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REVIEW ON IMMUNOBIOLOGY OF MACROPHAGES

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ABSTRACT

The macrophage is the major differentiated cell of a phylogenetically primitive system of cells termed the mononuclear phagocyte system. Macrophages are widely distributed throughout the body, displaying great structural and functional heterogeneity. Macrophages act as a second line of defense against such foreign invaders, either as stationary or as mobile cells and are also able to signal other types of white blood cell, particularly lymphocytes, and other immune cells to the site of infection to help fight it off. They are specialized phagocytic cells that chase down and destroy cancer cells. In most tumors, tumor-associated macrophages (TAMs) show properties of an alternative polarization phenotype characterized by the expression of a series of chemokines, cytokines, and proteases that promote immunosuppression, tumor proliferation, and spreading of the cancer cells. Macrophages function in both non-specific defense (innate immunity) as well as help initiate specific defense mechanisms (adaptive immunity) of vertebrate animals. Most importantly macrophages process and present antigens on the surface of the membrane.

KEYWORDS: Adaptive and innate immunity, Antigen processing & presenting, Cancer cells, Macrophage.

INTRODUTION

The term ‘macrophage’ was first used more than 100 years ago by Elie Metchnikoff, a Russian bacteriologist, in 1884, in Messina to describe the large mononuclear phagocytic cells he observed in tissues (Karnovsky, 1981). In 1924, Aschoff assigned these cells to the reticuloendothelial system (RES), a broad system of cells which included reticular cells, endothelial cells, fibroblasts, histiocytes and monocytes. However, because the RES included cells of non-macrophage lineage, it did not constitute a true system; in 1969, it was agreed to replace this term with the current title mononuclear phagocyte system (MPS), on the basis that macrophages shared important functional characteristics in vivo and were derived from monocytes (van Furth *et al*., 1972), whereas endothelial cells and fibroblasts were not. Phylogenetically, the mononuclear phagocyte is a very primitive cell type, with related cells being found in early life forms, and some single-cell protozoa exhibiting features similar to the mammalian macrophage. Ontogenetically, the macrophage originates in the yolk sac but in adult individual arises from the bone marrow (van Furth, 1989).

Thus macrophage is the major differentiated cell of the mononuclear phagocyte system. This system comprises bone marrow monoblasts and promonocytes, peripheral blood monocytes and tissue macrophages. Macrophages are widely distributed throughout the body, displaying great structural and functional heterogeneity. They are to be found in lymphoid organs, the liver, lungs, gastrointestinal tract, central nervous system, serous cavities, bone, synovium and skin, and participate in a wide range of physiological and pathological processes (Gordon, 2002).

Therefore, the objective of this paper was:

- To review the biology macrophages;
- To review the diverse functions of macrophages.

Biology of Macrophages

The origin and development of macrophages

As shown in Figure 1 below all the cells of mononuclear phagocytic system arise from bone marrow stem cells known as monoblasts. Thus, macrophages originate in the bone marrow since they are under mononuclear phagocytic system. Monoblasts develop into promonocytes and promonocytes develop into

monocytes, all under the influence of proteins called colony stimulating factor (CSF). Monocytes enter the blood stream and circulate for about 3 days before entering tissue and developing into macrophages. Immature macrophages found in the blood are called monocytes, where they form about 5% of the total blood leukocyte populations (Tizard, 1996).

