The Pathophysiologic Role of Monocytes and Macrophages in Systemic Lupus Erythematosus: A Reappraisal

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Objectives: To review current developments, regarding the pathophysiologic role of monocytes and macrophages in systemic lupus erythematosus (SLE).

Methods: We searched Medline for articles written in the English language using the following terms: monocyte(s) or macrophage(s) and lupus. Although our search spanned the years 1971 to 2008, the majority of the short-listed articles belonged to the period 2000 to 2008. Published literature on phenotypic and functional properties of monocytes/macrophages (Mo/Mφ) in SLE was reviewed. References from identified articles were also selected. Currently available experimental data and their relevance to the pathogenesis of SLE are critically discussed.

Results: It has traditionally been held that impaired phagocytosis by monocytes and macrophages in SLE allows for the accumulation of apoptotic debris leading to a sequel of autoimmune phenomena. Recent paradigms derived from animal models of systemic autoimmunity, however, has broadened our understanding regarding the possible pathophysiologic roles of Mo/Mφ in SLE. Data derived from studies in patients with SLE show multiple aberrations in activation status and secretory functions of circulating and tissue-infiltrating Mo/Mφ. Such aberrations may be associated with dysregulation of T-cell function and autoantibody production in SLE. Moreover, emerging evidence suggests that phagocytic capacity and antigen-presenting properties of Mo/Mφ are enhanced in some patients with SLE.

Conclusions: While defective phagocytosis represents a distinctive feature of monocyte function in some patients with SLE, aberrant activation of the Mo/Mφ system may be a more appropriate concept to encompass the broad spectrum of Mo/Mφ disorders in SLE. Aberrant function of lupus Mo/Mφ appears to play a dynamic role in the initiation and perpetuation of the systemic autoimmune response and organ damage. Delineation of the altered biology of lupus Mo/Mφ could provide possible future therapeutic targets for patients with SLE.

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Monocytes/macrophages (Mo/Mφ) are versatile cells aiming to defend, regulate inflammation, and induce immunity. Monocytes develop from pluripotent stem cells in the bone marrow under the influence of specific growth factors. Following the differentiation process that lasts less than 24 hours, mature monocytes leave the bone marrow and enter the bloodstream as quiescent cells. Circulating monocytes differentiate further into resident tissue macrophages and acquire specialized phenotypes and functions depending on the local microenvironment. Furthermore, blood monocytes are recruited to sites of inflammation where they become activated and evolve into cells that express the macrophage phenotype (1). Experimental evidence suggests that monocytes differentiate also into dendritic cells (DCs) in vivo (2,3).

The hallmark function of the Mo/Mφ system is phagocytosis and subsequent antigen presentation (1). Mo/Mφ recognize and remove pathogens as well as

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senescent, dead, or damaged host cells. Phagocytosis is a triggered process requiring the activation of receptors, which in turn transmit signals to the cell interior to initiate the response. Following digestion of the target, Mo/Mφ present target-derived antigen(s) to relevant T-cells, resulting in helper and/or effector T-cell functions. Consequently, Mo/Mφ possess a central role in initiating the immune response. In addition, Mo/Mφ have well-developed secretory functions and are an important source for a variety of cytokines, whereas more than 100 biologically active substances have been described as Mo/Mφ products. Cytokine receptors found on the surface membrane of Mo/Mφ allow them to become involved in indirect complex interactions with different cell type products. The main characteristics of monocytes are summarized in Figure 1.

Numerous studies have improved our understanding of the diverse components of immune dysregulation in systemic lupus erythematosus (SLE); however, the pathophysiologic role(s) of Mo/Mφ remains unclear (4). Theories formulated in the 1980s propose that lupus Mo/Mφ display defective phagocytic function, thus enabling the aberrant accumulation of apoptotic debris leading to a sequel of autoimmune phenomena. Recent studies, however, exploring mainly lupus nephritis suggest an active role of Mo/Mφ in mediating tissue inflammation and injury (5), broadening our understanding regarding the spectrum of Mo/Mφ aberrant function in SLE.

