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THERAPEUTIC TARGETS FOR SYSTEMIC LUPUS ERYTHEMATOSUS

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SUMMARY

Systemic lupus erythematosus (SLE) is a multifaceted, multisystemic connective tissue disorder characterized by autoimmunity and inflammation. Production of antinuclear autoantibodies by a hyperactive immune system results in damage to cells and tissues. Currently, there is no cure for SLE. The goal of treatment in SLE is to prevent and treat flares and minimize organ damage and complications. Available therapies include nonsteroidal anti-inflammatory drugs (NSAIDs), immunosuppressants, corticosteroids and cytotoxic agents. However, no new drugs targeting the underlying disease have been introduced in the last 50 years. Thus, the search continues for more effective treatment strategies for SLE, with investigation focusing on identifying novel targets for therapeutic intervention. This article presents those drug targets that are currently under active investigation for the treatment of SLE.

INTRODUCTION

Systemic lupus erythematosus (SLE), more commonly known as lupus, is a prototypic multisystemic connective tissue disorder characterized by autoimmunity and inflammation. Individuals suffering from the disease exhibit a progressively hyperactive immune system that produces antinuclear autoantibodies. The consequence is acute and chronic inflammation and damage to healthy cells and tissues, particularly in the joints, skin, kidneys, cardiovascular and nervous system, and other internal organs. Symptoms range from relatively mild (e.g., rash, arthritis) to life-threatening (e.g., glomerulonephritis, thrombosis) and may be intermittent or become progressively worse (1-3).

According to the Centers for Disease Control and Prevention (CDC), SLE affects approximately 1.4 million individuals in the U.S. alone. However, the prevalence of lupus varies widely from country to country, with the highest rates reported in Italy, Spain, Martinique and among Afro-Caribbean subpopulations of the U.K. Approximately 90% of all cases of lupus occur in women, although the disease may be more severe when it occurs in males. In general, both the prevalence and the severity of SLE are two to four times greater among nonwhite populations around the world (1, 4-6).

The pathogenesis of lupus is multifactorial, involving complex interactions of genetic and environmental factors. It is postulated that in a genetically predisposed individual, a hyperactive immune system responds in an overly aggressive manner to a foreign stimulus, pushing antibody-generating B cells and antibody response-enhancing T cells into overdrive. The patient's hyperactive immune system produces abnormal antinuclear autoantibodies which target not only the foreign matter but also healthy cells and tissue. An inappropriate inflammatory response is induced, with dysregulated function of inflammatory cells and the proinflammatory regulators they produce. For example, production of type I interferon in SLE patients is a central pathogenetic mechanism and is due to the alteration of dendritic cell function (2, 3, 6-8).

There are many exogenous factors that have been proposed to be responsible for initiating the hyperactive immune response characterizing SLE. These include bacteria (e.g., *Mycobacterium tuberculosis*) and viruses (e.g., Epstein–Barr virus), certain prescription drugs (e.g., combined oral contraceptives), exposure to sunlight, topical exposure to chemicals (e.g., in lipstick) and tobacco smoking. It has also been suggested that SLE may develop in response to an endogenous deficiency in the complement protein C1q, a protein that is normally responsible for eliminating apoptotic cellular debris. A deficiency in C1q would lead to accumulation of apoptotic material in blood and tissues, and thus trigger an exaggerated immune response (1, 2, 6, 9-11).

There is no cure for SLE at this time. Because SLE manifests as a variety of symptoms and fluctuations in the severity of those symptoms, treatment to date differs from one patient to another, as well as for the same patient over time. In general, the treatment of SLE attempts to prevent flares, treat them when they do occur and minimize organ damage and complications. Although elucidation of the pathogenesis of SLE has significantly increased over the years, no new drugs to treat the underlying disease have been introduced in the last 50 years. Nonsteroidal anti-inflammatory drugs (NSAIDs)