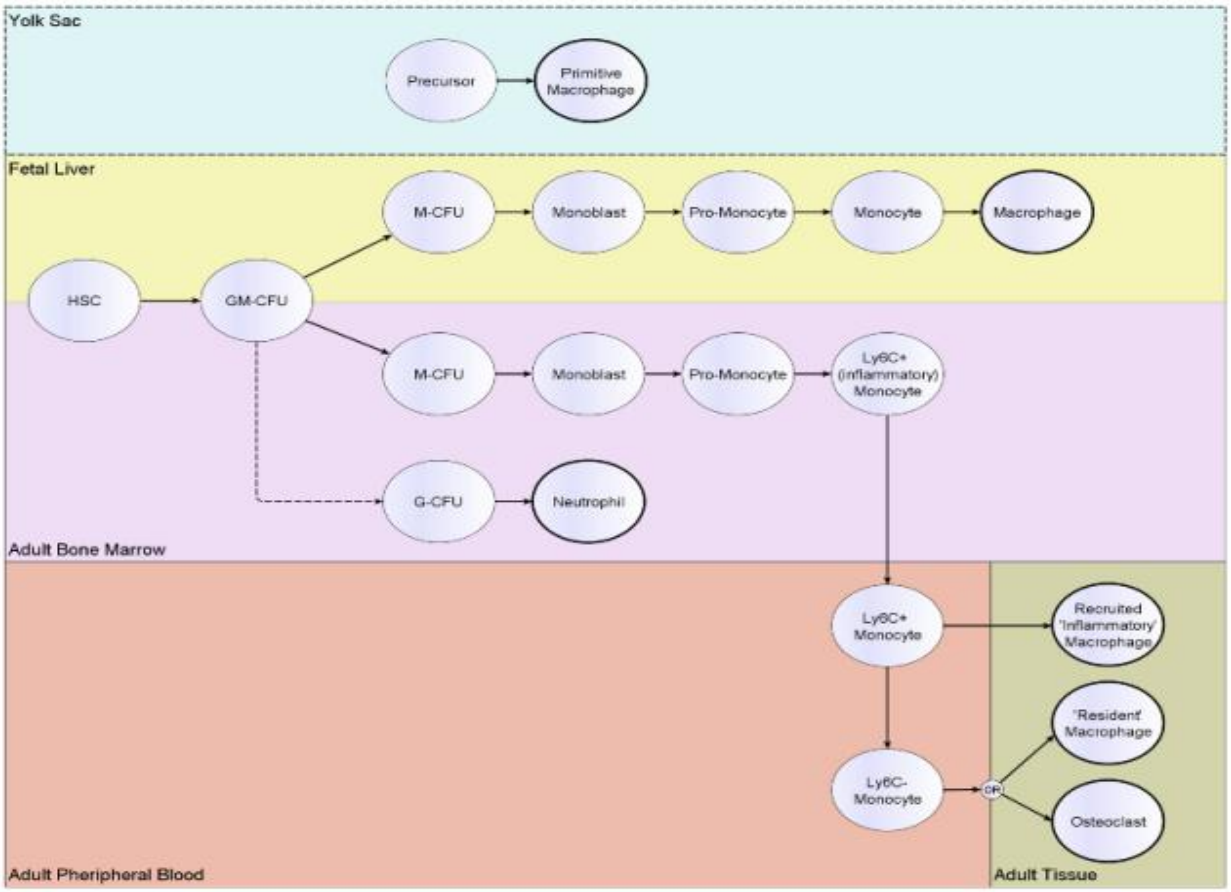

Figure 1: Origin and development of macrophage in mononuclear –phagocytic system(MPS). Source: (Gordon and Taylor, 2005).

Legend: Hematopoitic Stem cell (HTC) in the fetal liver or adult bone marrow develop into a progenitor of both macrophages and granulocytes; the granulocyte macrophage colony-forming unit (GM-CFU). The GM-CFU population can commit to the macrophage colony forming unit (M-CFU) or the granulocyte colony forming unit (G-CFU) groups of cells. The M-CFUdifferentiates into monoblasts, promocytes, and monocyte cell stages, prior to becoming macrophage, in a process requiring the growth factor CSF-1. In mice LyGC is the marker of inflammatory population of monocyte. The concept of the MPS has come under security following the discovery of a separate embryonic phagocyte lineage in the yolk sac.

Macrophage Heterogeneity

Macrophages are a heterogeneous group of cells with common blood-borne precursors, monocytes, originating from stem cells in the bone marrow (van Furth, 1982). The monocytes migrate into various tissues where they mature and become resident macrophages. A majority of macrophages are stationed at strategic points where microbial invasion or accumulation of dust is likely to occur. Each type of macrophage, determined by its location, has a specific name.There are various subsets of macrophages, (Fig. 2) such as Kupffer cells in the liver, alveolar macrophages in the lung, microglia in the central nervous system (CNS) and synovial macrophages in the joints, with differing expressions of surface molecules and differing morphology depending upon their localization and function (Radzun *et al*., 1988).

The seeding of monocytes to different tissues (Werb and Goldstein, 1987; Gordon *et al*., 1988; Papadimitriou and Ashman, 1989; Wintergerst *et al*., 1998) where they remain as macrophages is apparently random since there is no evidence that the tissue destination is pre-programmed. Resident macrophages are distributed constitutively throughout the normal body in the absence of any inflammatory signal and display regional heterogeneity.

Functional, morphological and phenotypic heterogeneity may reflect these cells' environments and involvement in many disease processes.

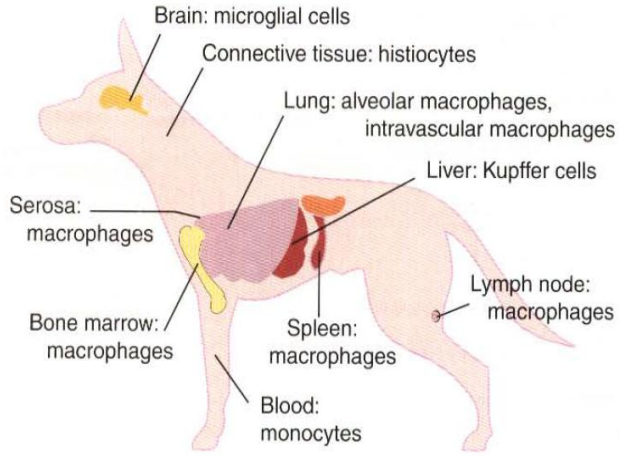

Figure 2: The location of the cells of the mononuclear phagocyte system.

