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Mononuclear phagocytes: Physiology and functional abnormalities

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Mononuclear phagocytes (blood monocytes and tissue macrophages) constitute a critically important component of the immune system and of the body's capacity to resist infection. These cells are distributed throughout the body in the "mononuclear phagocyte system" (formerly termed the "reticuloendothelial system"). Mononuclear phagocytes are probably essential for life, since a complete deficiency of cells of this lineage apparently has not been reported in a healthy individual. This presentation describes certain aspects of mononuclear phagocyte function, especially as related to host defense against infection. This subject has recently been reviewed in more detail [4].

Physiology

The macrophage cell line originates in the bone marrow as a common committed progenitor cell for the granulocyte and monocyte-macrophage pathways [4, 14]. Glycoprotein hormones termed colony-stimulating factors induce differentiation of this cell into a monoblast, which differentiates into a promonocyte, then a monocyte.

Newly formed monocytes can remain in the marrow for up to a day, but there is no marrow reserve like that for granulocytes. Human monocytes circulating in the bloodstream have been found to have a half-life of approximately 3 days. It is not clear whether humans have a pool of marginating monocytes (adherent to the endothelium of blood vessels), as they do a pool of marginating neutrophils.

Migration of monocytes into the different tissues appears to be a random phenomenon in the absence of localized inflammation. Once in the tissues, monocytes undergo transformation into tissue macrophages with morphologic and sometimes functional properties that are characteristic for the tissue in which they reside [14]. The life span of individual macrophages in human tissues is believed to be months, but precise data are not available. An estimate of life span has been obtained by studying patients receiving a bone marrow transplant after the ablation of their own marrow. The recipients' tissue macrophages were replaced by donor macrophages after approximately 3 months [4].

The terminal stage of development in the mononuclear-phagocyte line is the multinucleated giant cell. Macrophages appear to be the precursors to the multinucleated cells. The function of the multinucleated giant cell has not been clear. Monocytes kept in culture for 3 to 10 days develop the general features of tissue macrophages, and some of them are fused into large multinucleated cells [9]. Comparative studies of the two cell types indicate that giant cells can phagocytose opsonized erythrocytes through Fc or C3 receptors and that they can phagocytose and kill candida as effectively as do macrophages (Table I). The production of superoxide anion, the expression of membrane Ia antigen, and the content of certain hydrolytic enzymes also appear comparable in macrophages and giant cells under similar conditions [9].

Macrophage Activation

The most important step in the maturation of macrophages from the standpoint of host defense is the lymphokine-driven conversion of the normal, or resident, cell to the "activated macrophage". By definition, activated macrophages have increased microbicidal activity against a variety of organisms [5, 10]. These cells also express a large number of morphologic, functional, and metabolic differences between them and resident cells

Table I

Comparison of Functional and Antigenic Characteristics of Macrophages and Multinucleated Giant Cells (MGC)*

Characteristic	Macrophages	MGC
	% of cells that were phagocytic+	
Phagocytosis of:		
IgG-coated red cells	79±3 (8)	67±6
C3-coated red cells	41±8 (5)	45±8
Candida albicans	89±6 (7)	88±8
	% of ingested fungi killed	
Killing of *Candida albicans*	21±5 (6)	24±4
	% of cells positive	
Production of superoxide		
No stimulus	11±3 (12)	13±3
Phorbol myristate acetate (PMA)	67±5 (12)	70±5
PMA + superoxide dismutase	12±5 (6)	12±4
	% of cells positive	
Presence of HLA-Dr (Ia) antigen	75±5 (4)	74±2

* Studies were performed on the two cell types present within the same culture dishes. The values represent mean ± SEM; the number in parentheses in the macrophage column indicates the number of experiments performed.

+ The percentage of cells that ingested at least one particle is shown. (Data from reference 9, with permission)

TABLE II

Functional Modification of Activated Macrophages*

microbicidal activity (↑)
tumoricidal activity (↑)
chemotaxis (↑)
phagocytosis (varies with particle)
pinocytosis (↑)
glucose transport and metabolism (↑)
respiratory burst (↑)
antigen presentation (↑)

* ↑ indicates that the activity is increased in activated macrophages. This list is based primarily on studies with macrophages from animals and humans infected with intracellular parasites; in some cases, the findings have been confirmed by the addition of interferon gamma in vitro. (Adapted from reference 4)

[1, 3, 4, 10]. Activated macrophages are bigger and display pronounced ruffling of the plasma membrane, an increased capacity for adherence and spreading on surfaces, increased formation of pseudopods, and increased numbers of pinocytic vesicles, as well as the functional differences described in Table II.

Macrophage activation is accomplished during infection through the release of macrophage-activating lymphokines from T lymphocytes specifically sensitized to antigens from the infecting organism [4]. This interaction constitutes the basis of cell-mediated immunity. Interferon gamma appears to be an especially important macrophage-activating lymphokine, and granulocyte-macrophage colony-stimulating factor (GM-CSF) is a second such lymphokine. Activation and accompanying enhanced resistance to infection have been achieved in animals by injection of interferon gamma or the adjuvant muramyl dipeptide, a small peptide sugar derived from the cell wall of bacteria (reviewed in reference 4). These and similar findings have supported the possibility that macrophage activation may be induced as a means of treating patients with intracellular infection or cancer.