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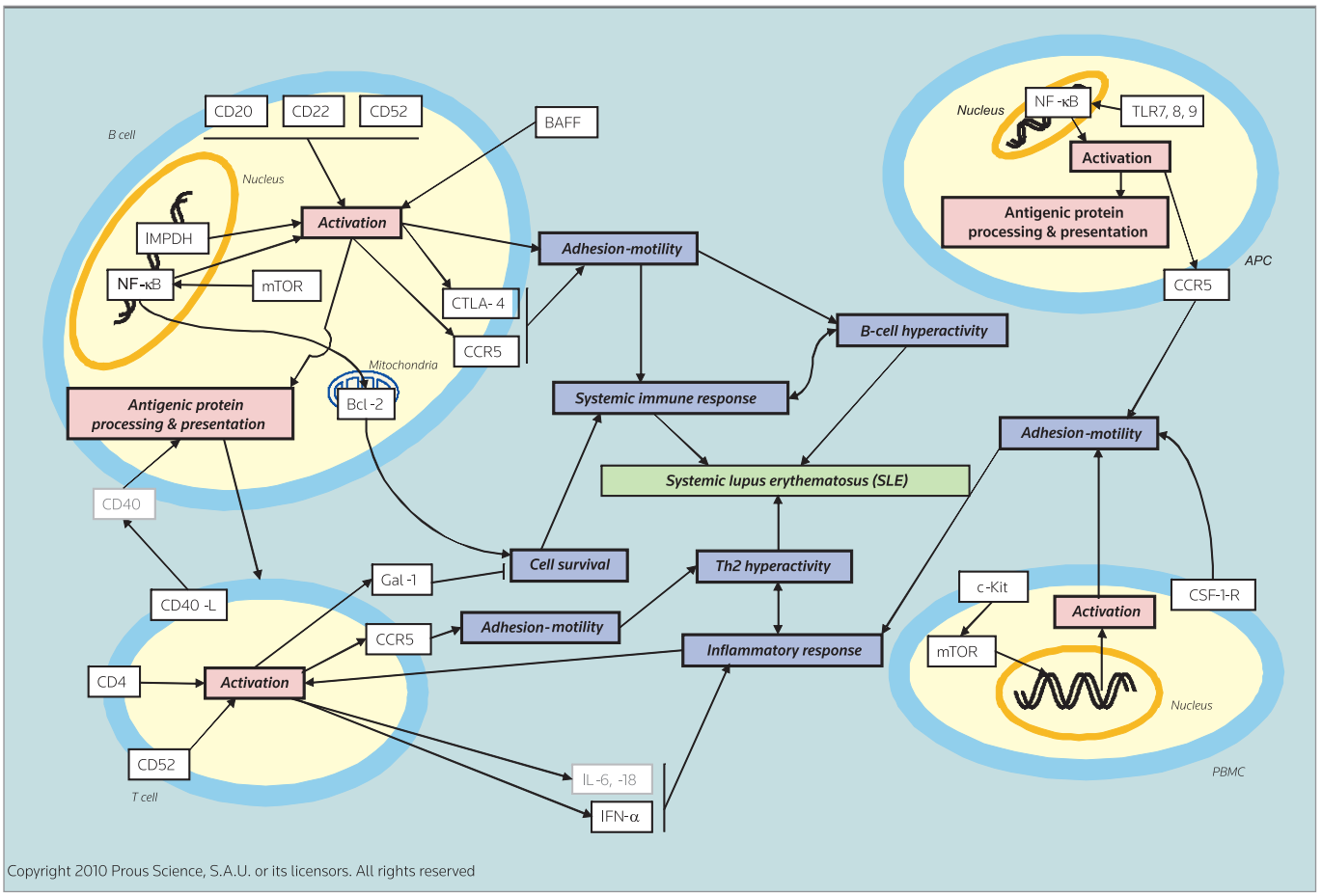

Figure 1. Systemic lupus erythematosus (SLE) targetscape. A diagram showing an overall cellular and molecular landscape or comprehensive network of connections among the current therapeutic targets for the treatment of SLE and their biological actions. Gray or lighter symbols are targets that are not validated (i.e., targets not associated with a product that is currently under active development for SLE). Abbreviations: APC, antigen-presenting cell; BAFF, B-cell-activating factor; Bcl-2, apoptosis regulator Bcl-2; CCR5, chemokine CCR5 receptor; CD4, T-cell surface glycoprotein CD4; CD20, B-lymphocyte antigen CD20; CD22, B-cell receptor CD22; CD40-L, CD40 ligand, CD154; CD52, CAMPATH-1 antigen; c-Kit, tyrosine-protein kinase Kit; CSF-1-R, macrophage colony-stimulating factor 1 receptor; CTLA-4, cytotoxic T-lymphocyte-associated protein 4, CD152; Gal-1, galectin-1; IMPDH, inosine 5'-monophosphate dehydrogenase; IFN-α, interferon α; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor NF-kappaB; PBMC, peripheral blood mononuclear cell; TLR, Toll-like receptor.