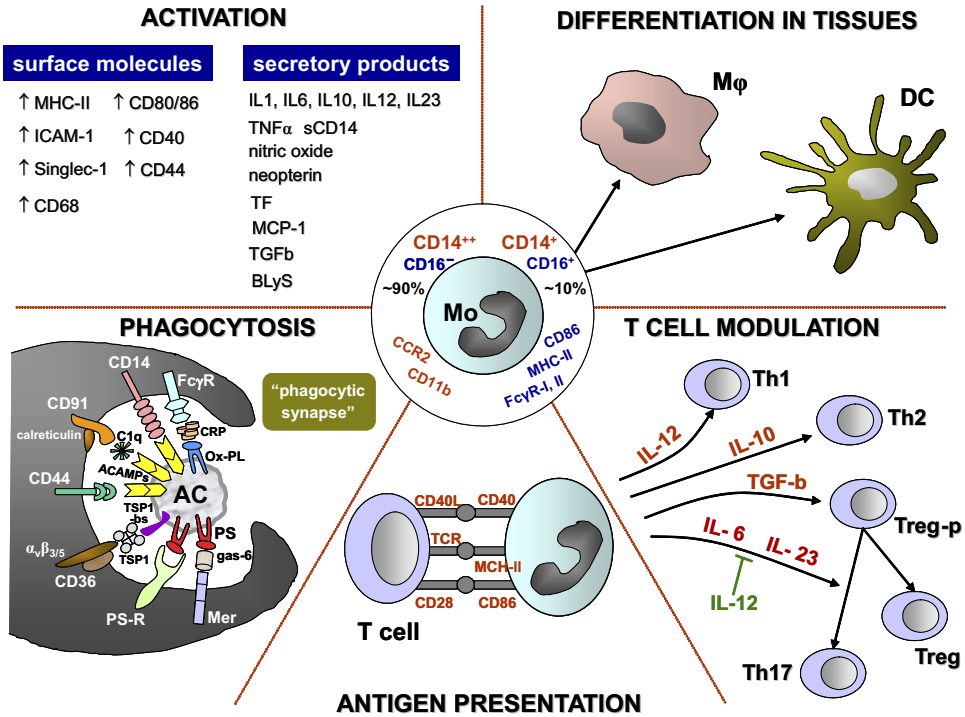

Figure 1 Synopsis of monocytes characteristics. Circulating monocytes are divided into 2 subsets based on the expression of CD14 (LPS receptor) and CD16 (FcγR-III). Approximately 90% of monocytes express high levels of CD14 but not CD16 ($CD14^{2+}/CD16^{-}$) and the remaining 10% express CD16 and lower levels of CD14 ($CD14^{+}/CD16^{+}$). Surface molecules expressed on monocytes present a preferential expression between $CD14^{2+}/CD16^{-}$ (red color) and $CD14^{+}/CD16^{+}$ (blue color) cells indicating distinct functional properties. Because, during infections, $CD14^{+}/CD16^{+}$ monocytes are increased and produce high levels of TNFα and low levels of IL-10, they are also called pro-inflammatory monocytes (central panel). Activation of monocytes results in the upregulation of several surface molecules and the secretion of multiple monokines (upper left panel), which participate in various functions such as chemotaxis (eg, CCR2, MCP-1), adhesion (eg, ICAM-I), coagulation (eg, TF), phagocytosis (lower left panel), antigen presentation and costimulation (lower central panel), modulation of lymphocyte effector functions (lower right panel), and differentiation to macrophages and DCs (upper right panel). In the lower right panel, cytokines enhance (in red) or inhibit (in green) the depicted polarization of Th cells.

Abbreviations: $\alpha_v\beta_{3/5}$, vitronectin receptor integrins; AC, apoptotic cell; ACAMPs, apoptotic cell-associated molecular patterns; BlyS, B-lymphocyte stimulator; C1q, 1st component of complement; CCR2, chemokine (C-C motif) receptor 2; CD40L, CD40 ligand; CRP, C-reactive protein; DC, dendritic cell; FcγR, Fc gamma receptor; gas-6, growth arrest-specific gene-6; ICAM-1, intercellular adhesion molecule 1; IL, interleukin; MCP-1, monocyte chemoattractant protein 1; Mer, myeloid epithelial reproductive tyrosine kinase; mGCR, membrane glucocorticoid receptor; MHC-II, major histocompatibility complex class II; Mo, monocyte(s); Mφ, macrophage(s); Ox-PL, oxidized phospholipids; PS, phosphatidylserine; PS-R, PS-receptor; Siglec-1, sialic acid-binding Ig-like lectin 1; sCD14, soluble CD14; TCR, T-cell receptor; TGFb, transforming growth factor beta; Th, T-helper cell; TF, tissue factor; TNFα, tumor necrosis factor α; Treg, T-regulatory cell; Treg-p, Treg-precursor; TSP-1, thrombospondin-1; TSP1-bs, TSP-1 binding site. (Color version of figure is available online.)

Table 1 Major Aspects of the "Defective Model" of Monocyte Function in SLE

Defect	Selected Ref.	Functional Consequence
Decreased autologous MLR	(7)	Impaired ability to activate T-cells
Decreased accessory function for T-cell activation	(8)	
Decreased of MCH II surface expression	(8)	Inability to process and present antigen and to provide appropriate co-stimulation to lymphocytes
Decreased expression of CD80	(9)	
Decreased production of IL-1b	(10)	
Decreased phagocytosis	(6,77,82,92)	Impaired clearance leading to accumulation of apoptotic cells and immune complexes

MLR: mixed lymphocyte reaction.

As recent advances have improved our understanding of the role of innate immunity in the expression and progression of SLE, we present, in brief, data derived from animal studies regarding the central role of Mo/Mφ in systemic autoimmunity and we discuss several functional aspects of Mo/Mφ in patients with SLE. In interpreting these data we propose that the role of Mo/Mφ in the pathogenesis of SLE should reach beyond the "defective phagocytosis" model and that aberrant activation of Mo/Mφ may be a more appropriate concept underlying the pathophysiologic role of these cells in SLE.

METHODS

We searched Medline for articles written in the English language using the following terms: monocyte(s) or macrophage(s) and lupus. The abstracts were screened for relevance and the publications relating to Mo/Mφ in SLE were obtained. Additional references were identified from the bibliographies of the retrieved reports. Although our search spanned the years 1971 to 2008, the majority of the short-listed articles belonged to the period 2000 to 2008. Published literature on phenotypic and functional properties of Mo/Mφ in SLE was reviewed. Currently available experimental data and their relevance to the pathogenesis of SLE are critically discussed.

RESULTS

The Model of "Defective" Monocyte Function in SLE

Defective clearance represents the hallmark of the model of "defective" monocyte function in SLE (6). Reduced clearance of apoptotic cells led to the hypothesis that uningested apoptotic cells might represent an important source of autoantigens with the potential to trigger an autoimmune process such as the one seen in SLE. Moreover, defective clearance of immune complexes (IC) allowing tissue deposition of IC represents a mechanism by which tissue damage may occur in SLE. Data on phagocytosis and clearance by monocytes from patients with SLE will be discussed in detail below.

Other studies have shown that monocytes from patients with SLE when cultured with autologous T-cells induce a defective proliferative T-cell response (7). Decreased accessory functions for T-cell activation were also described and linked to decreased expression of HLA-DR antigens. Low levels of surface HLA-DR (8) and CD80 (9) expression along with reduced production of interleukin-1 (IL-1) (10) have been linked with a decreased ability of lupus monocytes to process and present antigen as well as to provide appropriate costimulation to T-cells. The major aspects of the model of "defective" monocyte function in SLE are summarized in Table 1.

