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It is all about fluidity: Fatty acids and macrophage phagocytosis

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SUMMARY

Phagocytosis is an early and fundamental step for the effective clearance of disease causing agents. The ability to engulf and kill pathogens is considered as a major effector function of macrophages. In their phagocytic role macrophages are part of the first line of innate immune defense. A number of studies investigating fatty acid effects on macrophage phagocytosis have been conducted over many years. *In vitro*-data consistently report that alterations in macrophage membrane fatty acid composition are linked to an altered phagocytic capacity, i.e. an increase in membrane unsaturated fatty acid content is associated with an increase in engulfment and killing rate. The mode of action of fatty acids seems to be the modulation of the physical nature of the macrophage plasma membrane. It appears that the saturated-to-unsaturated fatty acid ratio of macrophage membrane phospholipids is of importance in determining macrophage phagocytic capacity. Available *in vivo*-data are less clear. At present, there is a lack of systematic studies elucidating key factors such as fatty acid efficacy, effective dose or dosing intervals. Without this knowledge the targeted modulation of macrophage phagocytosis *in vivo* by fatty acids is still a distant possibility.

1. Phagocytosis

Humans and other animals are constantly exposed to pathogenic bacteria and the resistance to these microorganisms is of crucial importance for health maintenance. In addition, multicellular organisms have to get rid of endogenous apoptotic cells as well as cell debris which are generated in the course of development, tissue turnover and repair. The removal of particles the size of 0.5–5.9 μm in diameter (Ernst, 2000) is performed by a specialized mechanism: the process of phagocytosis. Phagocytosis encompasses particle recognition, particle binding, regulated ingestion and, finally, particle destruction. The highly conserved and complex process is receptor-mediated, membrane-directed and actin-driven (Groves et al., 2008). Of note, internalization and killing of pathogens not only prevents their dissemination throughout the host's body but also precedes antigen procession and presentation thereby triggering the acquired immune response. Phagocytosis, therefore, is an early and fundamental step for the effective clearance of disease causing agents.

1.1. Phagocytes

There are three classes of phagocytic cells in the immune system: monocytes/macrophages, neutrophilic granulocytes and dendritic cells.

Macrophages are relatively long-lived cells. They act as general scavengers thereby clearing the human/animal body of pathogens, dead cells and debris. The ability to engulf and kill bacterial pathogens is considered as a major effector function of macrophages. In this phagocytic role macrophages are part of the first line of innate immune defense.

The neutrophilic granulocytes or neutrophils are relatively short-lived cells (i.e. surviving for only a few days) which are found in the bloodstream in high numbers. As opposed to macrophages they are not found in healthy tissue. Due to infection increased numbers of neutrophils are produced which leave the blood stream and migrate to sites of infection/inflammation where they efficiently phagocytose pathogenic microorganisms and destroy them intracellularly by means of degradative enzymes as well as antimicrobial substances synthesized in their cytoplasmatic granules.

Dendritic cells continually take up particulate matter by phagocytosis and extracellular fluid by pinocytosis. Ingested pathogens are degraded, and pathogen antigens are displayed on the surface in a way to activate lymphocytes thereby initiating adaptive immune responses. Accordingly, the main role of dendritic cells is not the clearance of microorganisms but the presentation of antigens to other immune cells. Macrophages can act as antigen-presenting cells as well; however, dendritic cells are a specialized link between the innate and the adaptive immune responses.

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Table 1
Macrophage surface receptors.

Receptor type	Recognized pathogen-associated patterns
C-type lectin receptors (CLR)	*Cell wall carbohydrates of bacteria, yeast, fungi*
Mannose receptor	Mannose, N-acetylglucosamine, fucose
Glucan receptor	β-glucans
Scavenger receptors (SR)	*Modified lipoproteins, negatively charged molecules*
SR-A I	Lipopolysaccharide (LPS) lipoteichoic acid (LTA)
SR-A II	Lipopolysaccharide (LPS) lipoteichoic acid (LTA)
Toll-like receptors (TLR)	*Characteristic components of microorganisms*
TLR-2	Lipopeptides/lipoproteins, glycolipids, zymosan
(*heterodimer with either TLR-1 or TLR-6*)	Lipoteichoic acid (LTA)
TLR-4	Lipopolysaccharide (LPS)
(*homodimer in association with MD-2 and CD14*)	
TLR-5	Flagellin
(*monomer*)	

1.2. Macrophages

The focus of this review is set on macrophage phagocytosis.

