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Opsonin and its mechanism of action in secondary immune response

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ABSTRACT

Opsonins are specialized biomolecules responsible for recognizing the pathogens to be crushed by our immunity which, is considered as the main precursor of undergoing any phagocytosis reaction inside the body environment. In the absence of these molecules autoimmunity and hypersensitivity may take place on regular basis. A number of research programs and projects have been launching for the opsonin research purpose, where new theories of human immunity and molecular interference in our defense mechanism are revealed from each project. Complement cascade produces opsonin as a by-product. The complement receptor 3(CR3) and Fc gammareceptor (FcgamaRs), two important phagocytic receptors, mediate phagocytosis in the cellular level. In the following passages the pathways of opsonin activity in secondary immune response, mechanism of phagocytosis reaction, role of other complement system and antibody in defense purposes, clinical aspects of opsonization and the future of opsonin research are described quite transparently. The molecular structures and proteomic modeling is the main way of revealing new technologies of drug designing both in molecular and nano-scale level.

Key Words: *Phagocytosis, Complement, Immune system, Receptor and Defense mechanisms*

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I. Introduction

Opsonin refers to any molecule that boosts phagocytosis by representing an antigen for an immune response. Opsonin actually doesn't mean any single molecule, but there are a number of biomolecules involved in recognizing antigens to our body environment and lead to synthesize immune activity. The recognition of antigens is the main precursor of generating defense mechanism, where opsonisation process acts as the patron. This typical recognition by opsonin induces the phagocytosis mechanism to the remarked area of infection (Barret and James, 1980). The name "Opsonin" came from a Greek word *opsōneîn*, which refers to prepare for eating, considered as the motto of phagocytosis. Few molecules are engaged in activation of the complement system, are also termed as opsonin. Opsonins can also refer to molecules that target a cell for destruction through the action of natural killer (NK) cells. So, it

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is clear enough to realize that opsonins are complicated and diversified molecules interfere our defense mechanism via recognizing the pathogens through a process named opsonization. Opsonin and complement receptors work together to run the complex protocol of our immune system in many extents (Nasr et al., 2006). In the twenty first century, opsonins are considered to be major factors in case of treatment and drug designing (Didar et al., 2014). Therefore, the main objectives of this review is to emphasize the role of opsonin and its activity in our immune system so that advanced study can be done to strengthen the immune responses of human. The review also accumulates the probable researches on opsonin in future.

II. Materials and Methods

This review article has been prepared from secondary study materials such as published journal articles, conference papers, technical and theoretical notes, reports, books and relevant information found from various online sources.

III. Results and Discussion

Mechanism of opsonin in the secondary immune system

Phagocytosis is the process by which cells recognize and engulf large particles which are specifically more than 0.5 micro meters and is very important for host defense mechanism as well as to tissue repair and morphogenetic remodeling. During infection, uptake of opsonized microorganism is mediated by phagocytic receptor on the surface of macrophage, most notably complement receptor 3 and Fc gamma receptor (Caron and Hall, 1998). In case of human our immunity regulated with three lines of defense. The first and second lines of human body are nonspecific immune response, while the third line of defense mechanism our immunity reacts in a specific way. Phagocytosis mainly is on the second line of defense. Nonspecific defense mechanisms actually rely on phagocytosis. There are various types of phagocytic cells engaged in defence mechanisms i.e., neutrophils, macrophages/monocytes, eosinophils, basophils and dendritic cells. Both macrophages and microphages do the invasion and lysis of pathogens according to Metchnikoff. Neutrophil and macrophage both are able to engulf pathogenic molecules. Neutrophil contains two types of granules; primary azurophil granule (develops early, has typical lysosomalmorphology), secondary specific granules (Delves et al., 2006a).

Macrophages is present in bone marrow as promonocyte which then move to blood as monocyte and few of them are finally deposited in the tissue as macrophages. .They are found in the connective tissue and around the basement membrane of small blood vessels and are particularly connected in the lung, liver, and lining of spleen sinusoids and lymph node medullary sinuses where they are strategically placed to filter off foreign materials. More recent research has focused on the membrane receptors and the dynamics of the responses of phagocytes to the external factors including immunoglobulin complement proteins, cytokines, chemokines, integrins and selects. Phagocytes express toll like receptors that aid in the clearance of a wide range of microbial pathogens and their products. Phagocytes are also important sources of pro-inflammatory and anti-inflammatory cytokines thus participating in host defenses through a variety of mechanisms (David et al., 2008). Neutrophil cytoplasm supplies very rich amount of glycogen required for enzymatic contents come from neutrophil granules (Valentine and Beck, 1951). The burst of glycolysis that occurs associated with phagocytosis (Sbarra and Karnovsky, 1959). Myeloperoidase generates H_2O_2 can be considered as the most potential antimicrobial substance comes into action for pathogenic infection (Klebanoff, 1968).

