

# Monocyte and Macrophage Abnormalities in Systemic Lupus Erythematosus

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**Abstract** Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with profound effects on multiple organ systems. In patients with SLE, the immune system is subverted to target numerous self antigens and the ensuing inflammatory response elicits a vicious cycle of immune-cell activation and tissue damage. Both genetic and environmental factors are essential for the development of this debilitating condition, although the exact cause remains unclear. Early studies on the pathogenesis of lupus centered on the adaptive immune system as lymphocyte abnormalities were thought to be the primary cause of autoimmunity. In the past decade, however, this paradigm has shifted with rapid advances in the field of innate immunity. These developments have yielded important insights into how the autoimmune response in SLE is initiated and maintained. Monocytes and macrophages are an essential arm of the innate immune system with a multitude of immunological functions, including antigen presentation, phagocytosis, and cytokine production. Aberrations of monocyte/macrophage phenotype and function are increasingly recognized in SLE and animal models of the disease. In this review we summarize the current knowledge of monocyte/macrophage abnormalities in human SLE and discuss their implications for understanding the pathogenesis of lupus.

**Keywords** Systemic lupus erythematosus · Monocytes · Macrophages

## Abbreviations

|        |                                        |
|--------|----------------------------------------|
| SLE    | Systemic lupus erythematosus           |
| DC     | Dendritic cell                         |
| PAMPs  | Pathogen-associated molecular patterns |
| TLR    | Toll-like receptor                     |
| MHC    | Major histocompatibility complex       |
| FcγR   | Fc gamma receptor                      |
| ICAM-1 | Intercellular adhesion molecule-1      |
| IFN-1  | Type-1 interferon                      |
| ISG    | Interferon-stimulated gene             |
| Th     | T helper                               |
| BLyS   | B lymphocyte stimulator                |
| RA     | Rheumatoid arthritis                   |
| HSC    | Hematopoietic stem cell                |

## Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disorder characterized by autoantibody production and chronic inflammation targeting multiple organs (Reeves et al. 2004). In healthy individuals, the immune system defends against microbes by distinguishing self from foreign antigens. For reasons not completely understood, immune tolerance is breached in SLE and the immune system actively responds to a wide array of autoantigens (Hanh 2005). The resulting immune-cell activation leads to autoantibody production and establishes a vicious cycle of chronic inflammation and tissue destruction.

Although the etiology of SLE remains unknown, early studies focused on the adaptive immune system as primary

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abnormalities of B and T lymphocyte functions were considered the likely basis of the disease (Hanh 2005). This paradigm has shifted with recent advances in the field of innate immunity. It is now increasingly recognized that components of the innate immune system, which normally function to detect invasion by microbial pathogens, play an essential role in the recognition of self antigens in SLE (Marshak-Rothstein 2006; Theofilopoulos et al. 2005).

Monocytes are a key component of the innate immune system involved in the regulation of the adaptive immune response (Unanue 1978). These bone marrow-derived myeloid cells and their derivatives, including tissue macrophages, Kupffer cells, and conventional dendritic cells (DCs), are equipped with an arsenal of conserved innate sensors designed to recognize pathogen-associated molecular patterns (PAMPs) (Takeda et al. 2003). Activation of these receptors leads to the production of a wide spectrum of cytokines and chemokines. This capacity of monocytes to initiate inflammation and recruit other immune cells is coupled to their ability to present antigens in the context of products of the major histocompatibility complex (MHC), making them an important link between the innate and adaptive immune systems. Monocytes also serve as direct precursors to tissue macrophages found in almost every organ in the body (Gordon and Taylor 2005). Tissue macrophages can be further divided into different subsets based on their specialized functions in immune regulation and wound healing (Mosser and Edwards 2008). Importantly, both monocytes and tissue macrophages also possess potent phagocytic activity essential for the clearance of dead or dying cells, cellular debris, microbes, and other foreign material (Aderem and Underhill 1999). Current knowledge in these areas is summarized in several excellent reviews of monocyte biology (Auffray et al. 2009; Gordon and Taylor 2005; Grage-Griebenow et al. 2001a, b; Mosser and Edwards 2008).