Alveolar macrophages

An alveolar macrophage (or dust cell) is a type of macrophage found in the pulmonary alveolus, near the pneumocytes, but separated from the wall. Activity of the alveolar macrophage is relatively high, because they are located at one of the major boundaries between the body and the outside world. Alveolar macrophages are phagocytes that play a critical role in homeostasis, host defense, the response to foreign substances, and tissue remodeling (Lambrecht, 2006). Nonspecific and specific defense mechanisms protect the lung from environmental pathogens. Coughing and sneezing as well as the mucociliary blanket remove most of the larger particulates from the upper airways. The innate immune system is very well developed in the deeper parts of the lung and is made up of a humoral arm (lactoferrins, lyzozyme, surfactant proteins, mannose binding lectin, and defensins) and a cellular arm, consisting mainly of alveolar macrophages that express numerous pattern recognition receptors for foreign antigen. If these nonspecific mechanisms fail, a highly developed network of epithelial and alveolar dendritic cells (DCs) is responsible for mounting the adaptive immune response. It has been estimated that the pool of alveolar macrophages can handle many intratracheally injected bacteria before there is "spillover" of bacteria to DCs and before adaptive immunity is induced (MacLean *et al.*, 1996).

Kupffer cells

It is believed that Kupffer cells' responses to LPS and other gut-derived stimuli may be important in their interactions with hepatocytes. Indeed these cells may be at least partially responsible for regulating the acute phase response in injury and malignancy, possibly producing IL-6 which appears to deliver the final signal to hepatocytes in initiating the altered metabolism associated with the acute phase response. Large numbers of monocytes are recruited to the liver following uptake of microorganisms by Kupffer cells and contribute to the immune response against the invaders. Kupffer cells are also believed to be involved in reperfusion injury after liver preservation for transplantation (Lemasters and Thurman, 1997). Activated Kupffer cells release a number of inflammatory mediators including TNF-α, IL-1, IL-6, prostaglandins and nitric oxide (NO), and subsequent changes in endothelial cell, leukocyte and platelet behavior may contribute to the ischemic process.

Bone marrow

Macrophages play an integral role in the support of hemopoiesis. Bone marrow and fetal liver contain a network of mature macrophages which ramify through the stroma. These stromal macrophages make intimate contact with a 'nest' of surrounding developing hemopoietic cells (Crocker and Gordon, 1985) which can be isolated intact. The stromal macrophages appear to be essential for maintaining the growth and differentiation of hemopoietic precursors *in vitro* and possess adhesion molecules for maintaining contact with developing hemopoietic cells (Hanspal, 1997).

Intestine

The gut lamina propria in both the large and small intestine contains a large population of macrophages (Mikkelsen and Thuneberg, 1999). They are also present in the specialized gut-associated lymphoid tissue with a well-defined structure, such as the tonsils and Peyers patches (Hume *et al*., 1987).

Structure of Macrophages

Macrophages assume a wide variety of shapes in response to their environment. They are round cells measuring about 15µm in diameter and possess abundant cytoplasm with single round, bean shaped or indented nucleus at the center of it. The perinuclear cytoplasm contains mitochondria, a number of lysosomes, some rough endoplasmic reticulum and a Golgi apparatus (Fig. 3) (Tizard, 1996).

Unlike polymorphs, macrophages are long lived cells with significant rough surfaced endoplasmic reticulum and mitochondria (Roitt and Delves, 2001).

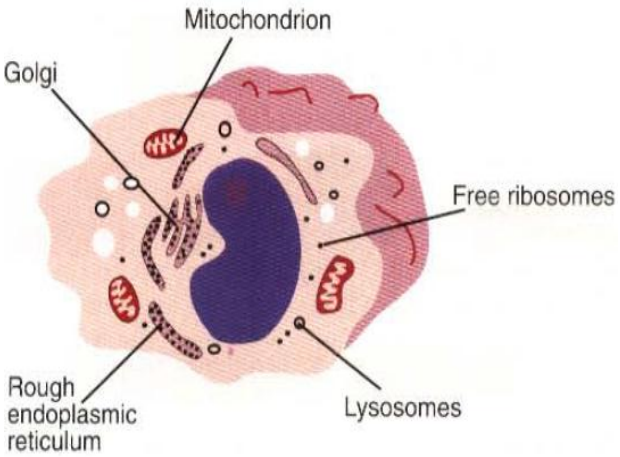

Figure 3: The major structural features of macrophage, Source: (Tizard, 1996).

Macrophage Activiations

Although monocytes and resting macrophages are effective phagocytes, they can be readily activated so that their functions are significantly enhanced. A variety of substances including cytokines, growth factors, and bacterial cell-wall products are capable of activating macrophages and regulating their cellular functions (Nathan, 1991).

When monocytes first move into inflamed tissue they enhance phagocytic activity, the expression of phagocytic antibody and complement receptors, and the secretion of protease and lysosomal enzymes. These cells are called inflammatory macrophages. Inflammatory macrophage can be still activated further to become activated macrophages as a result of exposure to bacterial products and proteins called interferon. These activated macrophages have a greatly enhanced ability to kill bacteria (Tizard, 1996). Different levels of activations are recognized, to day. But in general their activation is classified broadly into classically-activated and alternatively-activated macrophages.