In case of phagocytosis neutrophil surface and its receptors are great factors. The surface is complexed with myriad of folds, crevices and site for interaction of the neutrophil with the surroundings (Parent, 2004). There are few receptors responsible to react with opsonins are expressed on both neutrophil and monocytes (receptors Fc R- I, II, III etc.), and CR3 critical surface receptors for facilitating phagocytic movement and ingestion through pathways affecting cytoskeletal recognization (Stossel,

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1993) and (Kim et al., 2003). The complement mediated reactions that generate chemotactic factors in plasma also catalyze by-products that coat microbes and opsonize them such as C3b to be crucial and critical in preventing infection in patients with C3 deficiency. IgM in minority of cases IgG, can activate complement component which ultimately causes deposition of C3 on microbial surface and initiate complement dependent opsonization of encapsulated microorganisms. Deficiencies in C3 and C5 results in defective opsonization and chemotaxis of netrophil respectively (Sullivan and Winkelstein, 2007).

The neutrophil is responsive to chemotactic factors and ingested particles, and undergoes metabolic and morphologic changes. Ligand binding to the neutrophil surface induces hyperpolarization and calcium fluxes increase, consequently cyclic AMP rises transiently. Thus, phagocyte membrane dynamics and stimulus-response coupling acts fruitfully in case of our defense mechanism (Smolen et al., 1980; Whitin et al., 1980; Naccache et al., 1979). Major Histocompatibility Complex (MHC) is a major fact for the running of the phagocytosis process. A genetic region encoding molecules involved in antigen presentation to T-cells. Class I MHC molecules are present on virtually all nucleated cells and are encoded mainly by the H-2K, D and L loci in mice and by HLA-A, B, C in man, whilst class II MHC molecules are expressed on antigen-presenting cells (primary dendritic, macrophages and B-cells) and are encoded by HLA-2A and E in mice and HLA-DR, DQ and DP in man. Allelic difference can be associated with the most intense graft rejection within species (Delves et al., 2006b). MHC proteins are coated by a gene and are specific for individuals. Each MHC molecule has a deep groove that displays a peptide which is a normal cellular product of protein recycling. In infected cells MHC proteins bind with the pathogenic molecules and play a massive role in mobilizing the immune system. Phagocytosis is actually a second line of defense (Figure 01).