Abnormalities in monocyte phenotype and function have been associated with a variety of autoimmune disorders, including SLE (Katsiari et al. 2010). While animal models have significantly enhanced our understanding of monocyte/macrophage involvement in lupus, this review will mainly focus on findings in human SLE. We will briefly review the classification of monocyte subsets and the current understanding of monocyte defects associated with human SLE, including abnormalities in (1) surface marker expression, (2) phagocytosis of cellular debris, and (3) cytokine production.

## Monocyte Subsets and SLE

The heterogeneity of human peripheral blood monocytes has been known for decades and early studies distinguished

subsets of regular monocytes and intermediate monocytes based on phenotypic and functional characteristics (Akiyama et al. 1983; Grage-Griebenow et al. 2001a, b). Regular monocytes were defined by their larger size, significant peroxidase activity, and enhanced capacity to mediate antibody-dependent cellular cytotoxicity (Figdor et al. 1982; Grage-Griebenow et al. 2001a, b). The intermediate monocyte subset, on the other hand, possesses a greater ability to secrete inflammatory cytokines (Akiyama et al. 1983).

Subsequently it was found that human monocyte subsets can also be distinguished based on the surface expression of CD14 and CD16 (Passlick et al. 1989). A population that expresses high levels of CD14, but not CD16, accounts for the majority of circulating monocytes (Ziegler-Heitbrock et al. 1988; Ziegler-Heitbrock 1996). These CD14<sup>+</sup>CD16<sup>−</sup> monocytes express the chemokine receptor CCR2 and may correspond to the Ly6C<sup>hi</sup> inflammatory monocyte subset in mice (Passlick et al. 1989). However, unlike their murine counterparts, CD14<sup>+</sup>CD16<sup>−</sup> monocytes do not seem to be the predominant cytokine-producing monocyte subset in humans. A small population of circulating monocytes with strong surface expression of CD16, on the other hand, is responsible for the inducible production of inflammatory cytokines upon stimulation (Grage-Griebenow et al. 2001a, b). Based on the prominent surface expression of CX<sub>3</sub>CR1 (fractalkine/CX<sub>3</sub>CL1 receptor), CD14<sup>+</sup>CD16<sup>+</sup> monocytes are thought to be the human equivalent of the Ly6C<sup>lo</sup> residential monocytes in mice (Passlick et al. 1989). A third subset of human monocytes, characterized as CD14<sup>dim</sup>CD16<sup>+</sup>, has also been described, although its functional significance is less clear (Skrzeczynska-Moncznik et al. 2008).

The homeostasis of monocyte subsets is often altered in various disease states. In patients with rheumatoid arthritis (RA), an increased number of CD14<sup>+</sup>CD16<sup>+</sup> monocytes correlates with elevated erythrocyte sedimentation rate and serum C-reactive protein levels (Kawanaka et al. 2002; Wijngaarden et al. 2003). In addition, expansion of the CD14<sup>+</sup>CD16<sup>+</sup> monocyte population is described in patients with coronary artery disease and is positively associated with the severity of hypercholesterolemia (Hornung et al. 2002). This population is also expanded in patients with sepsis (Skrzeczynska et al. 2002), inflammatory bowel disease (Hanai et al. 2004), and hemolytic uremic syndrome in children (Berland et al. 2006).

Monocyte subsets have also been examined in SLE, but the findings vary among several studies. Two groups reported that the percentages of CD14<sup>+</sup>CD16<sup>+</sup> monocytes in SLE versus healthy subjects were not significantly different (Asahara et al. 1997; Cairns et al. 2002). In contrast, an expansion of CD14<sup>+</sup>CD16<sup>+</sup> monocytes was reported in another study in which it was shown that steroid treatment