are used to treat arthritis and pleurisy, and topical corticosteroids may be applied to treat skin rashes. Skin and arthritis symptoms may also be treated with antimalarial drugs such as hydroxychloroquine or low-dose systemic corticosteroids. Immunosuppressants and corticosteroids may be prescribed to control the various symptoms of severe disease. Cytotoxic agents (cyclophosphamide, azathioprine, etc.) are frequently administered in combination with corticosteroids to patients with major organ involvement in order to prevent or minimize irreversible damage (1, 12-14).

The search for effective treatment strategies for SLE continues, with research focusing on the identification of novel targets for drug development. Those targets which are currently under active investigation are discussed below (see Fig. 1). Table I provides a selection of products under active development for each target and Table II includes selected patents.

TARGETS

Apoptosis regulator Bcl-2

Apoptosis regulator Bcl-2 is a member of the Bcl-2 family of proteins. It inhibits the mitochondrial apoptotic pathway by preventing cytochrome *c* release and caspase-9 activation. It was first identified in human follicular B-cell lymphoma cells resistant to apoptosis and has been shown to protect a variety of cell types from programmed cell death. During embryonic development, Bcl-2 protein is widely distributed throughout the central nervous system (CNS) and peripheral nervous system (PNS). Postnatally, Bcl-2 protein is found predominantly in the granule cells of the cerebellum, dentate gyrus of the hippocampus and throughout the PNS. Many cancer types overexpress the *BCL2* gene, and thus drugs inhibiting Bcl-2 activity or *BCL2* gene expression are useful therapeutic options for the treatment of cancer. Altered expression of *BCL2* has been observed in

Table I. *Selected targets and products launched or being actively investigated for systemic lupus erythematosus (from Thomson Reuters Integrity[SM]).*

Target name	Product	Source	Phase
Apoptosis regulator Bcl-2	Cyclophosphamide	Northwestern University	I
B-cell-activating factor (BAFF)	Belimumab	GlaxoSmithKline/Human Genome Sciences	Prereg.
	Atacicept	Merck Serono	II/III
B-cell receptor CD22	Epratuzumab	UCB	III
B-lymphocyte antigen CD20	Rituximab	Northwestern University	I
	PF-5230895	Pfizer	I
CAMPATH-1 antigen (CD52)	Alemtuzumab	Northwestern University	I
CD40 ligand (CD40-L)	CDP-7657	UCB	I
Chemokine CCR5 receptor	Sirolimus	SUNY Upstate Medical University	II
Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)	Abatacept	Brystol-Myers Squibb	II
Galectin-1	Cyclophosphamide	Northwestern University	I
Inosine 5′-monophosphate dehydrogenase (IMPDH)	Mycophenolic acid sodium salt	Novartis	III
Interferon α (IFN-α)	IFN-α kinoid	Neovacs	I/II
	Sifalimumab	MedImmune, Medarex	II
	Rontalizumab	Genentech	II
Macrophage colony-stimulating factor 1 receptor (CSF-1-R)	PLX-3397	Plexxikon	Preclinical
Mammalian target of rapamycin (mTOR)	Sirolimus	SUNY Upstate Medical University	II
Nuclear factor NF-kappaB (NF-κB)	Acetylcysteine	SUNY Upstate Medical University	I/II
T-cell surface glycoprotein CD4	TRX-1	Tolerx	Preclinical
Toll-like receptor TLR7	CPG-52364	Coley Pharmaceutical	I
	IMO-3100	Idera	Preclinical
Toll-like receptor TLR8	CPG-52364	Coley Pharmaceutical	I
Toll-like receptor TLR9	CPG-52364	Coley Pharmaceutical	I
	IMO-3100	Idera	Preclinical
Tyrosine-protein kinase Kit	PLX-3397	Plexxikon	Preclinical

patients with SLE and has been implicated in the development of this and other autoimmune diseases. Upregulated Bcl-2 would lead to dysregulation of apoptosis and antigen-presenting cell (APC) function, resulting in inflammation. Thus, inhibition of Bcl-2 may be effective in the treatment of SLE (15-17).