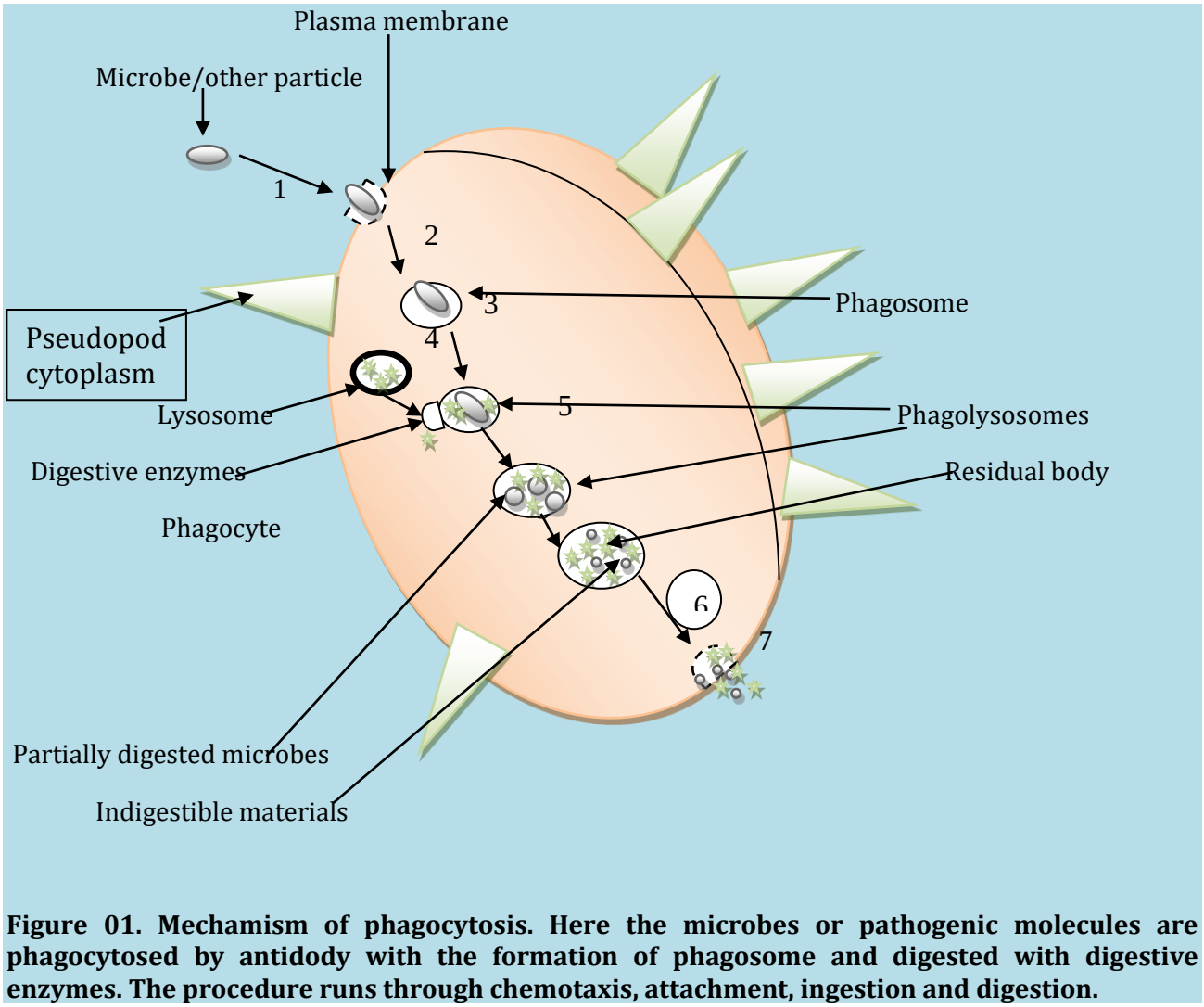

Figure 01. Mechamism of phagocytosis. Here the microbes or pathogenic molecules are phagocytosed by antidody with the formation of phagosome and digested with digestive enzymes. The procedure runs through chemotaxis, attachment, ingestion and digestion.