Lupus Mo/Mφ Beyond the Impaired Phagocytosis Model: Lessons From Animal Models

New insights on the possible mechanisms underlying the role of monocytes in the autoimmune process have emerged from studies in animal models. Tyro3, Axl, and Mer comprise the TAM receptor family of receptor protein tyrosine kinases and are expressed on Mo/Mφ and DC, but not on lymphocytes or granulocytes. The biologic role of these receptors has been recently explored and appears to be essential in immunoregulation. In particular, macrophages from mice lacking the cytoplasmic tail of Mer (c-mer) are characterized by phagocytic deficiency restricted to apoptotic cells. This abnormality leads to anti-dsDNA autoantibody production but without concomitant significant polyclonal B-cell expansion or significant renal pathology (11). Triple Tyro3/Axl/Mer knockout animals developed a lupus-like disease with overt arthritis, skin lesions, and nephritis along with production of multiple autoantibodies; their Mo/Mφ (and DC) display phenotypic and functional features that characterize activated cells (12). Although the expression and function of the Tyro 3 receptor molecules in Mo/Mφ derived from patients with SLE has not been examined, these studies provide paradigms where aberrant activation of Mo/Mφ (triple knockouts) promotes the expression of systemic autoimmune disease, while isolated Mo/Mφ phagocytic deficiency of apoptotic cells (c-mer knockouts) is not adequate to lead to overt disease.

Clearance of apoptotic cells is usually described as noninflammatory phagocytosis where macrophages actively produce anti-inflammatory cytokines such as transforming growth factor-beta (13). Molecules that

participate in macrophage–apoptotic cell interaction have distinct functions. For example, CD14 on the surface of macrophage facilitates the binding of the apoptotic cell but has no effect on the production of anti-inflammatory cytokines. On the contrary, macrophage protein kinase Mer has the potential to mediate an anti-inflammatory signal through its interaction with phosphatidylserine on apoptotic cells via the product of the growth arrest-specific gene, gas6 (13). Loss of either CD14 or Mer results in the accumulation of apoptotic cells. However, only c-Mer knockout mice and not CD14 knockout mice display autoimmune phenomena (11,14), suggesting that in this murine model it is not the mere persistence of apoptotic cells but rather the absence of the macrophage anti-inflammatory response that defines autoantibody production. Therefore, an attractive hypothesis could be that decreased production of anti-inflammatory signals during phagocytosis of apoptotic cells by macrophages may contribute to the initiation of an autoimmune response.

Studies by Levine and coworkers (15, 16, 17) challenge the concept that delayed clearance of apoptotic cells is sufficient to cause autoimmunity. The model of delayed clearance of apoptotic cells assumes that late, but not early, apoptotic cells escape (impaired) phagocytosis, lose their membrane integrity, and act as necrotic cells. Subsequently, such cells are capable of presenting apoptotic antigens in an inflammatory context. In contrast to this model, Levine and coworkers showed that apoptotic cells cannot be distinguished between early and late (appear to be functionally equivalent throughout their existence) irrespective of membrane integrity. Moreover, they showed that either cell-associated material or soluble material recovered from late apoptotic cells was not proinflammatory (15). They proposed that autoimmunity ensues when macrophages "misread" apoptotic cells due to abnormalities in signaling events following their interaction(s) with apoptotic cells. Consistent with this hypothesis, it was shown that macrophages from the major murine models of lupus have an identical abnormality in the expression of multiple cytokines following the encounter with apoptotic cells (16). Among 15 different cytokines examined, increased, decreased, and unaffected expression was documented in a similar manner between the different strains. Affected SLE-prone strains include MRL/+, MRL/lpr, NZB, NZW, NZB/W F1, BXSB, and LG/J, while no similar abnormality in cytokine expression could be found in 16 nonautoimmune strains. Lupus Mo/Mφ from different strains was also shown to share an apoptotic cell-related abnormality of their adhesion properties (17). Mo/Mφ from the major murine models of lupus (MRL/+, MRL/lpr, NZB/WF1, BXSB, LG) but not from 7 nonautoimmune strains, displayed increased adhesion and increased spreading, often assuming a highly elongated dendritic-like morphology. Abnormal apoptotic cell-related abnormalities in adhesion properties by lupus Mo/Mφ were due to reduced activity of Rho, a cytoplasmic G protein and cytoskeletal regulator. Importantly, aberrant regulation of cytokines and Rho activity precede the onset of clinically overt disease. Although the phagocytic capacity of Mo/Mφ was not addressed in these studies, no data support a definite and/or shared defect in the phagocytosis of apoptotic cells by of Mo/Mφ from the major murine models of lupus. Also, it was reported that no intrinsic defect of the phagocytic capacity of peritoneal macrophages was found in premorbid lupus-prone mice (18). On the other hand, the studies by Levine and coworkers suggest that Mo/Mφ from all autoimmune-prone strains have a shared "autoimmune" phenotype triggered by the uptake of apoptotic cells. Aberrations within a broad range of Mo/Mφ functions, including the expression of multiple cytokines and regulation of Rho, may thus be associated with abnormalities in signaling events following their interaction(s) with apoptotic cells.

The view that accumulation of apoptotic cells is adequate to produce circulating DNA and nucleosomes, the main source of autoantigens in SLE, also has been recently challenged by work from Jiang and coworkers (19). In elegant experiments these authors showed that apoptotic cells are not sufficient per se to generate nucleosomes in the absence of macrophages or in the presence of defective macrophages. Dose–response experiments showed a clearly linear and positive correlation between macrophage function and the production of circulating DNA (19). Moreover, analysis of circulating DNA revealed that it originated from both apoptotic cells and macrophages (19). Consequently, at least in this experimental setting, it is not the accumulation of apoptotic cells that leads to nucleosome production but the presence of functional Mo/Mφ.