B-cell-activating factor (BAFF)

BAFF is also known as tumor necrosis factor ligand superfamily member 13B, B lymphocyte stimulator (BLyS), TNF- and APOL-related leukocyte expressed ligand (TALL-1) and dendritic cell-derived TNF-like molecule (CD257 antigen). It is a 285-amino-acid transmembrane glycoprotein expressed on several cell types, including monocytes, dendritic cells and bone marrow stromal cells; there is also a soluble protein fragment resulting from the cleavage of the transmembrane form from the membrane. BAFF binds to three TNF receptors: BAFF-R expressed on mature B lymphocytes, TACI expressed on mature B lymphocytes and a subset of T cells, and BCMA expressed on mature B lymphocytes and plasma cells. Signaling through BAFF-R and BCMA stimulates B-lymphocyte proliferation. BAFF has been implicated in the pathogenesis of autoimmune diseases such as multiple sclerosis, myasthenia gravis, rheumatoid arthritis and SLE through the role it plays in promoting survival and maturation of autoreactive B cells. Thus, inhibition of this regulator may be therapeutically effective in the treatment of SLE (18-21).

B-cell receptor CD22

CD22 (Siglec-2) is a sugar-binding transmembrane protein belonging to the sialic acid-binding IG-like lectin family. It binds sialylated glycoproteins (e.g., sialic acid) at an immunoglobulin (Ig) domain located at its *N*-terminus. CD22 is involved in B-cell–B-cell interactions. It may also act as an inhibitory receptor for B-cell receptor signaling, which prevents the overactivation of the immune system and the development of autoimmune diseases. Agents targeting CD22 modulate B-cell function and may be effective in the treatment of SLE (19, 21, 22).

B-lymphocyte antigen CD20 (CD20)

CD20 is a 33- to 37-kDa transmembrane glycoprotein of the Ig superfamily that is expressed on the surface of normal and pathogenic B cells. It is located within lipid rafts of the phospholipid membrane, where it functions as a store-operated calcium channel following ligation of the B-cell receptor with antigen. No natural ligands for CD20 have been identified. However, CD20 has been shown to participate in antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cellular cytotoxicity (CDCC) and cell growth. SLE is characterized by abnormal B-cell homeostasis. Antibodies directed against CD20 could eliminate pathogenic B cells and could therefore be effective in the treatment of SLE and other autoimmune diseases (19-23).

Table II. *Selected patents for targets being validated for systemic lupus erythematosus (from Thomson Reuters Integrity℠).*

Target	Patent	Source	Phase
CD40 ligand	WO 2008118356	Biogen Idec/UCB	Biological testing
Chemokine CCR5 receptor	WO 2004031172	Novartis	Biological testing/ Preclinical
	WO 2004050024	Incyte	Biological testing
	WO 2004054581	GlaxoSmithKline	Biological testing
	WO 2004055010	GlaxoSmithKline	Biological testing
	WO 2004055011	GlaxoSmithKline	Biological testing
	WO 2004055012	GlaxoSmithKline	Biological testing
	WO 2004055016	GlaxoSmithKline	Biological testing
	WO 2005059107	AnorMED	Biological testing
	WO 2006138350	AnorMED	Biological testing
	WO 2007022371	AnorMED	Biological testing
	WO 2009010477	Euroscreen	Biological testing
	WO 2009058919	GlaxoSmithKline	Biological testing
	WO 2009058921	GlaxoSmithKline	Biological testing
	WO 2009058923	GlaxoSmithKline	Biological testing
	WO 2009058924	GlaxoSmithKline	Biological testing
Interferon α	WO 2002066649	Genentech	Biological testing/Phase II
	WO 2005059106	Medarex	Biological testing
	WO 2006002177	Medarex	Biological testing
	WO 2006086586	Baylor Research Institute	Biological testing
	WO 2008021976	Baylor Research Institute	Biological testing
	WO 2008121616	MedImmune	Biological testing
	WO 2010042705	MedImmune	Biological testing
NF-κB	US 2006154973	Bristol-Myers Squibb	Biological testing
	US 2006154975	Bristol-Myers Squibb	Biological testing
	WO 2003024913	Asubio Pharma	Biological testing
	WO 2005070207	Bristol-Myers Squibb	Biological testing
	WO 2005072132	Bristol-Myers Squibb	Biological testing
	WO 2005072729	Bristol-Myers Squibb	Biological testing
	WO 2005072732	Bristol-Myers Squibb	Biological testing
	WO 2005073203	Bristol-Myers Squibb	Biological testing
	WO 2005073221	Bristol-Myers Squibb	Biological testing
	WO 2006076702	Bristol-Myers Squibb	Biological testing
	WO 2006138373	Bristol-Myers Squibb	Biological testing
TLR9 receptor	WO 2005007672	Coley Pharmaceutical Group	Biological testing
	WO 2007047396	Idera Pharmaceuticals	Biological testing
	WO 2010036905	Eisai R&D Management	Biological testing