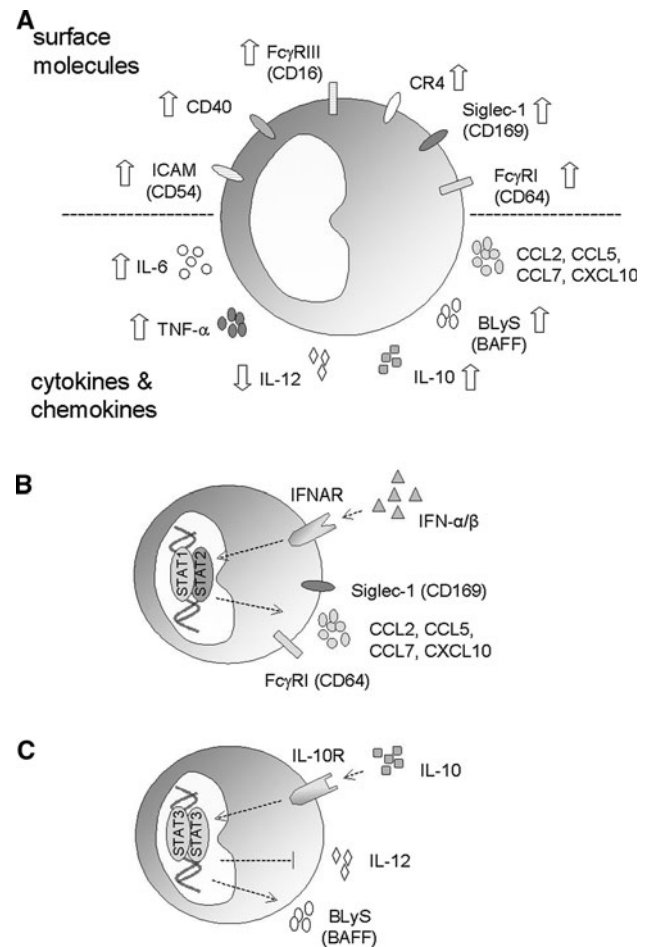
decreased the number of these monocytes in a dose-related manner (Sumegi et al. 2005). In the largest study to date, with 205 SLE patients and 74 normal healthy controls, we recently demonstrated that although the absolute monocyte count is decreased in SLE patients, there is no relative difference in proportion of  $CD14^+CD16^-$ ,  $CD14^+CD16^+$ , or  $CD14^{dim}CD16^+$  monocytes between the groups (Li et al. 2009b, c). Neither the percentage nor the absolute number of monocytes in the different subsets correlates with disease activity or manifestations, however. It remains unclear whether the reduction in total monocyte count in SLE is due to a defect in monocyte development or active recruitment of these cells to sites of inflammation, such as the kidneys. The latter view is supported by increased expression of CX<sub>3</sub>CL1 and accumulation of  $CD16^+$  monocytes in glomeruli of active lupus nephritis, which correlates with impaired renal function and the presence of anti-double-stranded (ds)DNA autoantibodies.

### Aberrant Monocyte Surface Marker Expression

Monocytes express a variety of surface molecules that confer the ability to recognize the environment and respond to changes induced by exogenous as well as endogenous stimuli. Aberrant expression of these surface markers may therefore skew the immune response. A number of abnormalities have been described in monocytes from SLE patients and may contribute to disease pathogenesis (Fig. 1a).

Fc gamma receptors (FcγRs), which are involved in phagocytosis, cytolysis, degranulation, and induction of inflammatory cytokines (Nimmerjahn and Ravetch 2008), are among the surface molecules dysregulated in SLE. The outcome of interactions with immune complexes, which are produced abundantly in SLE, is determined by the balance of activating and inhibitory FcγRs on the cell surface of antigen-presenting cells (APCs) such as monocytes. Deletion of the Fc receptor γ-chain, an essential signaling component of activating FcγRs, is sufficient to inhibit the development of glomerulonephritis lupus-prone mice (Clynes et al. 1998). A subsequent study showed that the presence of Fc γ-chain on monocytes, but not renal mesangial cells, is required for this effect (Bergtold et al. 2006). In contrast, the absence of the inhibitory FcγRIIb induces autoantibody production and accelerates disease progression in experimental models (Bolland et al. 2002).

