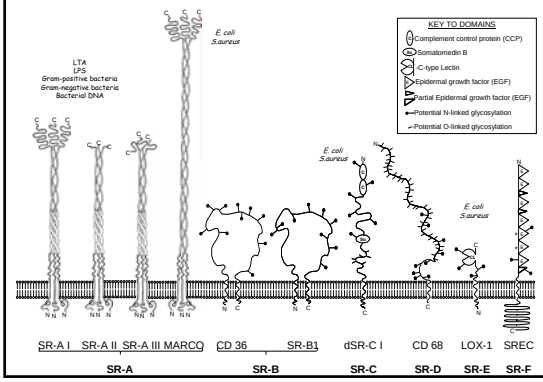


Examples of "Pattern Recognition Receptors" that Participate in Phagocytosis

Receptor	Expression	Target	Ligand
Integrins			
CR3 (CD11b/CD18; $\alpha_M\beta_2$)	PMN, Mo, Mϕ	Yeast	β-glucan
			C3bi, fibrinogen, LPS, ICAM
β_1 Integrins	Leuk	*Yersinia*	Invasin
Scavenger Receptors			
SR-AI/SR-AII	Mϕ	Gram-positive bacteria	Leipoteichoic acid
		Gram-negative bacteria	?
MARCO	Mϕ	*E. coli, S. aureus*	?
Lectins			
Dectin-1	Mϕ, DC	Yeast	β-glucan
CR3 (CD11b/CD18; $\alpha_M\beta_2$)	PMN, Mo, Mϕ	Yeast	β-glucan

QuickTime™ and a
Cinepak decompressor
are needed to see this picture.

The Scavenger Receptor Superfamily



QuickTime™ and a
Cinepak decompressor
are needed to see this picture.

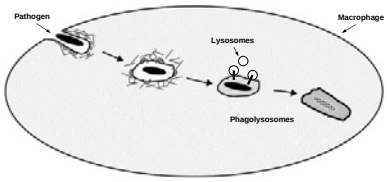
Elie Metchnikoff, 1845-1916

FIG. 34.—Microphage of guinea-pig filled with cholera vibrios, the majority of which are transformed into granules.

Phagosome-Lysosome Fusion?

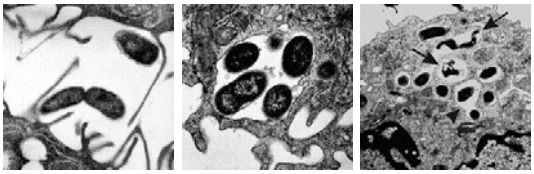
QuickTime™ and a
Cinepak decompressor
are needed to see this picture.

Post-phagocytic Events: Phagosome-Lysosome Fusion



Oxidant-dependent Killing of Bacteria and Fungi

Phagocytosis of Bacteria is Followed by Phagosome-Lysosome Fusion



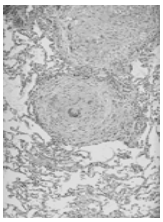
0-3 min 1-5 min 30 min-hrs

From: Allen et al., *J. Exp. Med.* 191:115, 2000

QuickTime™ and a
Cinepak decompressor
are needed to see this picture.

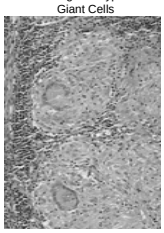
The Granuloma: a Delayed Response to Indigestible Pathogens and Particles in Macrophages

Granulomas



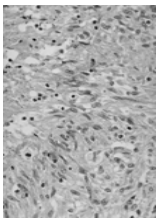
Granulomatous inflammation consists of epithelioid macrophages, giant cells, lymphocytes, plasma cells, and fibroblasts.

Langhans-type Giant Cells



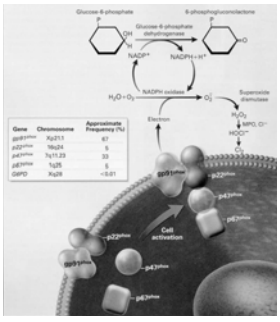
Langhans-type giant cells represent fused macrophages. The nuclei are lined up around the peripheryof the cell.

Epithelioid Cells



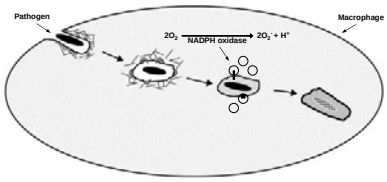
Epithelioid cells accumulate around the center of a granuloma. They get their name from the fact that they have pink cytoplasm similar to squamous epithelia.