Deposition of IC on glomeruli is generally thought to contribute to the development of lupus nephritis. It has been proposed that Mo/Mφ allow for the accumulation of IC through impaired FcγR-mediated phagocytosis. Studies in the NZB/WF1 murine model of lupus have shown, however, that deficient function of FcγR (in the absence of γ chain, NZB/WF1 FcR$^{\gamma-/-}$) protects from rather than contributes to the development of nephritis despite the abundance of IC depositions (20,21). Because FcγR are expressed on a variety of cells, including resident mesangial cells, experiments using NZB/WF1 bone marrow chimeras where the expression of γ chain was selectively abrogated in myeloid cells showed that FcγR on circulating myeloid cells, rather than on mesangial cells, are required for IC-mediated pathogenesis in NZB/WF1 mice (21). Moreover, lineage-specific transgenic reconstitution of FcγR in Mo/Mφ partially restored the ability to develop nephritis in FcR$^{\gamma-/-}$ mice (21). These studies show that IC deposition is not adequate to trigger the development of nephritis in the mice examined. They also propose that direct activation of circulating FcR-

bearing myeloid cells, including Mo/Mφ, by glomerular IC deposits is required for lupus nephritis.

Studies by Reeves and coworkers showed that experimental lupus induced by 2,6,10,14-tetramethylpentadecane (TMPD) is associated with excess interferon (IFN)-I production and upregulation of INF-I–stimulated genes (ISGs), a phenomenon termed "IFN signature" (22). TMPD-induced lupus is at present the only murine model of lupus reported to have the "IFN signature," a molecular phenomenon frequently found in patients with SLE (23). IFN-I signaling is critically required in this model as shown by the absence of lupus autoantibodies and kidney disease in IFN-I receptor α-chain-deficient (IFNAR–/–) mice (24). The source of INF-I in the TMPD murine model of lupus was a subset of monocytes (Ly6C^{high} monocytes) (25). Upregulation of IFN-I and ISGs occurred long before the clinical manifestations of lupus and coincided with an accumulation of Ly6C^{high} monocytes, which expressed large amounts of IFN-I. Depletion of Ly6C^{high} monocytes abolished the increased levels of INF-I and the upregulation of ISGs. On the contrary, systemic depletion of DCs did not alter IFN-I production triggered by TMPD. Although other factors such as IL-12 and INFγ may be important as well, INF-I production by monocytes appear to be the critical event for the development of the disease in the TMPD model of lupus (25) (Table 2).

Activation Status of Mo/Mφ From Patients with SLE

Histological data deriving from patients with lupus nephritis demonstrate that activated Mo/Mφ vigorously participate in renal inflammation and injury. Renal pathology in lupus nephritis is characterized by infiltrating Mo/Mφ bearing the activation markers CD68 (26,27), CD16 (FcγRIII) (28), and sialoadhesin (Siglec-1, CD169) (29). Also, cDNA microarray analysis of gene expression in glomeruli from patients with proliferative lupus nephritis revealed increased expression of myeloid lineage transcripts, characteristic of those found in isolated activated macrophages (30). Expression of myeloid-related protein-8 (MRP-8), MRP-14, and MRP-8/MRP-14 complexes, which indicates pro-inflammatory macrophage activity, is increased in infiltrating macrophages in the glomeruli in lupus nephritis (31). In addition, macrophage infiltrates in lupus nephritis contain high numbers of proliferating cells. Local proliferation of macrophages has been proposed as an important mechanism for amplifying renal injury (26), while the extent of glomerular and tubular infiltration by activated Mo/Mφ critically influences the outcome of lupus nephritis (32,33). Accordingly, monocyte numbers in the urine (28,34) and urinary monocyte chemoattractant protein 1 concentrations (35) have been proposed as useful markers for monitoring the activity of lupus nephritis. Increased

Table 2 Mo/Mφ Abnormalities and Clinical Outcome in Animal Models of Autoimmunity

Mice	Monocytes/Macrophages		Associated Outcome	Select Ref.
	Molecular Abnormality	Functional Properties		
c-mer$^{-/-}$	Absence of c-Mer kinase only in Mφ	↓ Phagocytosis of apoptotic cells only	Autoantibody production No polyclonal B-cell activation No clinical disease	(11)
Tyro/Axl/c-mer triple mutants	Inactive Tyro/Axl/c-Mer kinases in Mφ	Activated Mφ	Production of multiple autoantibodies Marked lymphoproliferation Marked T- and B-cell activation Arthritis Skin lesions IgG deposits in glomerulus Thrombosis/hemorrhages	(12)
MRL/lpr MRL+ NZBWF1 LG BXSB	Reduced activity of the cytoplasmic protein Rho	"Misreading" of apoptotic cells displayed as cytokine dysregulation, increased adhesiveness, and DC-like morphology	Lupus-like disease	(16,17)
NZB/WF1 FcRγ$^{-/-}$	Absence of γ chain	N/A	Abundance of IC kidney depositions No nephritis	(20,21)
TMPD model	N/A	Increased production of type I INF	Lupus-like disease	(25)

Mo, monocyte(s); Mφ, macrophage(s); TMPD, tetramethylpentadecane; N/A, not available.

expression of cyclogenase-2 (COX-2) in macrophages infiltrating the kidneys has been documented in patients with active lupus nephritis but not in nonlupus nephropathies, suggesting a disease-specific abnormality (27). Because monocytes derived form the peripheral blood of SLE patients with active nephritis also express increased amounts of COX-2 (27), COX-2 upregulation in infiltrating macrophages may represent a primary rather than a local secondary event during renal inflammation in lupus nephritis.

