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Monocyte and macrophage abnormalities in systemic lupus erythematosus.

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Source

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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.

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Macrophage Subpopulations in Systemic Lupus Erythematosus

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Abstract: Systemic lupus erythematosus (SLE) is a heterogeneous group of autoimmune disorders defined by a consensus of clinical and laboratory criteria. Much of the pathophysiology and therapy of SLE has focused on autoimmune B and T cells of the adaptive immune system. Recently, the role of macrophages, part of the innate immune system, in SLE pathogenesis has gained attention. The field of immunology in general has recently changed in the way that it approaches macrophages. Rather than viewing them as a single, concrete whole, it has become clear that different subpopulations of macrophages contribute to various immune and non-immune processes. Such a nomenclature may provide an ideal framework from which to study macrophage pathogenesis in SLE. Studies suggest that M1 subtype macrophages play an important inflammatory role in SLE pathogenesis. Further, apparently reduced populations of M2a and M2c subtype macrophages may contribute to the lack of anti-inflammatory activity apparent in the disease. M2b subtype macrophages may actually have a role in causing disease directly. Regulatory macrophages have yet to be explored thoroughly in SLE, though the presence of a few of their markers may mean that they are active in suppressing SLE-related inflammation.

Introduction

Systemic lupus erythematosus (SLE) is a heterogeneous group of autoimmune disorders defined by a consensus of clinical and laboratory criteria. Much of the pathophysiology and therapy of SLE has focused on autoimmune B and T cells of

the adaptive immune system. Recently, focus has shifted to the role of macrophages — part of the innate immune system — in SLE pathogenesis. Scientists' view of macrophages has changed significantly in the past decade. What was once considered a monolithic group of waste collectors is now a heterotypic, heterogeneous population of multipurpose cells. In much the same way as effector T cells have been parsed and scrutinized for their diversity, macrophages are now being subdivided and classified anew. These new classes have important and increasingly relevant roles in a number of disease states. However, the new nomenclature has yet to be used to study macrophage pathogenesis specific to SLE. In this review, we first give an overview of the latest macrophage nomenclature. We further discuss, per observations in the literature, the roles of various macrophage subtypes in the pathogenesis of SLE based on our current understanding of the disease.

Macrophage Subtypes Have Varying Roles

Table 1. Macrophage Subsets and Their Inducers, Markers, Targets, and Putative Roles.

	Inducers	Markers and Products		Suggested Roles	Changes in SLE and Evidence
M1 (Classically-activated)	GM-CSF IFNγ LPS TNF-α	CCL2 CCL5 (RANTES) CCR2 CCR7 CD14 CD86 CXCL8 CXCL8, 16 CXCL9, 10, 11 FCγR+ IFN IL-1	IL-6 IL-18+ IL-12+ IL-23 IL-R LysOC+ CCL2, 3, 4 MHC II TLR+ TNF-α iNOS (ROS)	Type I immunity bacteria, viruses, protozoa Type 4 hypersensitivity Tumor resistance	Likely to be increased Inducers are increased (IFNγ, TNF-α, GM-CSF, possibly CSF-1) Products are elevated (CD86, IFNγ, CCL2, CXCL16, IL-6, TNF-α) STAT4 polymorphisms predispose to SLE
M2a (Alternatively activated)	IL-4 IL-10 IL-13 PPARγ-agonists	Arginase CCL2 CCL16, 18 CCL17, 22 CD163 CXCR1-2b CCL24 (MPIF2) Dectin-1 FCεR IL-4R	IL-10+ IL-12+ IL-R, (decoy) Lectins MHC II+ MSR1 Mannose R Scavenger R P2Y12 P2Y13	Type II immunity Parasites Allergies Profibrotic	Likely to be decreased Products are depressed (MHC II, MSR1, mannose receptor, P2Y12) PPARγ agonists have shown promise in trials IL-4- and IL-13-stimulated macrophages transplanted into nephritic SCID mice ameliorate renal pathology
M2b	ICs (FCR agonists) IL-1R agonists LPS TLR agonists	CD86 CCL1 (MCP-1) IL-1 IL-6	IL-10+ IL-12+ MHC II+ TNF	Immune regulation Th2 activation	Likely to be increased Inducers are increased (ICs, TLR agonists) Products are elevated (IL-10, TNF-α, IL-6, CD86) Notch-1 and NF-κB signaling are overactive in SLE PPARγ agonists have shown promise in trials
M2c (Deactivated)	Glucocorticoid IL-10 TGF-β	Arginase CCL16, 18 CCR2+ CD14+ CD150 (SLAM) CD163 ECM IL-4R IL-10R IL-10+ IL-12+	IL-R LysC+ CXCL13 MHC II+ Mannose R P2Y14 RAGE Scavenger R TGF-β Vitronectin R	Immune suppression Tissue repair Matrix remodeling	Likely to be decreased Products are depressed (CD14, mannose receptor, MHC II) Scavenger receptor-blocking antibodies worsen disease
Mac-reg	CpG LPS TGF-β VEGF	Arginase CCL4 CD11B+ (ITGAM) CTLA4+ CXCL3 CXCL3 Foxp3	GITR+ IL-1α IL-4+ PDGF PGE2 VEGF	IL-4R–mediated immune suppression	Likely to be increased but not effective Inducers are increased (TGFβ, PDGF, Cpg) Products are elevated (PDGF, PGE2)