CAMPATH-1 antigen (CD52)

CD52 is a 21-kDa cell-surface glycoprotein that is expressed by B and T lymphocytes, natural killer cells, monocytes, macrophages, dendritic cells, red blood cells, platelets and hematopoietic progenitor cells. Engagement of CD52 induces lysis via activation of complement and direct cell-mediated cytotoxicity; however, the biological function of CD52 remains unknown. Because antagonism of CD52 leads to rapid and profound lymphopenia, the T and B cells believed to be responsible for initiating the destructive process seen in SLE are eliminated. CD52 antagonism may therefore be an effective therapeutic strategy for SLE (24, 25).

CD40 ligand (CD40-L, CD154)

CD40-L is a costimulatory transmembrane molecule primarily expressed on activated $CD4^+$ T lymphocytes and a member of the TNF family of molecules (also known as tumor necrosis factor ligand superfamily member 5, CD154, TRAP); it is also found in a soluble form (sCD40-L). CD40-L binds to CD40 on APCs to induce activation in association with T-cell receptor (TCR) stimulation by major histocompatibility complex (MHC) molecules also on APCs. CD40-L–CD40 ligation regulates B-cell function and activates nuclear factor NF-κB and c-Jun N-terminal kinase (JNK) signaling. It has been suggested that the aberrant signaling within and between B and T cells characterizing SLE may be due to enhanced CD40–CD154 activation. Studies have shown that CD40 is overexpressed in immature and mature bone marrow-derived dendritic cells and peripheral blood monocytes from SLE patients. CD40-L is also involved in platelet activation, which plays an important role in the inflammation seen in SLE. Antagonism of CD40-L binding may be effective in the treatment of autoimmune disorders such as SLE, which involves B- and T-cell hyperactivity and platelet activation (26-30).

Chemokine CCR5 receptor

CCR5 is a G protein-coupled, 7-transmembrane receptor expressed on monocytes, macrophages, T cells and B cells that binds the C-C motif chemokines MIP-1-α, MIP-1-β and RANTES with high affinity. It also binds viral MIP-2 with high affinity and has been shown to bind cyclophilin-18 and histidyl-tRNA synthetase. CCR5 plays an important role in inflammation and alterations in expression of this protein may affect the development and progression of several autoimmune diseases, including SLE. CCR5 aids in facilitating the migration of lymphocytes to specific target organs and is thus, in part, responsible for accumulation of T cells in different organs and the possible consequent disease pathogenesis. Studies have shown that $CD4^+$ T-cell surface expression of CCR5 may be increased in patients with active SLE. Inhibition of CCR5 expression may be therapeutically effective in the treatment of SLE (31-35).

Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4, CD152)

CTLA-4 is a T-cell surface protein and member of the Ig family. In T cells, costimulatory molecules regulate immunity through enhancement and inhibition of T-cell responses. T cells require two signals for activation and acquisition of full effector function. The first signal is generated from the TCR recognizing its cognate peptide in the context of MHC molecules. Upon activation, T cells express a second costimulatory molecule, which is then activated by molecules expressed on APCs. Costimulatory molecules regulate immunity through enhancement and inhibition of T-cell responses. CTLA-4, after B7-1 Ig and B7-2 Ig binding on APCs, inhibits T-cell responses, resulting in blockade of the immune response. Anti-CTLA-4 human monoclonal antibodies (mAbs) bind to this protein and prevent the binding of B7-1 Ig and B7-2 Ig expressed on antigen-bearing cells. This enables B7 molecules to continue to enhance TCR signaling, thereby propagating an ongoing immune response. Polymorphisms in the gene expressing CTLA-4 have been reported to be associated with the pathogenesis of SLE and selective modulation of a costimulatory signaling required for full T-cell activation (i.e., CTLA-4 modulation) may be effective in the treatment of SLE and rheumatoid arthritis (19, 30, 36, 37).