Classically Activated Macrophages

Classically activated macrophages arise following stimulation with the Th1 cytokines IFN-gamma alone or in concert with bacterial moieties, such as LPS or cytokines (TNF-α) (Mantovani *et al*., 2002). Classical macrophage activation refers specifically to the broad class of activation observed in response to challenge by microorganisms. The classical macrophage activating factor, produced by stimulated Th1 lymphocytes and NK cells, is interferon-gamma (Schroder *et al*., 2004). Classically-activated macrophages are strongly positive for class II-MHC, and adapted to kill microorganisms and tumour cells and present antigen to T lymphocytes. Therefore, it is important to remember that macrophages become classically activated by exposure to *two* signals. The first is the obligatory cytokine IFN-γ, which primes macrophages for activation but does not in itself activate macrophage**s** (Nathan, 1991). The second signal is TNF itself or an inducer of TNF. Exogenous TNF can act as the second signal, but the physiologically relevant second signal is generally the result of Toll-like receptor (TLR) ligation, which induces endogenous TNF production by the macrophage itself. Thus, classically activated macrophages are developed in response to IFN-γ, along with exposure to a microbe or microbial product such as LPS. In the murine system, these cells are now easily identified by virtue of their production of nitric oxide (NO) (Hibbs, 2002*;* MacMicking *et al*., 1997). Macrophages that have been primed with IFN-γ alone should not make NO,(NO is a free radical membrane-permeable inorganic gas) provided the system is free of LPS (a common contaminant in recombinant IFN-γ).

Alternatively Activated Macrophages

Pathogens that require Th2 response are effective clearance, such as parasitic worms, are strong inducers of alternatively activated macrophages (Fair-weather and Cihakove, 2009). These cells fail to make NO by virtue of their induction of arginase (Rutschman *et al.*, 2001) and consequently, are compromised in their ability to kill intracellular microbes. Although they up-regulate some MHC class II molecules, they are not efficient at antigen presentation, and in many instances, they actually inhibit T cell proliferation. Recent studies on this cell population have begun to focus on their potential to mediate wound-healing, angiogenesis, and extracellular matrix deposition. The induction of arginase in these cells may lead to polyamine and proline biosynthesis, promoting cell growth, collagen formation, and tissue repair (Hesse *et al*., 2001). In the lung, it is thought that alternatively activated macrophages may provide negative regulatory signals to protect the host from overzealous inflammatory responses to environmental stimuli (Goerdt *et al*., 1999). Contrary to popular belief, activated macrophages are not more phagocytic than resting cells. Although activated macrophages spread out more than resident cells and generally have a higher pinocytic rate, they express reduced levels of mannose receptor and Fc receptor for IgG (FcγR)II (Ezekowitz and Gordon, 1984). Activated macrophages do however possess a markedly enhanced ability to kill and degrade intracellular microorganisms,and for several years, this was the functional criterion used to define an activated macrophage. This killing is accomplished by an increase in the production of toxic oxygen species and an induction of the inducible NO synthase (iNOS) gene to produce NO. The restriction of various nutrients from the phagosome is an underappreciated but important aspect of microbial killing that is also used by activated macrophages. The restriction of iron and tryptophan (Carlin *et al*., 1989) from vacuolar organisms is a particularly well-established mechanism for limiting intracellular growth within activated macrophages.

Macrophage Surface Receptors and Their Function

Macrophages carry many different receptor proteins on their surface (Fig. 4). These receptors on the surface of the macrophage determine the control of activities such as growth, differentiation, activation, recognition, endocytosis, migration and secretion (Gordon, 2003). Each population of macrophage within a specific tissue expresses distinct receptors. For example, CD64 (FcγRI) is a high affinity antibody receptor expressed on monocytes and macrophages. Cattle have a unique FcR on their macrophages, Fcγ2R. It can bind particles coated with a specific type of antibody, IgG2. Human macrophages carry two other antibody receptors, CD32 (FcγRII) and CD16 (FcγRIII). These have a much lower affinity for antibody. Receptors like CD35 (CR1), the major receptor for C3b and CD11/CD18 which is also a receptor for fragments of C3b permit antigen particles coated with complement to bind to macrophages. Macrophages also possess mannose- binding receptors that can bind directly to nonopsonized bacteria (Tizard, 1996). Numerous ligands have been reported as binding to the surface of the macrophage. Their ability to recognize a wide range of endogenous and exogenous

ligands, and to respond appropriately, is central to macrophage functions in homeostasis as well as host defense in innate and acquired immunity, autoimmunity, inflammation, and immunopathology (Gordon, 2003).

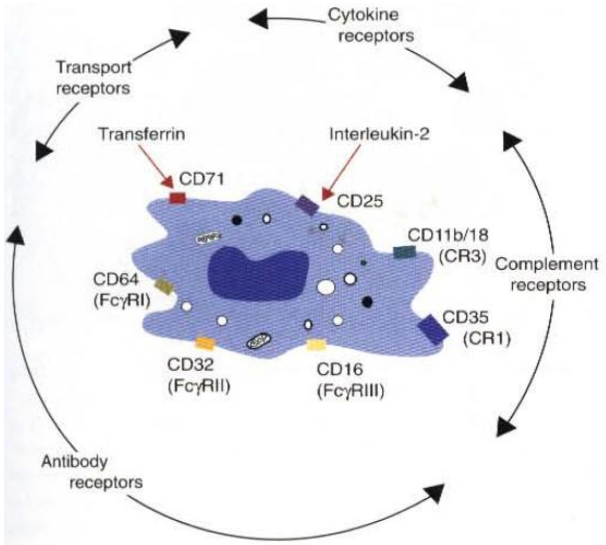

Figure 4: Some of the major surface receptors on macrophages and their functions. Source: (Tizard, 1996).