Note: Macrophage classification nomenclature was described by Mantovani and colleagues (Mantovani *et al.*, 2004; Martinez *et al.*, 2008) and others (Anders and Ryu, 2011; Benhiddi *et al.*, 2007; Zarco Manrique *et al.*, 2011).

In the last several years, macrophages have been increasingly subdivided and categorized based on apparent activity, location, and cell surface marker expression. One of the most useful classifications to emerge has been that of Mantovani *et al.* (2004) which subdivides activated macrophages into M1, M2a, M2b, and M2c subtypes (**Table 1**). Other subdivision methods as cited in the table help to round out a subpopulation-based view of macrophage classification.

These subdivisions can make reversible changes that respond to the micro-environmental milieu. While they do not necessarily represent distinct populations of cells, they do represent a useful functional nomenclature by which broad insights may be made into their function in disease.

As of yet, little work has been done to establish what the individual role of these macrophage subtypes might be in SLE pathogenesis. We undertake here a review of possible macrophage subtype contributions to disease based on current leads.

M1 Mayhem — The Runaway M1 Hypothesis Explains Some SLE Pathology

Type 1 versus type 2 immune responses

A useful and dominant nomenclature for $CD4^+$ T cells reflects the roles that these helper cells play in a given scenario of inflammation. Type 1 immune response, mediated by T_H1 cells, refers to the inflammatory response that clears viral, bacterial, and protozoan infections. Type 2 immune response, mediated by T_H2 cells, refers to a response that is more efficacious in clearing parasites. This classification has been extraordinarily useful in the systematic study of the adaptive immune response, and it has grown to include other subsets of helper T cells.

Not surprisingly, helper T cells are not the only player in any given immune response. It has since been discovered that distinct populations of macrophages, termed M1 and M2 cells, facilitate and control type 1 and type 2 immune responses, respectively. Just as T_H1 cells facilitate inflammation and help clear typical pathogens, M1 macrophages are pro-inflammatory and assist in controlling infections by expressing reactive oxygen species (ROS), complement and immunoglobulin receptors, and inflammatory cytokines. On the other hand, M2 macrophages express a different set of cytokines that appears related to type 2 immune responses and anti-inflammatory processes.

SLE is a markedly inflammatory disease in the absence of appropriate pathogens. One important theory in the pathogenesis of SLE is that inflammatory M1 macrophages could be out of control. An imbalance of M1 over M2 may explain the runaway inflammation that is an essential feature of SLE.

Evidence for the M1 dominance hypothesis

M1 macrophages are classical phagocytic, inflammatory macrophages that act in delayed-type (type IV) hypersensitivities, tumor resistance, and type 1 inflammation. They have long been believed to be a source of pathology in SLE. Several markers of M1 macrophages are elevated in SLE macrophages, as highlighted in Table 1. These include CD86 (Sui *et al.*, 2010), which correlates with the severity of renal pathology; IFN-γ (Jin *et al.*, 2005), IL-6 (Hagiwara *et al.*, 1996), CCL2 (Li *et al.*, 2009), and CXCL10 from circulating macrophages (Lee *et al.*, 2009); CXCL10 from neurological lupus macrophages (Santer *et al.*, 2009); and CCL2 from intrarenal macrophages (Marks *et al.*, 2008; Wagrowska-Danilewicz *et al.*, 2005). These markers are important in macrophage activation state, chemotaxis, and general pro-inflammatory activity.