Chronic Granulomatis Disease, an Inherited Defect of the NADPH Oxidase Complex

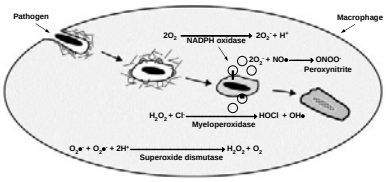


From: Lekstrom-Himes and Gallin, *N Engl J Med*, 343:1703, 2000

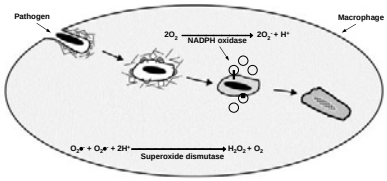
Post-phagocytic Events: "Phagosome-Oxidase Fusion"



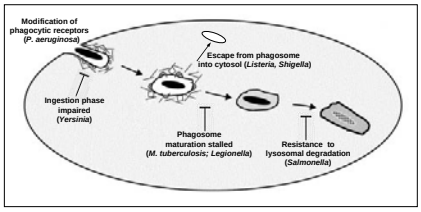
Post-phagocytic Events: Peroxynitrite Production



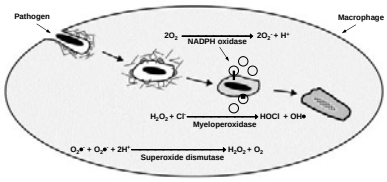
Post-phagocytic Events: Generation of H_2O_2



Bacterial Virulence Factors Subvert Host Defenses



Post-phagocytic Events: Myeloperoxidase Activity



Non-oxidative Killing Mechanisms

Quick Time™ and a TIFF (Uncompressed) decompressor are needed to see this picture.

Epithelial Cells Express Defensins, Too

HD-5

HBD-2

H. pylori, untreated

HBD-1

HBD-2

H. pylori, treated

HBD-2

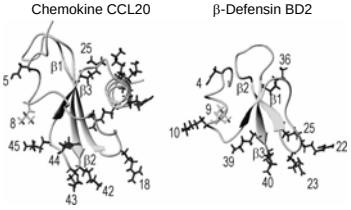
From: Wehkamp et al., *J. Clin. Path.*56:352, 2003; Hamanka et al., *Gut* 49:481, 2001

The Relationship Between the Innate Immune Response and Acquired Immunity

Structural Similarity of a Chemokine and a Defensin

Chemokine CCL20

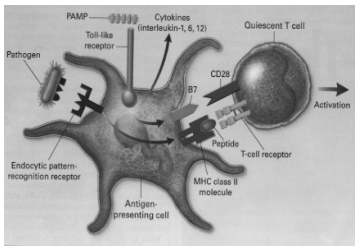
β-Defensin BD2



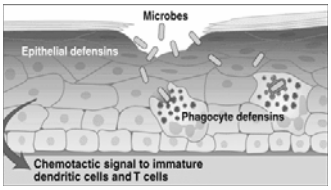
β-pleated sheets are represented by ***green arrows***; arginine and lysine residues are shown in ***blue***

From: Perez-Canadillas et al., *J. Biol. Chem.* 2001 276:28372

The (Primary) Acquired Immune Response is Initiated by Innate Immune Recognition



The Role of Defensins in Orchestrating the Immune Response



Inflamed defenders. A model of defensin activity in an infected epithelium. Epithelial cells synthesize antimicrobial defensins (red) both constitutively and in response to infectious and inflammatory stimuli. Other defensins are introduced by the influx of phagocytic cells that use them to kill ingested microbes. Released defensins attract dendritic cells and memory T cells, setting the stage for the adaptive phase of the immune response. From Ganz, *Science* 286:420, 1999.

Phagocytosis: Not Just for Bugs

Phagocytosis is the Principal Mechanism of Disposal of Apoptotic Corpses

Macrophage
Apoptotic Thymocyte

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

Implications: Disposal of apoptotic corpses occurs continuously during the lifetime of an individual. In this setting, phagocytosis is not accompanied by inflammation, but rather by an anti-inflammatory signal (the production of TGF-β). As apoptotic corpses contain many potential self antigens, the lack of an appropriate anti-inflammatory signal has the potential to trigger autoimmunity.

From: Jennings et al., *Am. J. Resp. Cell Mol. Biol.* 32:108, 2005

Immunological Consequences of Phagocytosis

Clearance of pathogens

Death of pathogenic microbe
Resolution of infection

Persistence of pathogenic microbe
Failure of resolution of infection

Clearance of apoptotic corpses

Suppression of inflammation
Tolerance

Inappropriate inflammation
Break in tolerance

Summary

1. Innate immunity represents the first-line of host defense. Its receptors are germline-encoded and recognize pathogen-associated "molecular patterns."
2. Phagocytosis is a component of innate and aquired immunity. It is the principal means of destroying pathogenic bacteria and fungi. Phagocytosis initiates the process of antigen presentation.
3. Many phagocytic receptors recognize a diverse array of microbial pathogens. Some pathogens (e.g., *S. pneumoniae*) require opsonization for their clearance. However, bugs fight back.
4. Phagocytic leukocytes employ oxidative and non-oxidative means of killing. The NADPH oxidase generates reactive oxidants, such as superoxide anion and hypochlorous acid (bleach).
5. Innate immunity ushers in acquired immunity: innate immune activation of APCs results in up-regulation of co-stimulatory molecules and enhances the effectiveness of antigen presentation.
6. Phagocytosis is an essential component of development and tissue remodelling. Ingestion of apoptotic bodies is immunologically "silent" and is normally accompanied by a suppression of inflammation. Failure of this mechanism may result in autoimmunity.