Functions of Macrophages

Macrophages are not so fast at killing most bacteria, and phagocytosis can take many hours in these cells. Macrophages are slow and untidy eaters; they engulf huge quantities of material and frequently release some undigested back into the tissues. This debris serves as a signal to recruit more phagocytes from the blood (Sompayrac, 2008**).** In spite of this fact, macrophages can carry out many duties that are discussed below briefly.

Phagocytosis

Even though one of the major functions of phagocytosis is to mediate the ingestion and sterilization of infectious agents, many pathogens such as *Salmonella typhimurium* (Finlay and Cossart , 1997) , *Legionella pneumophila* (Shuman and Horwitz, 1996; Vogel, *et al.*, 1998) , and *Mycobacterium tuberculosis* (Ernst, 1998) have evolved mechanisms for survival and even growth inside macrophage vacuoles. Once again, phagocytosis of bacteria involves a large variety of heterogeneous mechanisms.

The neutrophil, in general, is a more efficient phagocyte, except when the particle is large in relation to the cell or when the particle load is great. Under these circumstances, mononuclear phagocytes (Aderem and Underhill, 1999) are more effective than neutrophils. Whenever there is microbial attachment to the surface of macrophage cell, phagocytosis process will be started. After adherence of the microbe to the surface of the macrophage through recognition of pathogen associated molecular patterns, the resulting signal initiates the ingestion phase by activating an actin-myosin contractile system which extends pseudopods around the particle as adjacent receptors sequentially attach to the surface of the microbe, the plasma membrane is pulled around the particle just like a 'zipper' until it is completely enclosed in a vacuole (phagosome). Events are now moving smartly and the cytoplasmic granules fuse with the phagosome (Fig. 5) and discharge their contents around the imprisoned microorganism which is subject to a formidable battery of microbicidal mechanisms (Roitt and Delves, 2001).

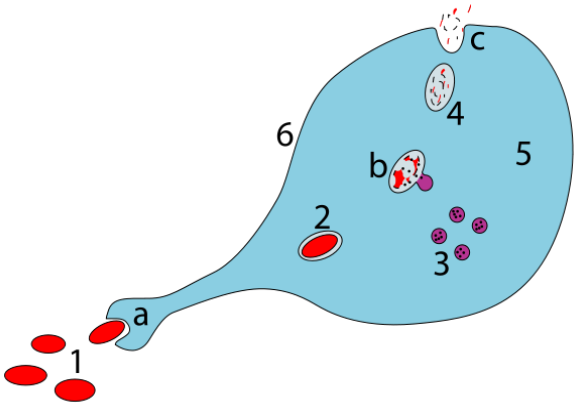

Figure 5: Schematic representation of phagocytosis.

Steps of macrophage ingesting a pathogen

a. Ingestion through hphagocytosis a phagosome is for med.
b. Thefusionof lysosomes with the phagosome creates a phagolysosome; the pathogen is broken down by enzymes.
c. Waste material is expelled or assimilated (the latter not pictured).

Parts

1. Pathogens
2. Phagosome
3. Lysosomes
4. Waste material
5. Cytoplasm
6. Cell membrane.

Source: (From Wikipedia, the free encyclopedia).

Phagocytosis of microorganisms such as bacteria can be enhanced by binding of antibodies, complement factors (mainly C3b), or blood plasma proteins, which are also collectively termed opsonins. These endogenous proteins cover a pathogen and thereby make it "visible" for sentinel cells. Macrophages elicit receptors specific to the Fc part of IgG, termed FcRγ which binds, antibody bound bacteria to the macrophage surface. IgG is the only antibody doing this. However, the first antibody produced in response to antigen is IgM, and IgM bound bacteria cann't bound macrophage due to the absence of FcRμ receptor on the macrophage. So what guarantee the body to be protected from a first time infection? There are two possibilities for C3b. It can either go to the

complement cascade or bind to bacteria (for complement opsonization). Therefore, complement opsonization guaranties efficient removal of bacteria during early stages of infection, before IgG is produced.

With the antigen coated in these molecules, binding of the antigen to the phagocyte is greatly enhanced. In fact, most phagocytic binding cannot occur without opsonization of the antigen. (http://en.wikipedia.org/wiki/Opsonin), Accessed on March 15/ 2013.

Oxygen-Dependent Killing Mechanisms

Activated phagocytes produce a number of reactive oxygen intermediates (ROIs) and reactive nitrogen intermediates that have potent antimicrobial activity. When a phagocyte ingests bacteria (or any material), its oxygen consumption increases. The increase in oxygen consumption, called a respiratory burst, produces reactive oxygen-containing molecules that are anti-microbial (Dahlgren and Karlsson, 1999). The antimicrobial natures of these oxygen compounds are not only toxic to the invader but also to the cell itself, so they are kept in compartments inside the cell. This method of killing invading microbes by using the reactive oxygen-containing molecules is referred to as oxygen-dependent intracellular killing, of which there are two types (Fang, 2004).