In humans, polymorphisms of both activating and inhibitory FcγRs are implicated in the development of lupus and the surface expression of these molecules is altered in SLE (Li et al. 2009b, c). Several single-nucleotide polymorphisms of FcγRII and FcγRIII affecting protein expression, ligand interaction, and transcription



**Fig. 1** Abnormal monocyte surface marker expression and cytokine/chemokine production in SLE. **a** Illustration of surface marker abnormalities (*top*) and excess cytokine/chemokine production (*bottom*) associated with SLE. **b** Elevated serum levels of IFN-1 in SLE impacts the expression surface markers (FcγRI and Siglec-1) and chemokines (CCL2, CCL5, CCL7, and CXCL10) in monocytes. **c** Increased IL-10 production in SLE modulates the expression of IL-12 and BlyS. BlyS B lymphocyte stimulator, CR complement receptor, ICAM intercellular adhesion molecule-1, IFN interferon, IFNAR IFN-α/β receptor, STAT signal transducers and activators of transcription, TNF tumor necrosis factor

factor binding have been established as risk alleles for SLE (Blank et al. 2005; Floto et al. 2005; Su et al. 2007; Li et al. 2009b, c). Copy number polymorphisms of FcγRIII also influence the risk for SLE. A low copy number predisposes to the development of lupus while a high copy number protects against the disease (Aitman et al. 2006; Fanciulli et al. 2007).

Whereas decreased expression of the inhibitory FcγRIIb (CD32) is found on certain B lymphocyte subsets (Mackay et al. 2006), the activating receptor FcγRI (CD64) is over-expressed in monocytes from SLE patients and is expressed at even higher levels in the subset of patients with renal disease (Hepburn et al. 2004; Li et al. 2009c).

Fc $\gamma$ RI expression positively correlates with markers of renal dysfunction (blood urea nitrogen, serum creatinine, microalbumin/creatinine ratio) and parameters of ongoing systemic inflammation (C3, C-reactive protein), but is largely unaffected by conventional medications used in SLE (Li et al. 2009c). In the presence of immune complexes, the predominance of activating Fc $\gamma$ Rs may further augment the inflammatory response in SLE (Kawai and Szegedi 2007).

Over-expression of adhesion molecules and costimulatory molecules may lead to aberrant monocyte migration and lymphocyte activation. Monocytes from SLE patients with active disease display elevated surface levels of ICAM-1 (intercellular adhesion molecule-1, CD54), a transmembrane protein involved in endothelial transmigration and inflammatory cytokine production (Funauchi et al. 1993), an effect that may be partially offset by the inhibitory effect of corticosteroids on ICAM-1 expression (Hepburn et al. 2004). Compared with healthy controls, lupus patients' monocytes also express greater levels of the costimulatory molecule CD40, and this feature is most pronounced in patients with active disease and hypergammaglobulinemia (Katsiari et al. 2002). Interaction between CD40 and its ligand (CD40L) triggers lymphocyte activation, proliferation, and initiation of immunoglobulin isotype switch (Banchereau et al. 1994). Interestingly, CD40L expression is elevated concomitantly on T and B lymphocytes from lupus patients with active disease (Desai-Mehta et al. 1996; Koshy et al. 1996). Aberrant expression of CD40 on monocytes, therefore, may promote the proliferation of autoreactive lymphocytes and generation of autoantibodies through excess CD40-CD40L interactions.

Monocytes from lupus patients also exhibit abnormalities in antigen presentation. Decreased expression of class II MHC on monocytes is documented in patients with active disease (Shirakawa et al. 1985) and impaired antigen presentation is associated with defective upregulation of CD80 on activated APCs (Tsokos et al. 1996). However, monocytes from lupus patients have a propensity to differentiate into DCs with potent capacity to present self antigens (Blanco et al. 2001). Monocyte-derived DCs from lupus patients also appear to exhibit higher CD86 expression than those from healthy individuals (Decker et al. 2006; Ding et al. 2006).