M1 macrophages are also favored by the milieu they reside in. SLE serum contains large amounts of TNF-α (Bennett *et al.*, 2003), GM-CSF (Midgley *et al.*, 2009), and IFN-γ (Bennett *et al.*, 2003), each of which contributes to type 1 inflammation propagation. TNF-α is a particularly potent M1 cytokine that is known to change the ways in which macrophages respond to their environment. It is one of the "danger signals" described by Gallucci and Matzinger (2001) that fundamentally alters macrophage cell signaling calculus.

Predisposing genetic factors also support the M1 dominance hypothesis. IFN-γ production by M1 cells utilizes the STAT4 pathway and is inhibited by factors predisposing to the M2a phenotype (Schindler *et al.*, 2001). STAT4 polymorphisms have been linked intimately with SLE (Remmers *et al.*, 2007; Sigurdsson *et al.*, 2008) and appear to increase M1 sensitivity to cytokines in these patients (Kariuki *et al.*, 2009). Circulating CSF-1, which is elevated in SLE patient serum, appears to induce a $Ly6C^{high}$ M1 phenotype. Cutaneous manifestations of lupus in MRL-lpr mice exposed to sunlight are also mediated by CSF-1 (Menke *et al.*, 2008) and are therefore probably M1-mediated. Indeed, recent work in models of atherosclerosis — which occurs frequently in patients with SLE — showed the importance of the M1 subtype in instigating inflammation as well as M2 macrophages in reducing it (Feig *et al.*, 2011). While HMG-CoA reductase inhibitors may be expected to have multiple unrelated effects, they have also been shown to improve lupus symptoms by unknown mechanisms (van Leuven *et al.*, 2011).

M1 versus M2 as an insufficient paradigm

The M1 versus M2 paradigm may represent an oversimplification of the inflammation in SLE. M1 macrophages are unlikely to produce the large amounts of IL-10 seen in SLE (Hagiwara *et al.*, 1996; Viallard *et al.*, 1999); this expression pattern is a hallmark of all M2 subtypes (Mantovani *et al.*, 2004). Immune complexes and other Toll-like receptor (TLR) agonists, which are abundant in SLE serum, are further expected to favor the M2b subtype. M2b macrophages secrete IL-6 that is elevated in peripheral SLE macrophages (Hagiwara *et al.*, 1996) and the subtype has been induced in mouse macrophages using anti-dsDNA antibodies (Jang *et al.*, 2009). Further, CCL5 antagonists, which might be expected to blunt renal injury because they block M1 actions on cytotoxic T and NK cells, actually accentuate mouse models of renal damage even in the absence of lymphocyte infiltration (Anders *et al.*, 2003b). These findings paint a more nuanced picture of macrophage subpopulation contribution to SLE. A recent review by Anders and Ryu (2011) suggested that increased M1 as well as M2 macrophage subpopulations in various kidney pathologies could explain various findings and influence disease course.

M2 Subpopulations also Contribute to SLE Pathology

M2 macrophages are generally divided into a, b, and c subtypes. They appear to perform separate tasks in inflammation and are designated by different monikers in different publications. M2a macrophages are referred to as alternatively activated or profibrotic; M2b as regulator or T_H2-related; and M2c as deactivated, remodeling, or anti-inflammatory. Each may have its own role in the pathology of SLE. As discussed above, all M2 macrophages produce an IL-10:IL-12 ratio opposite of M1 macrophages (Mantovani *et al.*, 2004) that is found on both

peripheral and renal SLE macrophages (Alleva *et al.*, 1998; Hagiwara *et al.*, 1996; Liu and Beller, 2002; Triantafyllopoulou *et al.*, 2010; Viallard *et al.*, 1999; Yu *et al.*, 1998).

M2a macrophages

M2a macrophages have been characterized as profibrotic (Anders and Ryu, 2011). Fibrosis is a common finding in lupus and has been attributed to macrophage function (Davis and Lennon, 2005), though not definitively attributed to any particular macrophage subpopulation.

M2a macrophages do not appear to be a major macrophage subpopulation in SLE. While data only exists for a few M2a markers, the expression of these markers uniformly decreased in human SLE peripheral macrophages, as highlighted in Table 1. These are MHC II (Shirakawa *et al.*, 1985; Steinbach *et al.*, 2000), MSR1 (CD204) type A scavenger receptor (Wermeling *et al.*, 2007), mannose receptor (Kavai and Szegedi, 2007), and possibly P2Y12 (Wang *et al.*, 2004).