The first type is the oxygen-dependent production of a superoxide, which is an oxygen-rich bacteria-killing substance. The superoxide is converted to hydrogen peroxide and singlet oxygen by an enzyme called superoxide dismutase. Superoxides also react with the hydrogen peroxide to produce hydroxyl radicals which assist in killing the invading microbe **(**Mayer, 2006).

The second type involves the use of the enzyme myeloperoxidase from macrophage granules. When granules fuse with a phagosome, myeloperoxidase is released into the phagolysosome, and this enzyme uses hydrogen peroxide and chlorine to create hypochlorite, a substance used in domestic bleach. Hypochlorite is extremely toxic to bacteria (Mayer, 2006). Myeloperoxidase contains a heme pigment, which accounts for the green color of secretions rich in macrophage, such as pus and infected sputum.

Oxygen-Independent Killing Mechanisms

This nonoxydative method of killing mechanism happens both at intracellular and extracellular level.

Intracellular: Phagocytes and hence macrophages can also kill microbes by oxygen-independent methods, but these are not as effective as the oxygen-dependent ones. There are four main types. The first uses electrically charged proteins that damage the bacterium's membrane. The second type uses lysozymes; these enzymes break down the bacterial cell wall. The third type uses lactoferrins, which are present in macrophage granules and remove essential iron from bacteria **(**Hoffbrand *et al*., 2005). The fourth type uses proteases and hydrolytic enzymes; these enzymes are used to digest the proteins of destroyed bacteria (Delves *et al.*, 2006).

Extracellular: Interferon-gamma, which was once called macrophage activating factor, stimulates macrophages to produce nitric oxide. The source of interferon-gamma can be $CD4^+$ T cells, $CD8^+$ T cells, natural killer cells, B cells, natural killer T cells, monocytes, macrophages, or dendritic cells (Schroder *et al*., 2004). Nitric oxide is then released from the macrophage and, because of its toxicity, kills microbes near the macrophage. Activated macrophages produce and secrete tumor necrosis factor. This cytokine, a class of signaling molecule, kills cancer cells and kills cells infected by viruses, and helps to activate the other cells of the immune system (Sompayrac, 2008).

Macrophage's secretory products and their functions

Over 100 substances have been reported to be secreted by mononuclear phagocytes whose biological activity ranging from induction of cell growth to cell death (Nathan, 1987).

Macrophages secrete a variety of biologically active substances into their local milieu, including proteins, lipids, nucleotide metabolites, and oxygen metabolites. Macrophage-derived products are probably important in the local environment, and they are believed to be important in the physiological and pathological functions of macrophages in inflammation, tissue repair, lipoprotein metabolism, acute phase response, and in microbicidal, antiviral, tumoricidal, and immunoregulatory activities. (http://ajpcell.physiology.org/content/246/1/C1.abstract): Accessed on March 22/2013.

However, macrophages may not be the sole source for the secretion of some of these products. The secretion of these products is intricately regulated developmentally and environmentally.

On the whole secretions of macrophages can be enzymes (lysozyme, protease, collagenase and elastases), cytokines (IL-1, IL-6, IL-12 and TNF-α) and/or other products (prostanoids, complement components, fibronectins, clotting factors) (Tizard, 1996).

Enzymes

Lysozyme mediates digestion of the cell walls of some bacteria and is a well-documented secretory product of macrophages (Gordon, 2002).

Cytokines

Macrophages are known to produce IFN-γ in response to viruses, bacteria and tumor or foreign cells (Pestka *et al*., 1987). The biological actions of IFN-γ include antiviral and antimitotic effects, up-regulation of MHC class II expression and an increase in natural killer (NK) cell

activity. Following stimulation by LPS or IL-1, cells of the monocyte/macrophage series produce M-CSF, GM-CSF and G-CSF (Metcalf, 1987). M-CSF induces the formation of monocyte precursor colonies and also induces production of Prostaglandin Endoperoxide 2, plasminogen activator, IL-1, IFN-gamma and TNF-α. GM-CSF induces the formation of granulocyte, eosinophil and monocyte colonies, is involved in radioprotection of marrow, fighting bacterial and parasitic infections by enhancing eosinophil and neutrophil function, and influences IL-1 and TNF production. G-CSF promotes the formation of granulocyte colonies, the terminal differentiation of myeloid cells and enhances mature neutrophil function.

Macrophages are also capable of secreting a number of the more recently described cytokines including IL-12 (Sinigaglia *et al*., 1999), IL-15 (Carson and Caligiuri, 1998) and IL-18 (Akira, 2000). IL-12 is required for the development of Th1 cells (Sinigaglia *et al.*, 1999), which are important for the cell-mediated immune responses against a variety of intracellular pathogens.

Antigen Processing and Presentation

Antigen processing and presentation are processes that occur within a cell that result in fragmentation (proteolysis) of proteins association of the fragments with MHC molecule and expression of the peptide-MHC molecule at the surface where they can be recognized by the T-cell receptor on a T cell. However, the path leading to the associations protein fragments with MHC molecule differ for class I and class II MHC. MHC class I molecules present degradation of products derived from intracellular (endogenous) proteins in the cytosol. MHC II molecules present fragments derived from exogenous proteins that are located in an intracellular compartment(Mayer, 2010).