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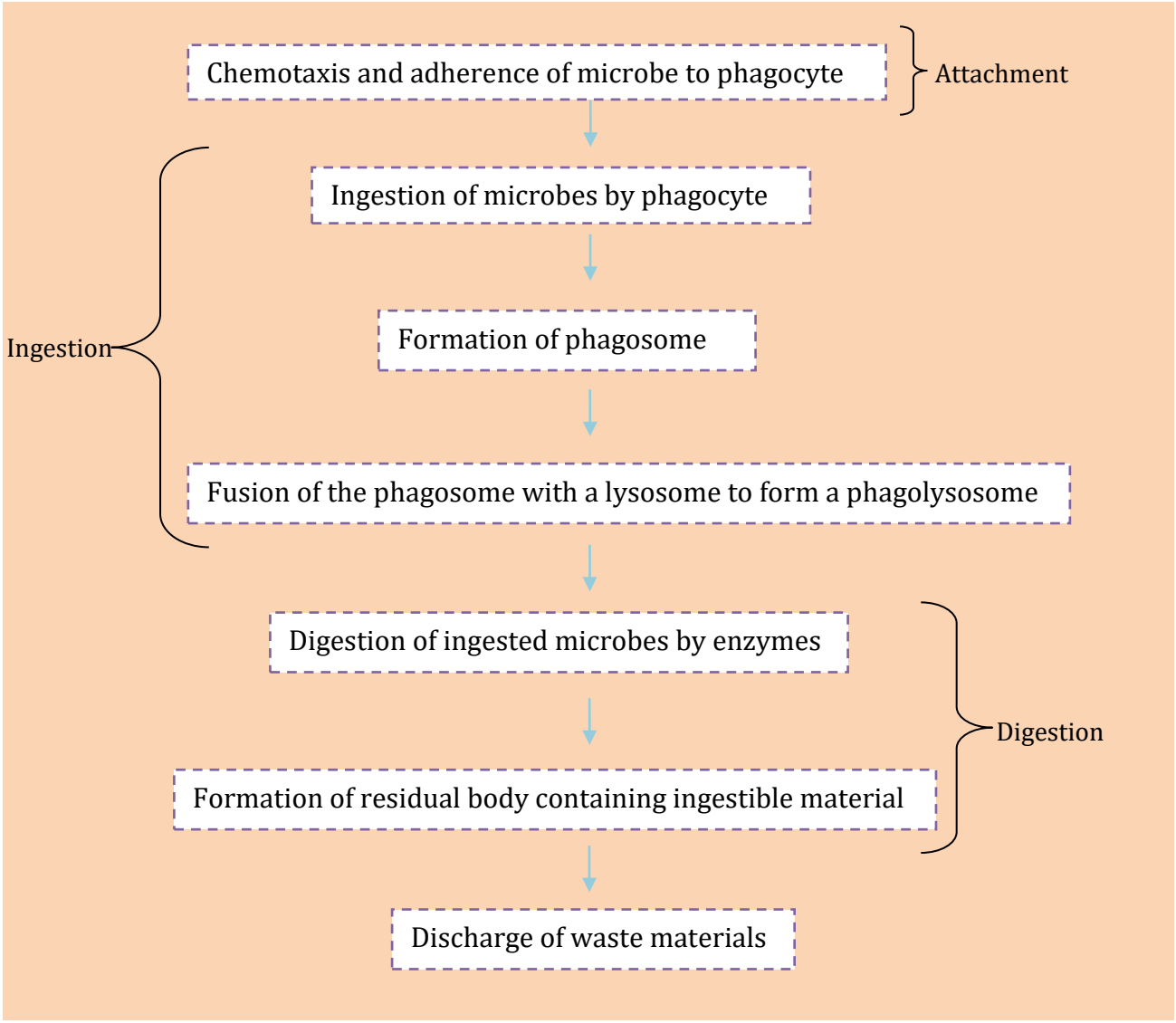
The level of acute phage proteins increased during infection enhances host defense mechanism e.g., complement proteins, coagulating factors, transferrins etc. Factors involved in case of secondary defense line are cytokines, fever (occurs for pyrogen) and interferons complement systems (consists of about 30 proteins).

Many white blood cells engulf invasive microorganisms through phagocytosis. Regardless of the organism or specific molecules concerned however, all phagocytic processes are driven by a finally controlled rearrangement of actin cytoskeleton. A variety of signals can converge to locally reorganize the actin cytoskeleton at a phagosome and there are significant similarities and differences between different organisms and between different engulfment processes within the same organism. A wide variety of effector molecules can be implicated in actin re-modelling downstream of these receptors (May and Machesky, 2001). The steps of phagocytosis are arranged into four phases.



Usually lysozyme acts as the main digestive enzyme where many other enzymes of equal purposes also present. After phagolysosome formation and partial digestion, ingestible materials like the residual bodies are present. Then, the waste materials are discharged to conform that the cell is infection free. The process by which phagocytosis is facilitated by deposition of opsonins is called opsonization. These opsonins can be complement proteins or antibodies which play very important roles (Figure 02).