The mechanisms underlying these phenotypic changes on monocytes are largely unknown, although contributions from both genetic and environmental factors have been described. The involvement of genetic factors is best illustrated by natural polymorphisms and copy number variations found in Fc $\gamma$ Rs (as discussed above) and complement receptors (Dykman et al. 1984; Li et al. 2009b, c; Yang et al. 2007). Recent studies demonstrate that the

serum cytokine milieu in SLE may also play a role. Several groups have identified a panel of type-1 interferon (IFN-1)-stimulated genes (ISGs) highly expressed in peripheral blood mononuclear cells (PBMCs) from lupus patients (Baechler et al. 2003; Bennett et al. 2003; Lee et al. 2007). This interferon signature is associated with a wide spectrum of clinical manifestations and with autoantibody production. Dysregulated IFN-1 production also may account for the over-expression of Fc $\gamma$ RI in monocytes from lupus patients, as IFN-1 signaling induces the expression of Fc $\gamma$ RI (but not other Fc $\gamma$ Rs) in monocytes and elevated levels of Fc $\gamma$ RI transcripts in PBMCs from lupus patients are noted in microarray studies (Bennett et al. 2003; Biesen et al. 2008; Li et al. 2010d). Sera from lupus patients can also induce Fc $\gamma$ RI expression in monocytes from healthy controls in an IFN-1-dependent manner (Li et al. 2010d). In addition, the expression of sialoadhesin (Siglec-1, CD169) on monocytes from lupus patients is also increased in SLE due to dysregulated IFN-1 production (Biesen et al. 2008). Both CD14<sup>+</sup>CD16<sup>-</sup> and CD14<sup>+</sup>CD16<sup>+</sup> monocyte subsets display elevated surface levels of sialoadhesin, a feature that correlates with disease activity and anti-dsDNA autoantibody levels, but inversely correlates with complement levels (Biesen et al. 2008). Interestingly, excess production of IFN-1 and expression of sialoadhesin are also present in patients with systemic sclerosis (York et al. 2007).

The elevated levels of IFN-1 found in lupus patients may also contribute to the accumulation of the inflammatory phenotype of monocytes at sites of tissue damage (Fig. 1b). Excess expression of IFN-1 and ISGs has been described at sites of inflammation, including the skin and kidneys of lupus patients (Farkas et al. 2001; Peterson et al. 2004). Among the genes induced by IFN-1 are the potent monocyte chemoattractants CCL2 and CCL7 (Bauer et al. 2006). As illustrated recently in a mouse model of SLE, recruitment of inflammatory monocytes in response to local secretion of these IFN-inducible chemokines may perpetuate the chronic inflammatory responses associated with lupus (Lee et al. 2008, 2009). Supporting a pathogenic role of IFN-1, early clinical data evaluating the utility of anti-IFN-1 antibodies in SLE suggested therapeutic efficacy (Liao et al. 2004).

### Abnormalities in Cytokine Production

Aberrant activation of the adaptive immune system in SLE is augmented by the dysregulated production of cytokines (Kyttaris et al. 2005). In many instances, monocytes/macrophages are a major source of these immunomodulators, which may promote the activation of autoreactive T and B cells (Fig. 1a).

In line with the excess generation of immunoglobulins, elevated serum levels of the T helper 2 (Th2) cytokines IL-6 and IL-10 are found in lupus patients (Linker-Israeli et al. 1991; Llorente et al. 1993). Both of these cytokines promote the production of IgG and IL-6 is also required (along with IFN-1) for the differentiation of B cells into antibody-secreting plasma cells (Jego et al. 2003). Monocytes are the primary source of both IL-6 and IL-10 in the peripheral blood (Hagiwara et al. 1996), although production by lymphocytes is also reported (Linker-Israeli et al. 1991; Llorente et al. 1993; Mellor-Pita et al. 2009). Monocytes are a significant source of B-lymphocyte stimulator (BLyS, also known as BAFF), which promotes the survival and proliferation factor for B lymphocytes (Moore et al. 1999; Nardelli et al. 2001). Lupus patients overproduce BLyS/BAFF and its levels correlate with the levels of autoantibodies against dsDNA (Zhang et al. 2001).

The cytokine dysregulation in lupus is further complicated by interactions among the different cytokines (Fig. 1c). For example, the secretion of BLyS/BAFF can be further enhanced by IL-10 and IFN- $\gamma$  (Nardelli et al. 2001). The elevated levels of IL-10, on the other hand, down-regulate the production of IL-12 (Liu and Jones 1998) and reduce the inhibitory effects of IL-12 on antibody production (Houssiau et al. 1997). IFN-1, a family of cytokines overproduced in the majority of lupus patients (as described above), acts synergistically with IL-6 to induce plasma cell differentiation (Jego et al. 2003), while priming with IFN-1 unleashes the proinflammatory functions of IL-10 (Sharif et al. 2004). IFN-1 also primes the IFN- $\gamma$  signaling cascade, and hyper-responsiveness of monocytes from lupus patients to IFN- $\gamma$  stimulation has been reported recently (Karonitsch et al. 2009).