Antigen Processing And Presentation in Cells Expressing Class I MHC

All nucleated cells express class I MHC. As shown in figure 6, proteins are fragmented in the cytosol by proteosomes (a complex of proteins having proteolytic activity) or by other proteases. The fragments are then transported across the membrane of the endoplasmic reticulum by transporter proteins. The transporter proteins and some components of the proteosome have their genes in the MHC complex. Synthesis and assembly of class I heavy chain and $beta_2$ microglobulin occurs in the endoplasmic reticulum. Within the endoplasmic reticulum, the MHC class I heavy chain, $beta_2$ microglobulin and peptide form a stable complex that is transported to the cell surface (Mayer, 2010).

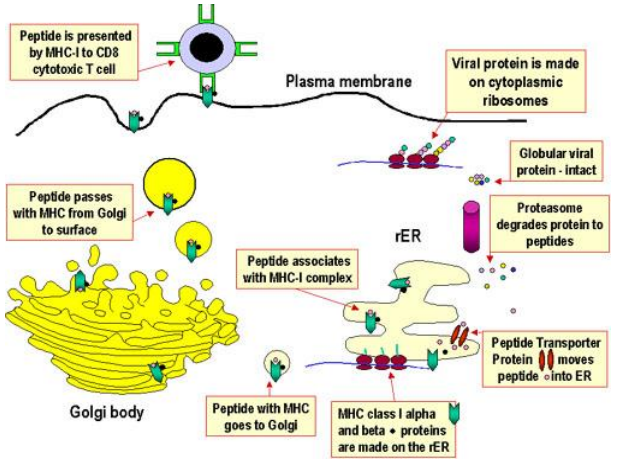

Figure 6: Pathway of class I MHC restricted presentation of an endogenously synthesized antigen. An example of such an antigen would be a viral protein made in the cell as a result of infection.
Key: rER=rough endoplasmic reticulum.

Antigen Processing and Presentation in Cells Expressing Class II MHC

Whereas all nucleated cells express class I MHC, only a limited group of cells express class II MHC, which includes the antigen presenting cells (APC). The principal APC are macrophages, dendritic cells (Langerhans cells), and B cells, and the expression of class II MHC molecules is either constitutive or inducible, especially by interferon-gamma in the case of macrophages (Mayer, 2010).

As shown in figure 7 below, exogenous proteins taken in by endocytosis are fragmented by proteases in an endosome. The alpha and beta chains of MHC class II, along with an invariant chain, are synthesized, assembled in the endoplasmic reticulum, and transported through the Golgi and trans-Golgi apparatus to reach the endosome, where the invariant chain is digested, and the peptide fragments from the exogenous protein are able to associate with the class II MHC molecules, which are finally transported to the cell surface (Mayer, 2010).

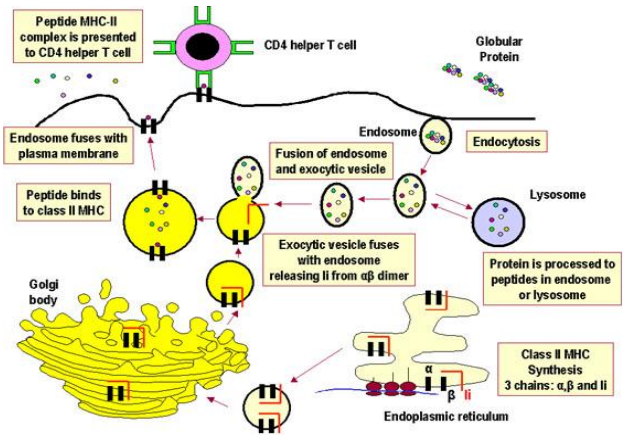

Figure 7: Pathway of class II MHC-restricted presentation of an exogenous antigen.
Key: Ii=invariant chain.

In general here are the most important aspects of antigen processing and presentation phenomenon.

One way of rationalizing the development of two different pathways is that each ultimately stimulates the population of T cells that is most effective in eliminating that type of antigen.

Viruses replicate within nucleated cells in the cytosol and produce endogenous antigens that can associate with class I MHC. By killing these infected cells, cytolytic T cells help to control the spread of the virus (Mayer, 2010).

Bacteria mainly reside and replicate extracellularly. By being taken up and fragmented inside cells as exogenous antigens that can associate with class II MHC molecules, helper Th2 T cells can be activated to assist B cells to make antibody against bacteria, which limits the growth of these organisms (Mayer, 2010).

Some bacteria grow intracellularly inside the vesicles of cells like macrophages. Inflammatory Th1 T cells help to activate macrophages to kill the intracellular bacteria (Mayer, 2010). Fragments of self, as well as non-self, proteins associate with MHC molecules of both classes and are expressed at the cell surface. Which protein fragments bind is a function of the chemical nature of the groove for that specific MHC molecule (Mayer, 2010).