Enhanced activation status of lupus Mo/Mφ may not be restricted only to inflammatory lesions in afflicted tissues such as the kidney. A validated marker of monocyte activation in humans is the serum and/or urinary concentration of neopterin. Serum levels of neopterin, a pyrazino-pyrimidine compound produced in large amounts by macrophages following stimulation, have been found increased in patients with SLE compared with healthy individuals and correlate with disease activity (36). Soluble CD14, another surrogate activation marker of the Mo/Mφ system, is also persistently elevated in the sera of patients with SLE (37,38). Furthermore, surface molecules upregulated on activated monocytes such as intercellular adhesion molecule 1 and membrane glucocorticoid receptor are overexpressed on monocytes from patients with SLE (39,40), whereas subsets of activated monocytes defined by the $CD14^+CD16^+$ and the $CD14^+CD11b^+$ phenotypes are expanded in the periphery (41,42). Tissue factor upregulation, another feature of monocyte activation, is enhanced in monocytes from patients with SLE (43). The activation marker Siglec-1 was recently found increased in peripheral blood monocytes from patients with SLE (44). Furthermore, unmanipulated peripheral blood monocytes from patients with SLE overproduce nitric oxide (NO), an additional typical marker of monocyte activation (45).

Increased Production of NO by Lupus Monocytes: Implications for T-cell Function

In contrast to lupus monocytes, which spontaneously produce increased amounts of NO, lupus T and B lymphocytes, as well as cells defined by the absence of CD14 or CD3 surface markers, produce normal levels of NO (45). NO is a key signal of mitochondrial hyperpolarization (MHP) that initiates mitochondrial biogenesis through enlargement and proliferation of mitochondria (46). Furthermore, NO mediates CD3/CD28 costimulation-induced MHP and cytosolic Ca^{2+} concentration in T-cells.

T-cells from patients with SLE display persistent MHP and increased mitochondrial mass, as well as increased and sustained concentrations of intracellular Ca^{2+} following stimulation (45,47). Interestingly, both increased MHP and aberrant Ca^{2+} kinetics encountered in SLE T-cells were reproduced in normal T-cells when cocultured with monocytes from patients with SLE. Although additional factors, such as soluble mediators and/or cell–cell contact could account for this effect, it was shown that pretreatment of purified normal T-cells with NO altered CD3/CD28 costimulation-induced Ca^{2+} signaling, mimicking the pattern observed in lupus T-cells. Therefore, excess production of NO by activated lupus monocytes may contribute to abnormalities that characterize lupus T-cells (48).

Aberrant Cytokine Production by Lupus Mo/Mφ: Implications for Autoantibody Production

Normal Mo/Mφ produce increased amounts of IL-12p70 following activation, along with the induction of NO production. It is of interest that although monocytes from patients with SLE secrete large quantities of NO (45), production of IL-12p70 is decreased (49). On the other hand, these same cells produce excessive amounts of IL-10 (50,51), a cytokine that has been implicated in the pathogenesis of SLE, and IL-12p70 concentrations in stimulated lupus monocytes culture supernatants correlate inversely with IL-10 concentrations. The addition of neutralizing anti-IL-10 antibodies increases the in vitro production of IL-12p70, suggesting that impaired production of IL-12p70 may result from the increased production of IL-10 (52). In control subjects, however, anti-IL-10 antibodies had no effect on monocytes IL-12p70 production, indicating an altered/defective responsiveness of lupus monocytes to IL-10 (52). Monocytes also contribute to the increased production of IL-6 (53) found in the sera and tissues from patients with SLE. Since the production of IL-6 by normal monocytes is downregulated in the presence of IL-10, this further points to an altered secretory function of monocytes in SLE (54).

Indirect evidence suggests that deregulation of IL-10, IL-6, and IL-12p70 production by lupus monocytes contributes to the development of pathogenic autoantibodies. Addition of recombinant IL-10 in peripheral blood mononuclear cells (PBMC) cultures from patients with SLE induces immunoglobulin production. Moreover, anti-IL-10 monoclonal antibodies strongly inhibits the production of anti-dsDNA autoantibodies in mice with severe combined immunodeficiency injected with PBMC from patients with SLE (55). It should be noted that B-cells from patients with SLE also overproduce IL-10. On the other hand, IL-10 produced from monocytes but not from B-cells contributes in estradiol-2-mediated anti-dsDNA Ab production in human SLE (56). Testosterone on the contrary reduces anti-dsDNA production by PBMCs from patients with SLE, which is partly due to the inhibition of IL-6 production by lupus monocytes (57). Addition of exogenous IL-12p70 to lymphocytes derived from lupus patients reduced spontaneous polyclonal IgG production by B-cells, as well as the number of anti-dsDNA-secreting cells. This

effect was directly mediated by IL-12p70 and not by IFN-γ upregulation or IL-10 downregulation (58). It could be therefore postulated that low IL-12p70 production by lupus monocytes may facilitate the opposite effects, ie, increased production of polyclonal IgG and anti-dsDNA autoantibodies. In addition, monocytes are the main producers of BlyS, a cytokine critical for the survival and function of B-cells that has been recently implicated in the development of SLE (59).

B-cell hyperactivity and autoantibody production in SLE may also mirror defective regulation by regulatory T-cells (Tregs). A delicate balance of cytokines promotes the differentiation of naive CD4+ T-cells into Th1, Th2, and either polarized autoreactive Th17 cells or autoimmunity-suppressing Treg cells (60) (Fig. 1). Because the absence of IL-12p70 leads to increased numbers of autoreactive IL-17-producing T-helper cells, while the presence of IL-12p70 inhibits IL-17 production (61), a plausible hypothesis to be explored could be that IL-12p70 deficiency in lupus monocytes contributes to the decreased function of Tregs documented in some patients with SLE (62,63). Interestingly, Yan and coworkers demonstrated that Tregs from patients with SLE display impaired function only in the presence of autologous antigen-presenting cells (64). Although the study did not address which particular cell type(s) suppress the function of Tregs, lupus monocytes represent probable candidates.