Galectin-1 (Gal-1)

Gal-1 is a secreted soluble protein that regulates cell–matrix interactions, immune cell interactions and T-cell activation and apoptosis. It may act as a cell growth regulatory factor and studies suggest that galectins are involved in immune and inflammatory responses. SLE patients exhibit significantly elevated Gal-1 levels and inhibition of the expression of this protein may be effective in the treatment of this disease (38-40).

Inosine 5′-monophosphate dehydrogenase (IMPDH)

IMPDH (EC 1.1.1.205) is a homotetramer consisting of a (beta/alpha) barrel core domain and a smaller subdomain. The active site has binding pockets for the two substrates, IMP and NAD. Two isoforms of IMPDH have been described; IMPDH 1 is ubiquitous and mostly expressed in normal cells, whereas IMPDH 2 is predominant in malignant cells. The intron structures of both genes are completely divergent and the 5′-regulatory sequences are highly different. The expression of the *IMPDH1* gene is controlled by three distinct tissue-specific promoters, while the *IMPDH2* gene is regulated by a single promoter. IMPDH catalyzes the dehydrogenation of IMP to XMP using NAD as the proton acceptor. This enzyme catalyzes a key step in purine nucleotide biosynthesis which is important for the proliferation of lymphocytes. IMPDH activity is upregulated in proliferating T and B lymphocytes, a process in which a large pool of guanine nucleotides are required and which is important in autoimmune diseases such as SLE. Therapeutic inhibitors of IMPDH may be useful for treating autoimmune diseases such as SLE (41, 42).

Interferon α (IFN-α)

IFN-α is a member of the type I interferon family of cytokines. Interferons are small glycoproteins released from several cell types (i.e., leukocytes, fibroblasts and T lymphocytes) in response to antigen (i.e., the presence of pathogens such as viruses, bacteria or parasites). IFN-α can activate immune cells (natural killer cells, macrophages) and upregulate antigen presentation to T lymphocytes, resulting in boosted immune responses. Type I interferons in particular appear to be involved in SLE pathogenesis through induction of feedback loops that disrupt peripheral immune tolerance. IFN-α could therefore be effective in the treatment of SLE (26, 43, 44).

Macrophage colony-stimulating factor 1 receptor (CSF-1-R)

CSF-1-R is a tyrosine kinase receptor for macrophage colony-stimulating factor 1 (M-CSF, CSF-1) and interleukin-34 (IL-34). It is involved in the regulation of the growth and differentiation of myeloid cells, among others. CSF-1 is overexpressed at sites of inflammation and CSF-1-mediated inflammation is suspected to be involved in the pathogenesis of SLE. Antagonism of CSF-1-R may therefore be an effective therapeutic strategy for reducing macrophage number in SLE (45, 46).

Mammalian target of rapamycin (mTOR)

mTOR (RAPT1) is a serine/threonine-protein kinase that belongs to a family of phosphatidylinositol 3-kinase (PI3K)-related kinases that mediate cellular responses to stress such as DNA damage and nutrient deprivation. mTOR acts downstream of PI3K activation. Activation of mTOR results in prosurvival signaling and consequent progression of the cell cycle from the G_1 to S phase. Growth factors or cytokines (i.e., mitogenic stimuli) binding to membrane receptor tyrosine kinases trigger the PI3K/Akt signal transduction cascade pathway. Activation of PI3K phosphorylates PIP_2 (phosphatidylinositol 4,5-bisphosphate) to PIP_3 (phosphatidylinositol [3,4,5]-trisphosphate). PIP_3 activates Akt, which subsequently activates mTOR. The downstream targets of mTOR are ribosomal p70S6 kinase (p70S6K) and eukaryotic translation initiation factor 4E (eIF4E)-binding protein (4E-BP1). mTOR-mediated activation of 4E-BP1 causes its dissociation from the RNA cap-binding protein eIF4E and formation of the eIF4F complex composed of eIF4E, the scaffold protein eIF4G and the RNA helicase eIF4A. This eIF4F complex enhances cap-dependent protein translation. Thus, inhibition of mTOR would block p70S6K and 4E-BP1 signaling and prevent translation of RNAs required for cell cycle progression from the G_1 to S phase. Inhibition also induces a proapoptotic effect and results in a deficiency in active

cyclin-dependent kinase 4 (CDK4/cyclin D1), which contributes to G_1 arrest. mTOR regulates the production of IFN-α and the maintenance of immune tolerance at the level of the regulatory T cells and the dendritic cells by promoting T helper 2 (Th2) versus Th1 immune responses. Thus, inhibition of mTOR may be effective in the treatment of immunological disorders such as SLE (47-49).