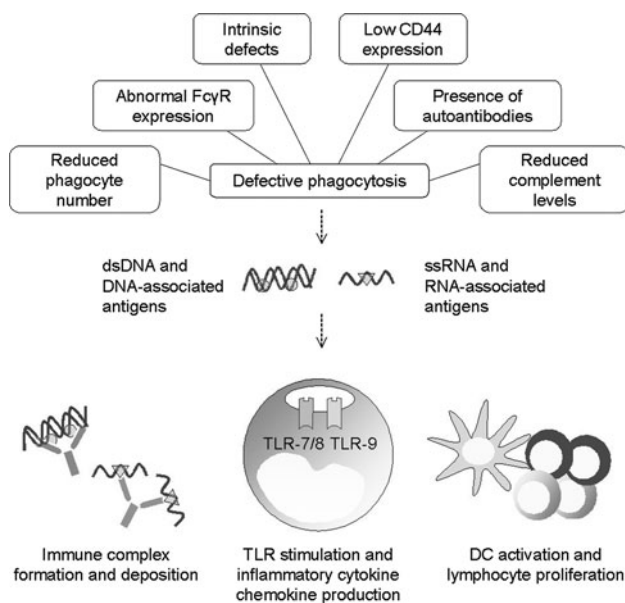
One explanation for the excess cytokine production is the presence of nucleic acid-containing immune complexes in the serum of lupus patients. Human monocytes express the endosomal nucleic acid sensors TLR7/TLR8 and TLR9, which mediate the inflammatory response to viral ssRNA and bacterial CpG DNA, respectively (Gorden et al. 2005; Klinman et al. 2002). However, endogenous nucleic acids are also capable of activating these receptors (Marshak-Rothstein 2006). Normally, the immune system is safeguarded from endogenous RNA and DNA by rapid degradation of nucleic acids during apoptosis. Grouping of these endosomal Toll-like receptors (TLRs) in the endoplasmic reticulum and late endosomes provides further insurance against unwanted responses to endogenous nucleic acids (Barton et al. 2006). These endogenous TLR ligands are normally restricted from entering the endosomal compartments where the nucleic acid-sensing TLRs are located. In SLE, however, autoantibodies against DNA- and RNA-associated antigens promote the formation of

nucleic acid-containing immune complexes (Barrat et al. 2005; Vollmer et al. 2005). Fc $\gamma$ R-mediated uptake of these complexes may interfere with the actions of endogenous nucleases, resulting in translocation of the endogenous nucleic acids into the endosomal compartment containing TLR7/8 and TLR9. This mechanism induces maturation of monocytes (Vollmer et al. 2005) and may be responsible for the excess production of inflammatory cytokines such as tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) by lupus monocytes (Steinbach et al. 2000). The same mechanism is believed to be responsible for the aberrant production of IFN-1 by plasmacytoid DCs in lupus (Barrat et al. 2005; Kelly et al. 2006; Vollmer et al. 2005). Furthermore, these effects on cytokine production may be augmented by the increased ratio of activating-to-inhibitory Fc $\gamma$ Rs (Kawai and Szegedi 2007) and/or delayed removal of endogenous nucleic acids secondary to deficiency of serum nucleases in lupus patients (Lee-Kirsch et al. 2007).

### Defects in Phagocytosis and Clearance of Cellular Debris

The phagocytic capacity of monocytes/macrophages is essential for the host defense against pathogens and homeostatic clearance of dead or dying cells (Aderem and Underhill 1999). Upon activation of the immune system through the detection of PAMPs, peripheral blood monocytes and tissue macrophages migrate to the site of infection and initiate phagocytosis of the invading organisms through several mechanisms. Cellular recognition of pathogen components by surface molecules such as mannose receptors, integrins, and scavenger receptors can directly induce the uptake of microbes. Moreover, opsonization by antibodies and complement potently stimulates phagocytosis via complement receptors and Fc receptors on the surface of phagocytic cells (Aderem and Underhill 1999).