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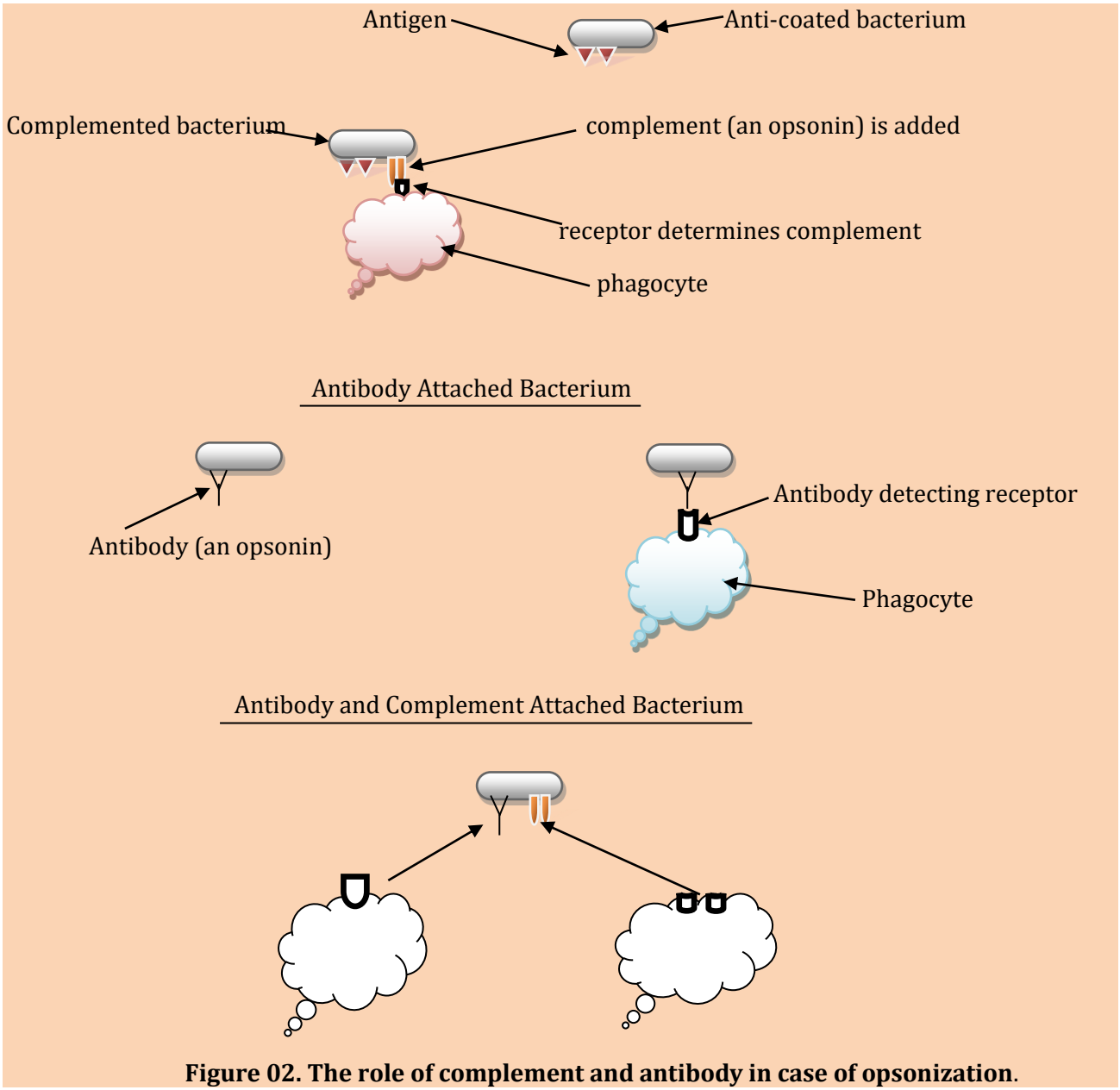

Figure 02. The role of complement and antibody in case of opsonization.

Complement system consists of some 20 proteins which, together with blood clotting, fibrinolysis and kinin formation, form one of the triggered enzyme systems found in plasma. The complement sysem is a rapid cascade where product from one step functions as the catalyst to the next. In some extent, C3 undergoes slow spontaneous cleavage. C3b levels are normally tightly controlled. C3 convertase is stabilized on microbial surfaces (Delves et al., 2006a). Complements can mediate an acute inflammatory reaction. In case of C3bBb stabilization on the surface of the microbe and cleaves large amount of C3.The C3a fragment is released but C3b molecules bind copiously to the microbe. These activate the next step in the sequence to generate C5a and the membrane attack complex but many organisms maybe resistant to its action. The detrimental effect of microbial infection leads to the evolution of a variety of host defense mechanism. In case of vertibrates innate and adaptive immunity are found, where the main distinction between these is the receptor types used to recognize pathogens (Janeway and Jr, 1989) and (Schatz et al., 1992).

Opsonin independent adhereance and phagocytosis of microbes is often identical by murine peritoneal macrophages e.g., in case of *Listeria monocytogens* (Pierce et al., 1996). Attachment and entry of bacteria occurs through their apical surfaces and these processes do not appear to be actin dependent (Karunasagar et al., 1994).phagocytosis is sometimes important for lung and few other body sites,

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considered as opsonin independent mechanism.. One such mechanism "surface phagocytosis" can be demonstrated in measuring the uptake of unopsonized [3H]-tagged *S. aureus* and *Pseudomonas aeruginosa* (David et al., 1984).