Deliberate expansion of M2a macrophages is one promising therapeutic approach. PPARγ agonists that induce M2a phenotypes in human macrophages (Bouhlel *et al.*, 2007) have shown some promise in mouse tests (Zhao *et al.*, 2009). Further, IL-4 and IL-13-induced macrophages transplanted to adriamycin-induced nephritic SCID mice ameliorates renal disease (Wang *et al.*, 2007).

Further studies on the expression of other important M2a-related markers, including $F_C\varepsilon R$ (CD23) and various lectins, may help elucidate whether there is a dearth of M2a macrophages that might promote SLE progression.

M2b macrophages

M2b macrophages are considered an immunity-regulating macrophage subtype that is associated with SLE and activated by immune complexes. In an activated lymphocyte-derived DNA (ALD-DNA) induced mouse model of lupus, Zhang *et al*. (2010) showed that increased Notch-1 signaling caused M2b macrophage differentiation. The Notch-1 signaling further caused a lupus-like phenotype. NF-κB p50 is an important part of M2 macrophage differentiation (Porta *et al.*, 2009) and has been shown to be increased in expression in kidneys of SLE patients with glomerulonephritis (Zheng *et al.*, 2006).

SLE serum samples are characterized by an increased ratio of IL-10 to IFNγ secretion (Hagiwara *et al.*, 1996), which could be a direct result of M2b activation. Indeed the surplus of unphagocytosed immune complexes (ICs) that occur in SLE are known to be inducers of M2b macrophages. TLR signaling is also important in renal pathology (Pawar *et al.*, 2006). M2b macrophages are known to produce nonspecific inflammatory factors that are elevated in peripheral SLE macrophages. These include IL-10 (Hagiwara *et al.*, 1996; Viallard *et al.*, 1999), TNF-α (Manfredi *et al.*, 1998; Steinbach *et al.*, 2000), and IL-6 (Hagiwara *et al.*, 1996), as summarized in Table 1.

PPARγ knockout mice, an SLE model, develop high serum anti-nuclear antibody (ANA) and a glomerulonephritis syndrome that is similar to human SLE (Roszer *et al.*, 2011). The M2b macrophage phenotype predominates in these mice and has deficiencies in phagocytosis and apoptotic cell clearance. The use of a PPARγ agonist rosiglitazone has been proposed to divert macrophage differentiation toward the M2a subtype from M2b (Bouhlel *et al.*, 2007; Lefèvre *et al.*, 2010). Rosiglitazone (Venegas-Pont *et al.*, 2009) and pioglitazone (Zhao *et al.*, 2009) have shown short-term therapeutic efficacy in murine lupus nephritis, though the mechanism is not known. With the comorbidity of atherosclerosis and type 2 diabetes with SLE, PPARγ activation is also expected to relieve disease by other mechanisms through adiponectin (Aprahamian *et al.*, 2009). Separately, thiazolidinediones have been shown to be anti-inflammatory independent of PPARγ modulation (Chawla *et al.*, 2001). Macrophage subtype is clearly an important phenomenon, because M2b macrophage levels have been shown to directly correlate with relapse (increasing and stimulating autoimmune response) and remission (decreasing along with a lower autoimmune response) in murine lupus nephritis (Schiffer *et al.*, 2008). This same study showed a dearth of M1 cells in active disease in murine lupus.

Further explorations of NF-κB signaling relating to SLE include the generation of cell-penetrating anti-dsDNA antibodies by Jang *et al*. (2009). These antibodies were found to induce TNF-α production and, in two cases, activate the NF-κB pathway in RAW264.7 mouse macrophages. Such an induction in a patient with SLE might be expected to drive macrophages toward the M2b phenotype. Paracrine LTB_4 appears to amplify the NF-κB and STAT1 transcriptional pathways (Serezani *et al.*, 2011). Both pathways contribute to lymphocyte survival and an inflammatory cytokine milieu. While SLE macrophages produce little LTB_4 (Shome and Yamane, 1991), it appears that other cells produce copious amounts of it in lupus nephritis (Spurney *et al.*, 1991).

M2c macrophages

M2c macrophages are alternatively designated deactivated, remodeling, or anti-inflammatory macrophages. This subtype reflects the various roles that M2c phenotype macrophages are thought to play in the immune system.