Similarly, apoptotic and necrotic cells are removed by phagocytosis (Birge and Ucker 2008). During necrosis, contents of the dying cell are released and may subsequently trigger an inflammatory response through innate sensors such as TLRs and inflammasome components (Cavassani et al. 2008; Iyer et al. 2009; Li et al. 2009a). Despite the continuous turnover of aging or injured cells, apoptotic cell debris normally does not activate the inflammatory response because the receptors responsible for its uptake by macrophages are linked to anti-inflammatory signaling pathways (Chung et al. 2006; Fadok et al. 1998a, b, 2001). Recognition of apoptotic cells through a receptor for phosphatidylserine on macrophages inhibits the production of inflammatory mediators, including IL-1 $\beta$ , IL-8, IL-10, TNF- $\alpha$ , leukotriene C4, and thromboxane B2



**Fig. 2** Defects in phagocytosis and apoptotic cell clearance in SLE. A number of intrinsic and extrinsic factors contribute to the phagocytic defects associated with SLE (*top*). Impaired clearance of apoptotic cells and debris results in the accumulation of endogenous nucleic acids and nucleic acid-associated antigens (e.g. histones bound to DNA and components of the small ribonuclear protein complex associated with RNA). Upon translocation of these autoantigens into endosomes via Fc $\gamma$ R-dependent uptake, endogenous nucleic acids stimulate the endosomal Toll-like receptors (TLRs) on monocytes and dendritic cells, triggering the production of inflammatory cytokines/chemokines and proliferation of lymphocytes. The presence of autoantibodies further perpetuates the inflammatory response due to immune complex formation and deposition within tissues. *ds* double-stranded, *ss* single-stranded

(Fadok et al. 1998a, b; Hoffmann et al. 2001). The anti-inflammatory effects are mediated by the synthesis of transforming growth factor (TGF)- $\beta$ 1, prostaglandin E2, and platelet-activating factor (Fadok et al. 1998a). Accumulating data from animal models and in vitro studies illustrate that removal of apoptotic cells by macrophages is likely mediated by multiple pathways in addition to phosphatidylserine receptor. The involvement of CD14, c-Mer, liver receptor X, and vitronectin receptor is well documented and deficiency of some of these components is associated with the development of autoimmune manifestations in mice (A-Gonzalez et al. 2009; Devitt et al. 1998; Fadok et al. 1992, 1998b; Scott et al. 2001), although their role on human SLE is less clear at this time.

Ineffective clearance of dying cells and debris may provide a source of autoantigens for the development of an autoimmune response (Fig. 2). Indeed, abnormal clearance of apoptotic cells by macrophages from patients with SLE was demonstrated more than a decade ago (Herrmann et al. 1998). In vitro phagocytosis of autologous apoptotic cells is significantly impaired in monocyte-derived macrophages

from SLE patients compared with healthy controls. Supporting these findings, examination of lymph node biopsy samples from SLE patients revealed an accumulation of apoptotic cells near germinal centers and a decreased number of phagocytic tingible macrophages (Baumann et al. 2002). The clearance defect is compounded by the burden of chronic inflammation and increased rate of apoptosis in SLE (Ren et al. 2003). Moreover, sera from lupus patients possess enhanced capacity to induce apoptosis (Bengtsson et al. 2004). An important question raised by these findings is whether the aberrant uptake of apoptotic cells represents an inherent defect of macrophage function or a secondary phenomenon driven by serum abnormalities associated with the disease (e.g. low complement levels and presence of autoantibodies).