Nuclear factor NF-kappaB (NF-κB)

NF-κB is a protein transcription factor and intracellular mediator of the inflammatory cascade involved in the generation of adhesion molecules (ICAM-1, VCAM-1), iNOS synthase, cyclooxygenase-2 (COX-2), cytokines (e.g., IL-1β, IL-2, TNF-α, IL-6, IFN-γ) and chemokines (e.g., IL-8). Other genes regulated by NF-κB include those encoding the IL-2 receptor, the IL-12 p40 subunit and c-Myc. NF-κB activation plays a role in inflammation and is an important signaling factor for cytokines that appear to participate in several pathological conditions, including SLE. NF-κB activation inhibitors may be effective for suppressing inflammation seen in Th17-mediated diseases such as SLE, rheumatoid arthritis, psoriasis and Crohn's disease (50-52).

T-cell surface glycoprotein CD4 (CD4)

CD4 is a transmembrane glycoprotein and member of the Ig superfamily of receptors that is expressed on the surface of Th cells, regulatory T cells, monocytes, macrophages and dendritic cells. It is a coreceptor that, together with the TCR, activates the T cell following interaction with MHC class II molecules present on the surface of APCs. CD4 amplifies the signal generated by the TCR by recruiting the tyrosine-protein kinase Lck. It has four Ig domains (D1-D4) exposed on the extracellular surface of the cell and uses the D1 domain to interact with the β2-domain of MHC class II molecules. T cells expressing CD4 molecules (but not CD8) on their surface are MHC class II-restricted, specific for antigens presented by MHC II and not by MHC class I. Commitment of T cells to proinflammatory effector Th cell lineages (e.g., IL-17-producing $CD4^+$ T cells, or Th17 cells) appears to be an important inducer of organ-specific autoimmunity and studies suggest that Th17 cells are the dominant pathogenetic cellular component in SLE and other autoimmune inflammatory diseases. Decreasing $CD4^+$ T-cell responses with an anti-CD4 antibody, for example, could reduce immune cell infiltration, and reduce subsequent initiation and progression of the autoimmune response in SLE (53-56).

Toll-like receptors 7, 8 and 9 (TLR7, TLR8, TLR9)

TLRs are a class of single-membrane-spanning, noncatalytic receptors that are the key recognition structures of the innate immune system, recognizing molecules shared by pathogens but distinct from host molecules. When activated, TLRs initiate signaling pathways leading to NF-κB activation and the production of inflammatory cytokines, chemokines, tissue-degrading enzymes and type I interferons. TLR signaling is involved in inflammation and activation of the adaptive immune system via upregulation of costimulatory molecules of APCs. TLRs participate in pathogen recognition and innate immunity activation and can therefore link innate and acquired immune responses. Inhibition of TLR7, TLR8 and TLR9, in particular, would dampen the immune response and therefore be effective in the treatment of autoimmune diseases such as SLE (51, 57-63).

Tyrosine-protein kinase Kit (c-Kit)

c-Kit is a transmembrane receptor tyrosine kinase that regulates the function of primitive hematopoietic cells, melanocytes and germ cells. Under normal conditions, binding of stem cell factor (SCF), an endogenous ligand for c-Kit, induces receptor dimerization, autophosphorylation and activation of multiple downstream pathways, including PI3K, phospholipase PLC-γ, Src kinase, Janus kinase (JAK)/signal transducer and activator of transcription (STAT) and mitogen-activated protein (MAP) kinase pathways. Defects in stem cells may be involved in the development of SLE and inhibition of c-Kit, a modulator of stem cell function, may be effective in the treatment of SLE (64-66).

DISCLOSURES

The authors state no conflicts of interest.

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