A large amount of published experimental data has indicated that macrophages are important in the specific immune response [13]. Macrophages are believed to process antigen and present it in a more reactive form to lymphocytes and to serve as accessory (supportive) cells in the replication of lymphocytes. Evidence that macrophage activation leads to more effective antigen presentation is summarized in Table III and reviewed in references 4 and 13.

The heightened capacity of activated macrophages to synthesize and release a variety of hydrolytic enzy-

TABLE III

Evidence that Antigen Presentation is Increased in Activated Macrophages

1. Activated macrophages have increased expression of Ia antigen.
2. Macrophage antigen presentation varies directly with the extent of Ia expression.
3. Administration of interferon gamma leads to a marked increase in antibody formation.
4. Activated macrophages release increased amounts of IL-1, which supports B-cell proliferation and antibody formation, as well as T-cell release of lymhokines

TABLE IV

Changes in secreted proteins, lipids and oxygen metabolites in activated macrophages*

lysozyme (NC)
prostaglandins, leukotrienes (↓)
apolipoprotein E and lipoprotein lipase (↓)
elastase (↓)
complement components (↑ or NC)
acid hydrolases (↑)
collagenase (↑)
plasminogen activator (↑)
cytolytic proteinase (↑)
arginase (↑)
fibronectin (↑)
interleukin-1 (↑)
tumor necrosis factor-alpha (↑ when stimulated)
interferon alpha and beta (↑)
angiogenesis factor (↑)
superoxide and hydrogen peroxide (↑ when stimulated)

* Adapted from reference 4.

mes and potentially microbicidal materials (Table IV) probably plays a part in their increased killing capacity, although not every macrophage product is secreted in increased amounts by the activated cell. It is clear that macrophages are extraordinarily active secretory cells, perhaps second only to hepatocytes. Approximately 100 distinct substances have been identified as being secreted by macrophages [7, 12].

ABNORMALITIES OF MONOCYTES AND MACROPHAGES

Monocyte-macrophage function has been shown to be abnormal in a variety of disease states [4]. In most of them, abnormality is only partial

TABLE V

Abnormalities of monocyte-macrophage function

Chemotaxis (monocytes)
Phagocytosis (monocytes)
Bloodstream clearance
Cell-mediated cytotoxicity (monocytes)
Secretion of protective factors (fibronectin, C3, factor B)
Lipid metabolism
Phagocytic killing

and it has not been proved that the partial defect predisposes to infection. Some of the better defined abnormalities are summarized in Table V. Defective chemotaxis of monocytes has been described in newborn infants, diabetes, burns, acquired immune deficiency syndrome (AIDS), and patients treated with corticosteroids or immunosuppresive agents. Defective phagocytosis by monocytes can occur in monocytic leukemia, systemic lupus erythematosus (SLE), or deficiency of the CD11–CD18 complex of plasma membrane glycoproteins. The mononuclear phagocyte system clears the bloodstream of opsonized erythrocytes subnormally in SLE. Monocyte cell-mediated cytotoxicity can be abnormal in some patients with cancer and in children with Wiskott-Aldrich syndrome. Cultured monocytes from newborn infants have defective secretion of fibronectin, C3, and factor B.

The monocyte-macrophage system is prominently involved in several lipidstorage diseases (sphingolipidoses). In these conditions the expression in macrophages of a systemic

enzymatic defect permits the accumulation of cell debris that is normally cleared by macrophages. Resistance to infection can be impaired [11]. The prototype for these disorders is Gaucher's disease, in which there is accumulation of glucocerebroside from cell membranes in "Gaucher cells" throughout the body. In all locations the Gaucher cell is an altered macrophage.

Macrophage killing of microoganisms is primarily (and severely) defective in chronic granulomatous disease, and secondarily depressed in several conditions (Table VI). Lymphocytes from newborns and patients with AIDS or certain persistent intracellular infections, including visceral leishmaniasis, lepromatous leprosy, and tuberculosis, may have a defective release of macrophage-activating factors, especially interferon gamma [2, 4, 8].

In some cases, it appears that macrophage products, particularly prostaglandins, may suppress the release from lymphocytes of interferon gamma. This sort of defect might be treated by administration of interferon gamma to activate the macrophages directly, or by inhibition of the release of macrophage suppressive factors — e.g., by administration of prostaglandin-synthesis inhibitors such as indomethacin [3]. In fact, injection of interferon gamma has been shown to enhance in vitro killing by monocytes from patients with AIDS [6] and to normalize the skin response to *Mycobacterium leprae* in patients with lepromatous leprosy [8].

TABLE VI

Macrophage defects of phagocytic killing

I. Primary: chronic granulomatous disease

II. Secondary:
1. corticosteroid therapy
2. viral infection
3. newborn infancy
4. failure of activation resulting from decreased release of interferon-gamma:

AIDS

newborn infancy

intracellular infections (tuberculosis, leprosy, leishmaniasis)

CONCLUSIONS

Mononuclear phagocytes are perhaps the most versatile of all cell types. Much new understanding has been gained recently about their physiology, and experiments with animals and early clinical trials suggest that this new knowledge will lead to improvements in patient care.

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