Interesting findings regarding M2c macrophages in lupus include the fact that serum antibodies against scavenger receptors — expressed largely on the M2c subtype — tend to worsen SLE (Wermeling *et al.*, 2007). Further, CD14 levels, enriched on the M2c subtype, are low on peripheral monocytes and macrophages isolated from patients with SLE (Bijl *et al.*, 2006; Steinbach *et al.*, 2000). Taken together, these might be seen as evidence of a reduction of M2c macrophages in SLE, as summarized in Table 1.

One promising role of M2c macrophages is their reputed anti-inflammatory effect. High IL-10 levels seen in SLE might normally be expected to lead to M2c macrophage phenotype and a reining in of inflammation. However, high level of type 1 IFN production in SLE (Liao *et al.*, 2004) has been shown to change the ways in which macrophages respond to IL-10 (Sharif *et al.*, 2004). In fact, IL-10 becomes inflammatory in SLE, as evidenced by improvement in human SLE trials with IL-10-blocking antibodies (Llorente *et al.*, 2000). Some postulate that the loss of this subtype contributes greatly to autoimmunity. Indeed, the efficacy of glucocorticoid therapy may be partially due to M2c upregulation.

M2c macrophages also play a role in matrix deposition and tissue remodeling. TGF-β and IL-10, each increased in both peripheral and renal SLE macrophages (Hagiwara *et al.*, 1996; Viallard *et al.*, 1999; Wagrowska-Danilewicz *et al.*, 2005), lead to this phenotype. How their absence or presence might contribute to SLE pathology in this way has yet to be intensively studied. MRL mice show wound healing without fibrosis (Davis and Lennon, 2005). Perhaps this is due to a lack of M2c macrophages in the model.

Regulatory Macrophages (M_{regs}) May Be Part of the Equation

Long the subject of speculation, regulatory macrophages, termed Mac-regs or M_{regs}, have now been shown to exist (Zorro Manrique *et al.*, 2011). M_{regs} express Foxp3, a canonical regulatory T cell transcriptional regulator, and repress inflammation much like their regulatory T cell counterparts. These M_{regs} further secrete large amounts of PGE_2, consistent with a finding in several mouse lupus models (Chae *et al.*, 2008). PGE_2 inhibits M1 cell activity (Fabricius *et al.*, 2010) and appears to be a major regulatory mechanism. They further secrete PDGF, which has been shown to be increased on macrophages from polycytidylic acid-accelerated lupus in BWF1 mice (Triantafyllopoulou *et al.*, 2010). It has yet to be proved whether M_{regs} represent a distinct population from M2c macrophages, as a number of similarities exist.

Conclusions

Macrophage taxonomy is an attempt to rationally categorize an extended variety of cell functions. In that sense, the number of potential macrophage subdivisions is limited only by cell products, chromophores, and flow cytometry parameters. Similarly, macrophage phenotypes are fluid and reversible, unlike committed cell differentiations of pluripotent progenitor cells. The above classifications are likely to overlap, blur, and even bend in the face of disease processes like SLE and in normal physiology. Nevertheless, these classifications offer good starting points to consider potential mechanisms for macrophage contribution to disease.

It appears that the runaway M1 hypothesis has some validity, though it cannot explain all pathological features of SLE driven by macrophages. M2a and M2c populations appear to be reduced and fail to quell the inflammatory activity of M1

as well as other immune cells. On the other hand, M2b may itself contribute to pathology.

These findings suggest several therapeutic targets for treating SLE. By selectively inhibiting the activity of M1 and M2b macrophages, their pro-inflammatory effects may be averted. Anti-interferon, anti-TNF, or anti-growth factor treatments may help limit M1 differentiation. PPARγ agonists, already promising in mouse studies, may serve a dual role in depleting M2b macrophages and stimulating M2a expansion. Boosting M2a, M2c, or M_{reg} macrophages could help limit inflammation and control disease. As mentioned earlier, glucocorticoids may be partially effective by their positive effect on M2c expansion. However, caution is warranted, as CCL5 antagonists have actually been shown to aggravate kidney disease (Anders *et al.*, 2003a).

Further research may help to better elucidate the contributions of macrophages to SLE. More flow cytometric data comparing markers of healthy and SLE macrophages could facilitate this effort, as aggregated on SLE BASE (www.slebase.org). The development of a consensus of macrophage subpopulation nomenclature may also assist in simplifying the process.

Disclosure

The authors report no conflicts of interest.

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