Antigen-presenting Capacity of Lupus Monocytes

Despite the clear in vitro experimental evidence on the potential of monocytes to differentiate into DCs, it is a matter of controversy whether this process occurs under physiological conditions in vivo. When skin injections of *Leishmania major* were administered to mice, it was shown that only monocyte-derived DCs presented parasite antigens to T-cells (65) in the lymph nodes. Thus, there are data supporting the idea that monocytes differentiate to DCs comprising a significant part of the DC network (2,3). On the other hand, DCs but not Mo/Mφ are capable of priming naive lymphocytes in healthy individuals, as shown by naive allogeneic CD4+ T-cell proliferation in mixed lymphocyte reaction (allo-MLR) experiments.

Surprisingly, monocytes derived from patients with SLE but not from healthy- or disease-control individuals were able to induce strong allo-MLR (66) responses resembling those induced by DC. Addition of lupus sera to normal monocytes resulted in enhanced allo-MLR, while normal monocytes also acquired the phenotype of DC. The serum factor responsible for this in vitro effect was identified to be IFNα (66). It can be thus postulated that under the influence of circulating IFNα, lupus monocytes may acquire DC functions, ie, induce activation of naive T-cells and stimulate B-cell growth and differentiation in vivo.

A substantial body of evidence supports that INF type I plays an important role in the pathogenesis of SLE (23). Early studies reported increased serum levels of IFN-I in lupus patients that correlate with disease activity. Long-term INF-I treatment of patients with chronic viral infections and cancer can lead to the development of SLE manifestations. Microarray studies have shown that ISGs in PBMC from patients with SLE are upregulated. Upregulation of ISGs correlates with active disease, presence of certain autoantibodies, and an increased incidence of renal involvement. Biesen and coworkers have recently identified Siglec-1 expression on monocytes as a new biomarker for an activated type I IFN system in patients with SLE (44). Moreover, Junt and coworkers showed that Siglec-1-positive macrophages in lymph nodes facilitate the recognition of particulate antigens by follicular B-cells and initiate humoral immune responses (67). Interestingly, the frequencies of Siglec-1-positive monocytes from patients with SLE strongly correlate with serum titers of anti-dsDNA autoantibodies (44). Monocytes from patients with SLE also express high levels of interferon-induced protein with tetratricopeptide repeats 4 that positively correlate with the presence of autoantibodies. Interferon-induced protein with tetratricopeptide repeats 4 was shown to promote monocyte differentiation to DCs in terms of morphology, phenotype, and function (68).

Apart from the influence of serum factors, lupus monocytes may have an intrinsic propensity to differentiate into DC, since stimulation of lupus and normal monocytes results in altered patterns of differentiation under similar experimental settings (42,69,70). For example, when the differentiation process takes place in the absence of serum (69) or in the presence of IL-10 (42), only lupus and not normal monocytes differentiate into preactivated DC. Increased expression of HLA-DR, CD9, CD69, CD80, CD151, tetraspanin, and the FN1 MHC class II epitope on lupus monocyte-derived DC (42) suggest that these cells may have an enhanced capability for antigen presentation. It is therefore conceivable that apart from external signals, lupus monocytes may also display an intrinsically altered biology leading to an enhanced capacity to differentiate to preactivated DC under certain conditions.

Interactions between CD40 and CD40L costimulatory molecules are critical for antigen-presenting cell/T-cell crosstalk. Circulating monocytes from patients with SLE display increased surface expression of CD40 (71) and CD40L ex vivo, both at baseline and following LPS stimulation (72,73). Because CD40 and CD40L expression is enhanced following monocyte activation and during maturation to macrophages, spontaneous upregulation of these molecules on lupus monocytes reflects either an activated condition or an altered differentiation status and indicates an increased costimulatory potential.

Phagocytic Capacity of Lupus Monocytes

The "Phagocytic Synapse"

During phagocytosis, phagocyte membrane receptors, target cell-associated ligands, and intermediate molecules cooperate forming the "phagocytic synapse" (74). Receptors recognized on phagocytes include the molecules CD14 (lipopolysaccharide receptor), complement receptors, CD36 (thrombospondin receptor), c-mer, CD44, and phosphatidylserine receptor. Among structures described on target cells that provide an "eat me" signal, phosphatidylserine, a phospholipid normally confined to the inner part of the membrane lipid bilayer, has been studied in greater detail. An increasingly wide variety of intermediate serum factors has been described, whose role is to opsonize target cells creating molecular bridges between components of the target-cell and phagocyte surfaces. For example, C1q links the target-cell surface with the phagocyte receptor complex CD91/calreticulin (Fig. 1). Abnormalities in any part of the "phagocytic synapse" can result in abnormal phagocytosis and clearance.

In Vitro Studies

Several in vitro studies spanning more than 3 decades have documented that lupus monocytes display reduced clearance of different targets (6). It was reported early on that factors in SLE sera cause impaired phagocytosis of yeast cells by both lupus and normal macrophages (75). A subsequent study reported that the major underlying mechanism for this effect involved mainly complement and not Fc-mediated phagocytosis (76). In this study, though, lupus serum did not inhibit phagocytosis by normal monocytes. Moreover, levels of DNA, C3, and C4 as well as C1q-binding activity in lupus sera did not correlate with the observed defect. It was proposed that the central mechanism of impaired phagocytosis in SLE involves intrinsic abnormalities of complement receptors function in lupus monocytes (76).

Fc-mediated phagocytic capacity of lupus monocytes was also examined using IgG-sensitized erythrocytes. Interestingly, despite enhanced binding to the Fc receptors, lupus monocytes failed to adequately phagocytose their targets. The authors thus proposed that dissociation of receptor-ligand binding and receptor-mediated internalization may contribute significantly to the clearance defect in SLE (77). Indeed, while impaired Fc-mediated phagocytosis by lupus monocytes has been correlated with decreased expression of FcγRII and III on the surface of peripheral blood lupus monocytes (78), other studies suggest that impaired phagocytosis is not due to the amount or the membrane motility of these receptors but rather to a defect during internalization of the target (79).