Tumor Cell Destruction

Tumor cells are destroyed by tumor necrosis factor (TNF) which is released from macrophages. Tumor associated macrophages (TAMs) are alternatively activated macrophages that enhance tumor progression and growth by promoting tumor cell invasion, migration and angiogenesis. TAMs have an anti-inflammatory function. The interaction between TAMs and cancer cells may enhance the tumor cell phagocytosis, tumor cell lysis and tumoricidal activity of TAMs by inducing expression or translocation of GM-CSF, *migration inhibitory factor* and other cytokines, or other unknown mechanisms. Macrophages have been shown to infiltrate a number of tumors. Their number correlates with poor prognosis in certain cancers including cancers of breast, cervix, bladder and brain (Bingel *et al*., 2002).

Attracted to oxygen-starved (hypoxic) and necrotic tumor cells macrophages promote chronic inflammation. Inflammatory compounds such as TNF-α released by the macrophages activate the gene switch nuclear factor-kappa B which then enters the nucleus of a tumor cell and turns on production of proteins that stop apoptosis and promote cell proliferation and inflammation (Gary, 2007).

Inhibition of Tumor Cell Division

Inhibition of tumor cell division may occur by mediators secreted by macrophages which act on all proliferating cells present. These mediators are largely uncharacterized, but include prostaglandins, IL-1 and TNF. This inhibition is not thought to require cell contact and occurs rapidly (Steplewski *et al*., 1983).

Macrophage-Mediated Tumor Cytotoxicity

Macrophage-mediated tumor cytotoxicity (MTC) is a contact-dependent, non-phagocytic process which occurs very slowly over 1–3 days. It is selective for neoplastic cells and is independent of antibody production. After recognition of the neoplastic cells, the binding of macrophages occurs which is followed by the secretion of toxic substances, that result in the eventual lysis of the bound tumor cells. TNF and a novel serine protease are the major candidates for the toxic mediators. ROIs can probably potentiate MTC (Adams and Hamilton, 1988).

Antibody-Dependent Cellular Cytotoxicity

Antibody-dependent cellular cytotoxicity (ADCC) is a process whereby macrophages are able to lyse antibody-coated tumor cells (Adams and Hamilton, 1988, 1984). The classical form of ADCC by macrophages is rapid and mediated by polyclonal antisera. The mechanisms whereby the tumor suppresses the antitumor activity of the macrophage are of great interest and probably involve both regulatory T cells and substances derived from tumor cells themselves. As well as macrophages exerting some control over tumor cells, some tumor cells can interfere with mononuclear phagocyte function. Reduced monocyte chemotaxis and phagocytosis are well recognized in subjects with malignant disease (Sokol and Hudson, 1983).

Wound Healing

The tissue macrophage has been shown to play a critical role in the wound healing process. Macrophages are essential phagocytes within the wound, and are responsible for the removal of apoptotic and dying cells. While recruitment of macrophages to the wound is important, the subsequent activation of macrophages is also critical to their function in mediating wound repair. Many mediators and environmental factors within the wound influence macrophage phenotype and activation status. One obvious circumstance that affects macrophages in wounds is hypoxia. Hypoxic conditions, such as those within wounds, induce changes in macrophage phenotype and protein expression (Knighton *et al*., 1983; Lewis *et al*., 1999). Macrophages are well adapted to survive under hypoxic conditions, and indeed have been shown to exhibit enhanced secretory activity under such circumstances. So the exposure of macrophages to hypoxic conditions leads to enhanced expression of specific growth factors and cytokines that may be important in the reparative process. Macrophages are thus, following neutrophil, rapidly present in wounds after injury, where they can synthesize and secrete collagenase and elastase, helping to debride the wound.

CONCLUSION AND RECOMMENDATIONS

In this review a concise coverage has been assessed on both the biology and the miscellaneous role of

macrophages. As to the biology of macrophages; the origin and development, heterogeneity, structure, and activation of macrophages has been dealt with. Macrophages being involved both in specific and non-specific immunity do have a diverse meaning, having located throughout the body and positioned at a strategic sites in the body of individuals. The macrophage remains the most frequently studied and consequently best understood phagocyte of apoptotic cells. Macrophages having possessed surface receptors and significant secretory products can accomplish assorted responsibility starting from phagocytosis to destruction of cancer cells. The interaction between tumor progression and innate immune system has been well established. Indeed, several lines of clinical evidence indicate that immune cells such as tumor-associated macrophages (TAMs) interact with tumor cells. In most tumors, TAMs show properties of an alternative polarization phenotype characterized by the expression of a series of chemokines, cytokines, and proteases that promote immunosuppression, tumor proliferation, and spreading of the cancer cells. Tumor suppressor genes have been traditionally linked to the regulation of cancer progression; however, a growing body of evidence indicates that these genes also play essential roles in the regulation of innate immunity pathways through molecular mechanisms that are still poorly understood.

Even though macrophages are efficient at killing most invaders and removing debris, they do have crystal-clear limitations such as they are slow at killing bacteria and untidy eaters.

Based on the above conclusion the following recommendations are forwarded.

- Further study is needed to clarify the interaction network of cancer cells and TAMs.
- A thorough study on the factors (e.g. GM-CSF, and M-CSF) that regulate the differentiation and function of macrophage should be conducted because they remain largely unknown.

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