

Updates on cells and cytokines

Monocytes

Antonio M. Vignola, MD,^a Marco Gjomarkaj, PhD,^a Bernard Arnoux, PhD,^b and Jean Bousquet, MD^b *Palermo, Italy, and Montpellier, France*

Monocytes migrate from the bone marrow to the inflamed tissue through the peripheral blood system. They are mobilized and recruited from the blood by adhesion to the endothelium followed by transendothelial migration and locomotion to the target tissue after immunologic and/or inflammatory stimuli. In tissues monocytes differentiate and mature into macrophages, the functional cell of the lineage. In some inflammatory diseases such as asthma, monocytes may be in a primed or activated stage, although some studies did not find a difference between asthmatic and normal subjects.

A large number of studies have examined the phenotype, function, and secretion of cells of the monocyte/macrophage lineage. In this article only some of the most recent studies on monocytes will be reviewed. Although macrophages are well known to release fibrogenic growth factors, inducing tissue repair and remodeling, the role of monocytes is unclear. Nitric oxide production by human mononuclear cells will not be examined.

ORIGIN, RECRUITMENT, AND FATE OF MONONUCLEAR CELLS

In adult life the production of monocytes in the bone marrow is controlled by IL-3, granulocyte-macrophage colony-stimulating factor (GM-CSF), and macrophage colony-stimulating factor (M-CSF), which stimulate the production of monocytes, whereas prostaglandin E₂ (PGE₂) and interferon (IFN)- α/β are inhibitory mediators.

Unique combinations of signaling and adhesion molecules regulate the subsets of monocytes that are recruited into tissues. Selectins mediate the initial rolling contacts of monocytes with the endothelium. Firm adhesion of monocytes to the endothelium is the second step and involves other adhesion molecules such as CD11a, CD11b, CD18, and very late antigen (VLA)-4 on monocytes and CD54 (intercellular adhe-

Abbreviations used

G-CSF:	Granulocyte colony-stimulating factor
GM-CSF:	Granulocyte-macrophage colony-stimulating factor
IFN:	Interferon
MCP:	Monocyte chemotactic protein
M-CSF:	Macrophage colony-stimulating factor
MIP:	Macrophage inflammatory protein
NK:	Natural killer
PGE:	Prostaglandin
IL-1RA:	IL-1 receptor antagonist
TNF:	Tumor necrosis factor
VLA:	Very late antigen

sion molecule-1) and vascular cell adhesion molecule-1 on endothelial cells. Monocyte adherence to endothelial cells is modulated by endothelin-1 through the involvement of Src (p60src), JAK1-like kinases, and vascular endothelium growth factor by an increased flt-1 expression by monocytes. The third step is monocyte transmigration into the subendothelial space. However, the relative importance of adhesion molecules is different in the steady state and the inflammation process. L-selectin and CD11b were shown to be important in the recruitment of monocytes into inflammatory sites.¹

Mediators of inflammation such as cytokines and chemoattractants initiate and regulate the recruitment of monocytes. In particular, cysteine-cysteine (CC) chemokines differentially and selectively regulate the expression and avidity of integrins sharing common β -subunits. In particular, they cause a transient and subsequent activation and deactivation of VLA-4 and VLA-5, which may serve to facilitate the transendothelial diapedesis and the interactions with the basement membrane and extracellular matrix.

The capacity to inhibit apoptosis selectively is an important physiologic mechanism for controlling monocyte accumulation in inflammatory lesions. Monocytes can undergo spontaneous apoptosis on leaving the circulation. Monocyte apoptosis can be inhibited by adherence, microbial products, or pro-inflammatory cytokines (e.g., IL-1, tumor necrosis factor- α [TNF- α], and IFN- γ), which inhibit cell apoptosis, whereas T_{H2}-cytokines (e.g., IL-4) enhance cell apoptosis. Interaction of CD40 on monocytes with a CD40 ligand on activated T cells induces monocyte cytokine synthesis and rescues monocytes from

From ^aIstituto di Fisiopatologia Respiratoria, Consiglio Nazionale delle Ricerche, Via Trabucco, Palermo; and ^bClinique des Maladies Respiratoires and INSERM U 454-IFR 3, Hôpital Arnaud de Villeneuve, Montpellier.

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Reprint requests: Jean Bousquet, MD, Hôpital Arnaud de Villeneuve, 34295-Montpellier-Cedex 5, France.

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apoptosis. Genes controlling cell apoptosis (e.g., Bcl-x) may change the pattern of the life span of mature monocytes.