The presence of an intrinsic defect in the clearance of dying cells is supported by several lines of evidence. Despite normal surface binding of apoptotic cells, macrophages from lupus patients display reduced ability to internalize the targets compared with those from healthy controls or patients with RA (Tas et al. 2006). This defect may be partially explained by reduced surface expression of the glycoprotein receptor CD44 on monocytes. CD44 mediates the clearance of apoptotic neutrophils by monocytes and decreased expression of this molecule is found in lupus, but not RA, patients (Cairns et al. 2001). An intrinsic defect of phagocytosis was also revealed by a study comparing CD34<sup>+</sup> hematopoietic stem cell (HSC)-derived macrophages from lupus patients and healthy controls (Gaipal et al. 2005). Similar to monocytes freshly isolated from the peripheral blood, macrophages derived from CD34<sup>+</sup> HSCs of SLE patients demonstrated a reduced phagocytic capacity. This problem is compounded by the low number of CD34<sup>+</sup> HSCs in SLE patients and their ineffective differentiation into macrophages (Gaipal et al. 2005; Papadaki et al. 2001). Freshly isolated monocytes and cultured macrophages from SLE patients also display increased rates of spontaneous cell death due to fas-mediated apoptosis (Shoshan et al. 2001). Thus both quantitative and qualitative (functional) defects of the monocyte/macrophage lineage may contribute to the impaired apoptotic cell uptake in SLE. However, the phagocytic defect in macrophages from lupus patients can be partially reversed by sera from healthy controls (Ren et al. 2003). Conversely, addition of serum from lupus patients to macrophages from healthy controls reduces the uptake of apoptotic cells (Ren et al. 2003). These findings suggest that humoral mediators of phagocytosis may be dysregulated in SLE. The deficiency of complement in SLE perhaps provides the best supporting evidence for this hypothesis.

The complement system is comprised of a cascade of self-regulated proteins that directs bacteriolysis, antigen opsonization, neutrophil chemotaxis, and immune complex

clearance (Carroll 1998). Complement components also bind to apoptotic cells and promote phagocytosis by macrophages (Mevorach et al. 1998). This system is critical to the prevention of autoimmunity as genetic deficiencies of the early classical complement components (e.g. C1q, C4) are associated with the development of SLE in humans as well as in mouse models (Manderson et al. 2004). Autoantibodies to complement components such as C1q provide another mechanism to suppress the clearance of apoptotic cells (Uwatoko et al. 1984). Increased levels of anti-C1q antibodies are frequently found in lupus patients with renal disease (Coremans et al. 1995). Indeed, reduced serum levels of C1q, C3, and C4 in SLE may partially explain the inhibitory effect of lupus sera on the uptake of apoptotic cells by macrophages (Bijl et al. 2006). However, other factors are likely involved as sera from inactive lupus patients do not suppress phagocytosis despite the presence of decreased complement levels (Grevink et al. 2005).

Factors capable of inhibiting phagocytosis may provide an alternative explanation for the effect of lupus sera. Indeed, autoantibodies targeting nuclear antigens in SLE have been linked to the phagocytic abnormalities in macrophages. Opsonization by IgG from lupus patients, but not healthy controls, inhibits the phagocytosis of late apoptotic cells by macrophages (Reefman et al. 2007). Both Fc $\gamma$ RI and Fc $\gamma$ RII are required for this inhibitory effect, although the exact mechanism remains to be elucidated. Conversely, autoantibodies promote the uptake of necrotic cells (Grossmayer et al. 2008) and secondary necrotic cell-derived material, which induces the production of pro-inflammatory cytokines (Munoz et al. 2009).

In addition to these mechanisms, autoantibodies may also act directly on macrophages. Autoantibodies targeting surface molecules involved in the phagocytosis of apoptotic cells, such as scavenger receptors, have been demonstrated in sera from lupus patients and lupus-prone mice (Wermeling et al. 2007).

## Conclusion

SLE is a chronic autoimmune disorder associated with a plethora of immunological abnormalities. Phenotypic and functional abnormalities in monocytes/macrophages are increasingly recognized to play a role in this complex disease. Recent studies in lupus patients have identified numerous monocyte/macrophage defects involving surface protein expression, cytokine production, and phagocytic capacity. However, we are only beginning to understand the mechanisms underlying these abnormalities. While further studies are needed to define the genetic and environmental factors involved, abnormalities of immunomodulation also warrant exploration. With monocyte depletion therapy

already being assessed in inflammatory diseases such as RA, a better understanding of the causes and sequelae of the monocyte/macrophage abnormalities may aid in the design of novel therapeutic approaches in SLE.

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