Most of the microorganisms will not be phagocytosed without opsonins. Pseudopods extend to cover particles but only the part that is opsonized. Solid matters and pathogens can be internalized through endocytosis, as a specific form of phagocytosis. Macrophages are large, irregularly shaped cells that kill microbes by phagocytosis such as amoeba ingests a food particle, also called "big eaters".

Opsonin (complement and antibody) binding is a fundamental precursor of phagocytosis initiation and/or specific molecules on the surface of pathogen called pathogen-associated molecular pathogens [PAMPs] to cell surface receptor on the phagocyte e.g., phagocytosis of bacteria (Figure 03). Phagolysosome formed through maturity and acidification by fusing endosome and lysosome as a consequence of discreet phagosome formation. Activation of complement cascade causes proteolytic cleavage of complement factors. In the neutrophil surfaces ligands for complement receptors are created.

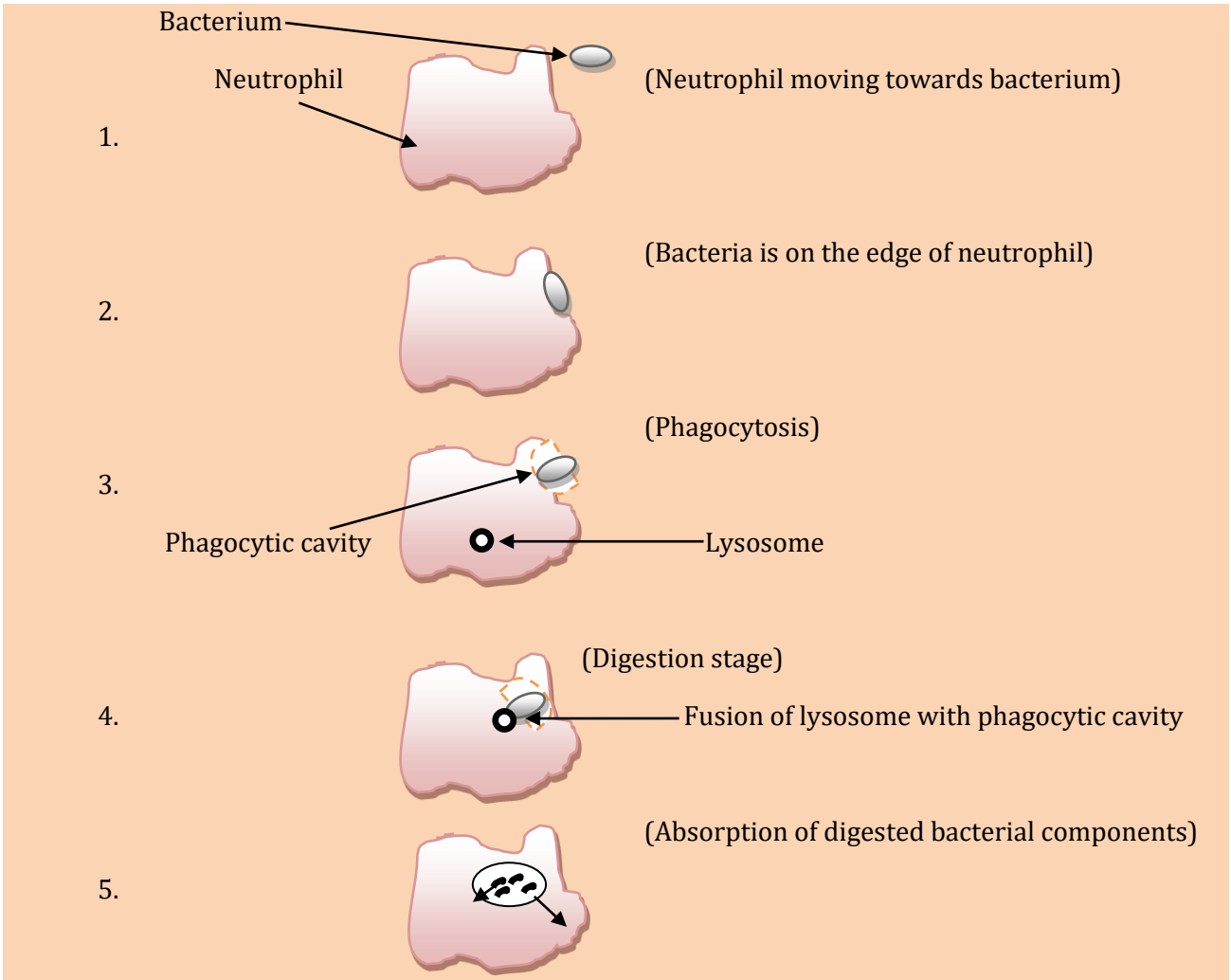

Figure 03. Schematic presentation of different stages of bacterium destruction by phagocytosis.

Neutrophil and monocyte are two phagocytic white blood cells. Neutrophils replenish themselves and place themselves into the vacant space of tissues through the capillary filaments. Monocytes are large W.B.C. They are converted into macrophage and enter into various tissues like the tissues involved in guarding liver, spleen etc. the macrophages can engulf comparatively larger molecules like R.B.C, malaria parasite etc which is next to impossible for neutrophils. These macrophages and neutrophils form reticulo-endothelial system of our body. In case of any injury or contamination, the surrounding locations of the infected area swelled up and generate pain. This is called inflammation. Pain mainly generates for the secretion of histamine and 5-hydroxitryptamicin. Oedema is the ultimate

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consequence. The plasma of oedema contains molecules that kill bacterium by inhibiting bacterial growth. The opsonins (i. e., antibodies) and phagocytes combined act to conceal the spreading of infection throughout the body. Interferon plays the major role in this case secreting from macrophages and other white blood cells. Viruses are also destroyed in the similar manner. Fibrinogen helps if blood coagulation required. The repair mechanism starts from the site of inflammation and pain. In this time phagocytes reach the location of interest and absorb digested bacterial components. Then fibroblast and epidermal cells repairs the affected location and make body disease free.

Opsonization in case of clinical aspects