MONOCYTE PHENOTYPE

Blood monocytes show heterogeneity in morphology, cytochemistry, expression of surface markers, and metabolic activity. The population of CD14 monocytes has been divided into two subpopulations according to the expression of surface markers. A minor subpopulation weakly expresses CD14 (CD14⁺), and a major population strongly expresses CD14 (CD14⁺⁺).² Only some cells of the monocyte/macrophage lineage express the CD16 molecule (FcγIII receptor). When blood monocytes are transformed into macrophages, expression of CD14 and CD11b is reduced and CD16 is expressed. CD14⁺ blood monocytes can also differentiate into functionally mature CD83⁺ dendritic cells and may function as antigen-presenting cells. FcγRI (CD64)-negative human monocytes are potent accessory cells in viral antigen-induced T-cell activation and exhibit high IFN-α-producing capacity.

Monocytes bear IgE receptors. The low-affinity IgE receptor (FcεRII or CD23) was demonstrated several years ago on cells of the mononuclear lineage. The expression of CD23 is increased in monocytes obtained from asthmatic subjects, probably because of the stimulatory effect exerted by inflammatory cytokines released in this disease. TNF-α and IL-4 have upregulated CD23 expression and sCD23 release. In some conditions monocytes express the high affinity IgE receptor (FcεRI).³ The role of FcγRI-bearing monocytes remains speculative, but they may remove IgE from the circulation and redirect the immune response from naive B cells.

CYTOKINES AND MONOCYTES

Human monocytes can release a wide range of cytokines such as IL-1, IL-6, IL-8, IL-10,⁴ IL-12,⁵ IL-15, IL-18, colony-stimulating factors, and TNF-α. The release of these cytokines by monocytes can be modulated by different infectious and noninfectious stimuli.

The phenotype and function of monocytes are modulated by several cytokines acting in a paracrine fashion, an autocrine fashion, or both and include IL-2, IL-3, IL-4, IL-7, IL-10, IL-13,⁶ IL-16, colony-stimulating factors,⁷ TNF-α, and IFN-γ. Many cytokines are proinflammatory and modulate monocyte and macrophage functions differently depending on their prior state of activation. On the other hand, IL-4, IL-10, IL-13, and transforming growth factor-β have antiinflammatory effects and inhibit some, but not all, monocyte/macrophage functions.⁸ In asthmatic subjects, IL-4 antiinflammatory effects are reduced as compared with normal subjects.

Two natural antagonists of IL-1 action have been characterized: the IL-1 receptor antagonist (IL-1RA) and a soluble form of the type II IL-1 receptor.

IL-1RA released by monocytes and macrophages acts as a receptor antagonist by binding to the IL-1 receptor. Moreover, IL-1RA suppresses IL-1α, IL-1β, IL-6, and IL-8 production by activated monocytes.⁹ The functional regulation of monocytes by arachidonic acid metabolites (PGE₂ and thromboxane A₂) interferes with cytokine production. Monocyte PGE₂ is increased in patients with atopic dermatitis and reduces the release of IFN-γ by T cells or that of TNF-α by fibroblasts.

IL-10, a pleiotropic cytokine produced by monocytes and T cells, promotes monocyte maturation and differentiation toward CD16⁺ macrophages. IL-10 inhibits the production of IL-6, IL-12, and TNF-α, as well as the IFN-γ-induced intercellular adhesion molecule-1 gene transcription in human monocytes; thus it may play an important immunoregulatory role in the pulmonary immune response. IL-10 inhibits the induced transcription of macrophage inflammatory protein (MIP)-α mRNA and the release of MIP-1α protein, with a greater effect on monocytes as compared with alveolar macrophages. IL-10 causes a fall in the basal level of CD23 expression on blood monocytes, this effect being more evident on IL-4-treated cells. Decreased IL-10 production was observed in neonatal monocytes. Type 4 phosphodiesterase inhibitors reduce IL-10 production by monocytes. Dexamethasone antagonizes IL-4- and IL-10-induced release of IL-1RA by monocytes but augments IL-4-, IL-10-, and transforming growth factor-β-induced suppression of TNF-α release.

IL-12 is produced primarily by antigen-presenting cells, including monocytes, by two pathways: a T-cell-independent pathway induced by bacteria or intracellular parasites involved in the early inflammatory response of innate resistance and a T-cell-dependent pathway induced by the interaction of CD40L on activated T cells with CD40 receptor on IL-12-producing cells, which is important in the regulation of adaptive immunity. IL-12 induces production of cytokines, especially IFN-γ, from both T cells and natural killer (NK) cells; enhances the cytotoxic activity of NK cells and the generation of cytotoxic T cells; and causes an increase in production of T cells and NK cells. Both in vivo and in vitro, IL-12 is a powerful inducer of T_{H1} response, whereas it inhibits T_{H2}-type responses. Corticosteroids inhibit IL-12 production by human monocytes and enhance their capacity to induce IL-4 synthesis in CD4⁺ lymphocytes.

Human monocytes can also be modulated by IL-13, another so-called antiinflammatory cytokine secreted by activated T cells, with a potent regulator effect on B-cell functions. IL-13 inhibits the production of MIP-1α, as well as that of inflammatory cytokines, cytokine inhibitors, and PGE₂. A novel action of IL-13 has been observed. It induces diminished monocyte glucocorticoid receptor-binding affinity and may contribute to impaired glucocorticoid responsiveness during inflammatory disease.