Of greater interest regarding possible mechanisms involved in tolerance breakdown in SLE, reduced clearance was furthermore documented when the target was apoptotic cells. Studies showing impaired clearance of apoptotic cells have implicated all parts of the "phagocytic synapse." In particular, reduced uptake of apoptotic neutrophils by monocytes was attributed to serum factors (80) or to impaired ability of the apoptotic neutrophils to be recognized, ie, to provide an adequate "eat me" signal (81), while low CD44 expression on the surface of lupus monocytes has also been implicated (82). Defective clearance was also demonstrated using autologous apoptotic lymphocytes and was shown to reflect phagocyte dysfunction and not abnormal execution of apoptosis (83). Similarly, a recent study employing an appropriate flow cytometry assay showed that while lupus monocytes binding capacity to apoptotic cells remains intact, their ability to engulf apoptotic cells was impaired, indicating an intrinsic cellular defect (84). On the other hand, uptake of apoptotic Jurkat T-cells by lupus monocyte-derived macrophages was intact when studied in normal serum but was significantly decreased in the presence of lupus serum and was paralleled with decreased levels of C1q, C3, and C4 (85).

Overall, in vitro studies unanimously show a clearance defect during phagocytosis in SLE. The underlying cause, however, is reported to stem from diverse abnormalities, and the intrinsic ability of macrophages to engulf their targets was found reduced in some studies or normal in others. Different results may indeed reflect different pathophysiologic mechanisms in different patients with SLE, a disease characterized by heterogeneity. Of interest, though, and relevant to the interpretation of in vitro data on phagocytosis are the findings of a recent study where it was shown that the ability to internalize apoptotic cells is dependent on contact of macrophages to other macrophages, a phenomenon termed "community effect" (86). Shoshan and coworkers demonstrated that in both healthy controls and patients with SLE, decreased macrophage density impairs the ability of individual macrophages to phagocytose. During maturation of lupus monocytes into macrophages accelerated apoptosis was observed, which resulted in lower density of macrophages in cell suspensions and reduced the ability to internalize apoptotic cells. Maintaining normal density restored the phagocytic capacity of macrophages from patients with SLE (86). Therefore macrophage density in in vitro cultures may represent a critical factor when evaluating phagocytic capacity of Mo/Mφ in SLE.

In Vivo Studies: Does the Concept of Anti-Inflammatory Phagocytosis Always Apply in SLE?

Defective clearance in in vitro experiments may not reliably depict what happens in vivo. In a scavenger receptor class A knockout mouse model, scavenger receptor class A deficient macrophages are compromised in their capacity to engulf apoptotic thymocytes in vitro. However, no persistence of apoptotic cells was apparent in the thymus, even following induction of massive apoptosis by irradia-

tion, suggesting that the phagocytic capacity of macrophages remained intact in vivo (87).

Early studies examined the half-life of radiolabeled IgG-coated erythrocytes in the blood as a measure of Fc receptor function in vivo (88,89). Half-lives were found prolonged in patients with SLE and correlated with increased levels of IC. It was thus proposed that defective Fc-receptor function might lead to the prolonged circulation of IC, thereby contributing to tissue deposition and damage. Delayed clearance of erythrocytes was shown to parallel reduced expression of FcγR II and III (78). In addition, certain FcγR polymorphisms appear to favor defective phagocytosis/clearance of immune complexes (90,91), which have also been linked with an increased risk for the development of SLE in some ethnic groups (90).

Only recently, data have emerged regarding defective phagocytosis of apoptotic cells in patients with SLE in vivo. The elegant work by Herrmann and coworkers showed that while some patients with SLE display increased accumulation of apoptotic cells in the germinal centers of their lymph nodes, the number of tingible body macrophages, which usually contain engulfed apoptotic nuclei, was significantly reduced. In addition, apoptotic material was observed to be directly associated with the surfaces of follicular dendritic cells that could potentially provide survival signals for autoreactive B-cells (92).

Another study has recently proposed a different role for macrophages during the clearance of apoptotic cells in SLE (93). Clearance of apoptotic cells is usually an anti-inflammatory process, which elicits only a marginal immune response. Patients with SLE and normal controls were subjected to minimal irradiation with UBV light to induce production of apoptotic material. Subsequently, biopsies of the irradiated skin from both groups were analyzed in parallel with biopsies obtained from cutaneous lupus erythematosus (CLE) lesions. The clearance rate of apoptotic cells after irradiation was similar in patients with SLE and controls, but the influx of macrophages in dermal and epidermal layers was significantly increased in patients with SLE. Furthermore, in some patients with SLE a dermal infiltrate developed that was associated with an increased epidermal influx of T-cells and macrophages but not with an increased number of

Table 3 Summary of Data Pointing to Aberrant Mo/Mφ Activation and Function in SLE

	Ref.
Activated Mo/Mφ determine renal inflammation and injury in lupus nephritis	
—Infiltrating Mo/Mφ:	
↑ Expression of activation markers (CD86, CD16, Siglec-1, MRP-8 and 14, COX-2)	(26-31)
↑ Proliferation rate	(32-33)
—The extend of infiltration is prognostic	(26)
—Activated Mφ in lupus nephritis may have disease-specific features (↑ COX-2)	(27)
—Parallel ↑ of COX-2 in peripheral blood Mo and infiltrating Mφ suggests that Mo/Mφ activation is a primary rather than a secondary event during renal inflammation	(27)
Elevated markers of Mo activation in the periphery	
—↑ Serum levels of neopterin and sCD14	(36-38)
—Spontaneous expression of the activation-induced molecules ICAM-1 and mGCR	(39,40)
—Expansion of CD14+/CD11+ and CD14+/CD16+ Mo subsets	(41,42)
—↑ Production of TF	(43)
—↑ Expression of Siglec-1	(44)
—↑ Production of NO	(45)
Deregulation of cytokine production	
—↑ Production of IL-10	(50,51)
—↑ » of IL-6	(53)
—↓ » of IL-12p70	(49)
Aberrant lupus Mo secretory functions promote abnormal lymphocytes functions	
—↑ Production of NO ⇒ ↑ MHP and aberrant [Ca^{++}] kinetics in T-cells	(45)
—↑ » of IL-10 and IL-6 ⇒ anti-dsDNA Ab production by B-cells	(55-57)
—↓ » of IL-12p70 ⇒ lack of inhibition of anti-dsDNA Ab production	(58)
Lupus Mo as competent antigen-presenting cells	
—Peripheral blood Mo stimulate strong allo-MLR	(66)
—↑ Expression of CD40	(71)
—↑ » of CD40L	(72,73)
Inflammatory phagocytosis by lupus Mo/Mφ	
—Increased influx of Mo, increased phagocytosis with inflammatory infiltrates in skin biopsies	(93)