The immature precursors of macrophages, the monocytes, circulate within the bloodstream from where they migrate into tissues to differentiate. Consequently, mature macrophages are distributed throughout the human/animal body. Macrophages are located in large numbers in connective tissues, in the submucosa of the intestinal tract, in the lung, in the liver, in the spleen and along specific blood vessels (Varol et al., 2009). Due to their targeted distribution macrophages efficiently monitor their surroundings for invading pathogens. To do so they express various cell-surface receptors such as the mannose receptor, the glucan receptor, the scavenger receptors as well as the Toll-like receptors (Table 1) which can discriminate several bacterial components from those of the host (Bryant and Fitzgerald, 2009). Ligand binding to such receptors initiates phagocytosis. This leads to the stimulation of lymphocytes by presentation of bacterial antigens as well as the activation of other immune cells by secretion of signaling proteins (i.e. cytokines and chemokines such as IL-1β, IL-6, TNF-α, CXCL8). The orchestration of the immune response by macrophages helps to induce inflammation which is a prerequisite for successful pathogen defense. In addition to fighting infections macrophages play a crucial role in maintenance of tissue health. For instance removal of dead cells and debris by macrophages is essential in wound repair (Murray and Wynn, 2011). Furthermore, in the spleen macrophages complete the task of eliminating senescent erythrocytes (Murray and Wynn, 2011).

1.3. The process of phagocytosis

Most bacterial pathogens which are encountered by a human or animal are detected and destroyed within minutes or hours by innate immune defense mechanisms. A microorganism that crosses epithelial barriers and replicates within host tissues is soon recognized by the macrophages residing in these tissues. Binding of bacteria to macrophage surface receptors activates phagocytosis (Fig. 1). Initially, the receptor-bound microorganism is surrounded by the membrane of the phagocyte. Active remodeling of the membrane and the cytoskeleton leads to the extension of membrane-pseudopodia and hence the encircling of the bacterium (Groves et al., 2008). This is followed by the internalization of the pathogen into an intracellular vesicle, the phagosome. Further on bacterial destruction is driven forward by phagosome maturation. The phagosome acidifies (pH value approximately 5.5 (Haas, 2007)) and fuses with lysosomes to form a phagolysosome which enables degradation of the pathogen by lysosomal enzymes. In addition, macrophage activation induces the production of antimicrobial peptides as well as the synthesis of reactive oxygen and nitrogen intermediates in a process called respiratory burst that help to kill engulfed microorganisms. Nitric oxide is formed by the inducible type of the enzyme nitric oxide synthase (iNOS). An additional enzyme frequently found in macrophages, the multicomponent, membrane-associated enzyme NADPH oxidase, synthesizes superoxide (O_2^-) which is further converted by the enzyme superoxide dismutase into hydrogen peroxide (H_2O_2) (Pourova et al., 2010; Robinson, 2009). Based on hydrogen peroxide a range of toxic substances such as the hydroxyl radical ($^{\cdot}OH$), hypochlorite (OCl^-) and hypobromite (OBr^-) are produced by chemical and enzymatic reactions (Pourova et al., 2010; Robinson, 2009). The combination of acidic pH, hydrolytic enzymes, pore-forming peptides as well as radical oxygen and nitrogen intermediates provides an antimicrobial milieu capable of the effective killing of a wide variety of bacterial pathogens.

1.4. Mechanisms of resistance and macrophage activation

As stated already, macrophages provide an important front line in immune defense. For that reason many pathogens have developed strategies to overcome macrophage phagocytosis and/or intracellular killing. One strategy that is frequently used by obligate extracellular disease causing agents is to coat themselves with a thick polysaccharide capsule which is not recognized by macrophage surface receptors hence preventing engulfment (Ernst, 2000;

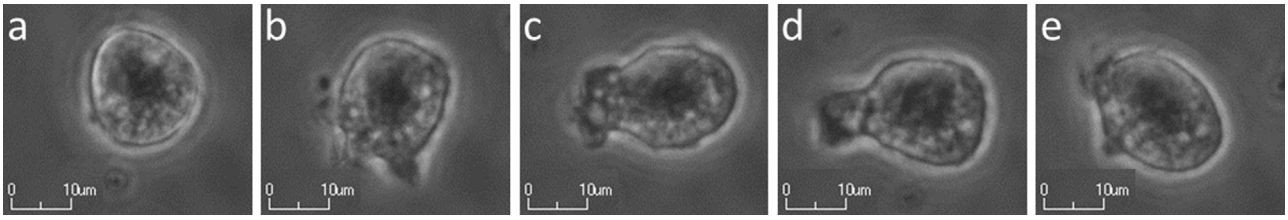

Fig. 1. Phagocyting macrophage. Macrophage during phagocytosis: (a) resting macrophage, (b) budding of macrophage plasma membrane, (c) surrounding of microorganism, (d) internalization of microorganism, and (e) involution of membrane budding.This picture series was gained due to live cell imaging of a co-culture of viable bacteria and RAW264.7 macrophages using the BioStation IM-Q microscope (Nikon, Düsseldorf, Germany) in phase contrast modus.