The ability of monocytes to modulate the function of T lymphocytes also depends on the release of IL-15, which has an effect similar to that of IL-2.

At least four distinct colony-stimulating factors have been identified, GM-CSF, M-CSF, granulocyte colony-stimulating factor (G-CSF), and IL-3.⁷ Cells of the monocyte-macrophage lineage produce M-CSF, G-CSF, and GM-CSF in response to various cytokines and stimuli by modulation of gene expression. Multiple cis-acting sequence motifs cooperate with one another to produce patterns of expression that are relatively unique to individual genes. GM-CSF increases the capacity of alveolar macrophages but not blood monocytes to generate eicosanoids. In vivo administration of GM-CSF primes peripheral blood monocytes to an increased release of cytokines (e.g., TNF- α and IL-1 β) or superoxide production.

Thus monocytes can produce a complex repertoire of cytokines; are regulated by cytokines; and can actively participate in the pathogenesis of infection and several inflammatory diseases (e.g., psoriasis, asthma, Crohn's disease, systemic sclerosis, and atherosclerosis). The three cytokines (IL-12, IL-10, and IFN- γ) have important and cross-regulatory roles in infection.¹⁰ IL-12 is rapidly produced after infection and acts as a proinflammatory cytokine eliciting the production, by T cells and NK cells, of IFN- γ , which activates phagocytic cells. If IL-12 and IL-12-induced IFN- γ are present during early T-cell expansion in response to antigen, T_{H1} cell generation is favored, and the generation of T_{H2} cells is inhibited. IL-12 promotes T_{H1} differentiation and is instrumental in the resistance to infection. Viruses inducing a permanent or transient immunodepression (e.g., HIV and measles) may act, in part, by suppressing IL-12 production.

CHEMOKINES PRODUCED BY MONOCYTES

Chemokines, together with adhesion molecules, cytokines, and proteases, are essential for the directional migration of leukocytes during normal and inflammatory processes.¹¹ Chemokines also play important roles in hematopoiesis, cellular activation, and leukocyte effector functions. Unlike the classic leukocyte chemoattractants, which have little specificity, members of the chemokine family induce recruitment of well-defined leukocyte subsets. More than 20 human chemokines have been identified. There are two major subfamilies based upon the position of cysteine residues: CXC and CC.¹² As a general rule, with some notable exceptions, only CC chemokines are chemotactic for monocytes.

Several monocyte chemotactic protein (MCP) families have been identified and cloned. MCP-1, MCP-2, and MCP-3 are also major attractants for CD4⁺ and CD8⁺ T cells. MCPs can act as autocrine factors. Chemokines of the MCP families are produced by almost all the cells in the body and may play a significant role in several inflammatory processes (in

both immunopathologic disorders such as atherosclerosis, psoriasis, and chronic inflammatory diseases of the liver and lungs and the normal immune response against microorganisms). Eosinophils are a source of MCP-1, indicating that these cells play a regulatory role within the allergic inflammatory cell network. Interestingly, the induction of epithelial cell MCP-1 is blocked by dexamethasone, a corticosteroid usually used in the treatment of many lung-based inflammatory diseases.

RANTES is produced by macrophages, endothelial cells, epithelial cells, fibroblasts, and T lymphocytes. Although the data regarding the role of RANTES in monocyte recruitment in vivo are limited, there is significant evidence that RANTES might be an important monocyte-macrophage chemotaxin during infection. RANTES production by human monocytes can be regulated differently according to the cytokine used. In particular, while IFN- γ and TNF- α cooperate to induce RANTES production by monocytes, N-acetylcysteine inhibits this effect, indicating that reactive oxygen intermediates are required for RANTES production. In addition, both IL-10 and corticosteroids antagonize the stimulating effect of IFN- γ and TNF- α on RANTES production. In contrast, IL-4 has no effect on IFN- γ -induced RANTES production. In fact, it potentiates the positive effect of TNF- α on this production, suggesting that the deactivating properties of IL-10 and corticosteroids on macrophage functions include RANTES production. This may contribute to the immunosuppressive effect of both compounds in immune reactions.

MIP-1 α is one of the major inducible cytokines secreted by mononuclear phagocytes with a potent chemotactic effect on monocytes, lymphocytes, and eosinophils. Corticosteroids, PGE₂, IL-10, and IL-13 inhibit its production, but monocytes and macrophages present differential sensitivities to these agents. MIP-1 α levels are increased in the bronchoalveolar lavage fluid of patients with bronchial asthma and interstitial pulmonary fibrosis. Alveolar macrophages, interstitial macrophages, and fibroblasts isolated from patients with interstitial pulmonary fibrosis actively produce MIP-1 α in vitro.

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