Mo, monocyte(s); Mφ, macrophage(s); MRP, myeloid related protein; COX, cyclooxygenase; sCD14, soluble CD14; ICAM-, intercellular adhesion molecule; mGCR, membrane glucocorticoid receptor; TNFα, tumor necrosis factor α; IL, interleukin; TF, tissue factor; Siglec, sialic acid-binding Ig-like lectin; NO, nitric oxide; MHP, mitochondrial hyperpolarization; [Ca^{++}], calcium concentration; MRL, mixed lymphocyte reaction.

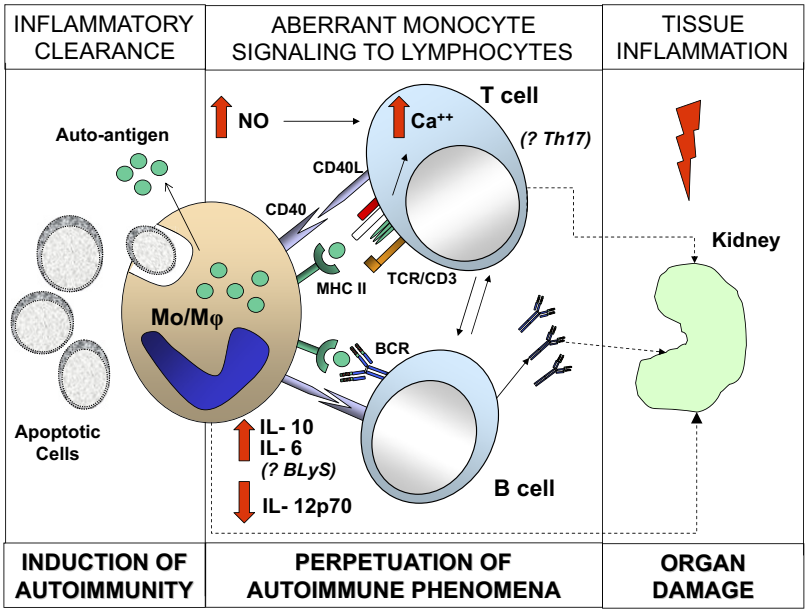

Figure 2 Simplistic scheme of a putative role of Mo/Mφ in the pathogenesis of SLE. Mo/Mφ from patients with SLE may participate in the pathogenesis of the disease at several levels. Mo/Mφ "misread" apoptotic cells and induce phagocytosis in an inflammatory context leading to the inappropriate presentation of autoantigens and the initiation of autoimmunity. Enhanced antigen presenting capacity and abnormal secretory functions provide abnormal signals to autoreactive T- and B-cells facilitating the perpetuation of the autoimmune phenomena. Finally, aberrantly activated Mo/Mφ instigate tissue inflammation and organ damage.
Abbreviations: BCR, B-cell receptor; BlyS, B-lymphocyte stimulator; Ca^{2+}, intracellular calcium concentrations; CD40L, CD40 ligand; IL-, interleukin; MCH-II, major histocompatibility complex class II; Mo/Mφ, monocyte(s)/macrophage(s); NO, nitric oxide; TCR, T-cell receptor. (Color version of figure is available online.)

apoptotic cells or epidermal deposition of immunoglobulins. Some lesional lupus macrophages displayed ingestion of multiple apoptotic bodies, a process not previously described. Inflammatory lesions in these patients were localized near accumulations of apoptotic keratinocytes, as was also evident in nonirradiated CLE skin lesions. Such inflammatory lesions in the vicinity of apoptotic cells suggest not only that anti-inflammatory phagocytosis may be inadequate but also that an inflammatory clearance of apoptotic cells takes place both in UVB-induced and in CLE skin lesions in SLE patients. This study supports the hypothesis that "inflammatory" phagocytosis of apoptotic cells, ie, in the relative absence of protective anti-inflammatory signals by Mo/Mφ, may play a role in the development of SLE.

DISCUSSION

It has traditionally been held that lupus Mo/Mφ are defective. The model of "defective" function supports the idea that lupus Mo/Mφ, either overwhelmed by their environment or because of intrinsic defects, become powerless cells unable to perform their physiologic tasks contributing in this way to disease expression (Table 1). While defective function of Mo/Mφ is encountered in some patients with SLE, emerging experimental data in murine models (Table 2) and humans with SLE (Table 3) support the notion that aberrant activation of the Mo/Mφ system could also lead to the expression of the disease. Altered functions of these cells may play a dynamic role not only in the initiation of autoimmunity through abnormalities in phagocytosis, but also in the perpetuation of the disease through abnormal signals such as increased costimulation of autoreactive T- and B-cells and in tissue damage (Fig. 2). Silencing or removing these "aggressive" cells that injure the kidney, skin, and perhaps other organs may represent a future treatment strategy in patients with SLE. In a small series of patients, selective removal of monocytes (and granulocytes) from the blood using an extracorporeal circulation system was recently applied (94) and led to clinical improvement of the disease. Better characterization of Mo/Mφ functions in SLE could provide further insight into the pathogenetic mechanisms of the disease and broaden our horizon toward new therapeutic approaches.

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