Opsonins are the precursors to track any pathogen or virulent molecule after invasion, by our body environment and to take steps to defend themselves from infections. At the same time opsonins have many outstanding applications as discussed below.

Mannose-binding lectin and innate immunity mechanism with the direct participation of opsonin is very effective to assess and design the kinetic of immune response in case of human (Eddie et al., 2009). The specific analysis of the role of non-contaminated serum and poly(L-lysin) on particle uptake by phagocytes, a kinetic analysis of attachment and ingestion of lipopolysaccharide-coated particles during phagocytosis in animal level has taken successfully by studying effects of heat-labile opsonins (Matsui et al., 1983). In case of inflammatory response analysis, opsonin is very handy in case of animals specifically (Drevets and Campbell, 1991). Opsonins have receptors which identify and bind to protein molecules on immune cells. Due to having negative charge in viruses and bacteria, it is tough to come in intimate contract with the pathogen and undergo direct lysis or destruction in general. Opsonins act as markers. Direct killing of pathogens without ingesting them through antibody dependent cellular cytotoxicity, lead by opsonization. Antibodies that activate immune cells termed granulocytes, can act as opsonins where, granulocytes are indispensible part of immune system and immune reaction. Granulocytes can perish pathogens releasing toxins. The role of opsonins should be judged in case of blood donation and risk assessment (Shapiro et al., 1993). Genetic diseases cause alternation in the orientation of opsonization process. People are susceptible to infection, particularly bacterial, in case of deficiency in complement cascade. Thus, opsonization analysis should be very effective in case of genetic disorder analysis.

Future research

In future opsonin can be designed to intensify themselves functionally as to mark a number of unknown particles with a single opsonin molecule to get simultaneous function and to determine encapsulated or synthetically generated foreign particles. Like monoclonal antibodies (used to treat cancer and to target drugs in any specific location), monoclonal opsonin can be designed though there are antibodies act as opsonin during our defense mechanism.

IV. Conclusion

Opsonin is a miscellaneous and rich effector bridges the innate and adaptive immune systems. It is vital to host defense and the expansion of its influence is becoming increasingly appreciated as additional information regarding the far-reaching effects of its activation is exposed. Further study should contribute significant knowledge in our understanding of host defense as a unified process and the roles opsonin plays in bridging innate and adaptive immunity.

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