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Review

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Involvement of NF-κB Signaling Pathway in the Pathogenesis of Systemic Lupus Erythematosus

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ABSTRACT

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by accumulation of anti-nuclear autoantibodies, hyperactivation. It can affect any organ, including brain, skin, joint, and kidney. The nuclear NF-κB pathway has long been considered a crucial pro- inflammatory signaling pathway. Its transcribed the genes involves in various autoimmune disease. Within the past year, many research studies have been conducted the role of NF-κB signaling in lupus. In this review, we will highlight some recent studies that support the potential link of NF-κB signaling pathway which play a crucial role in the pathogenesis of SLE.

KEYWORDS: Systemic lupus erythematosus (SLE); Nuclear factor kappa binding (NF-κB); Lupus; Toll-like receptors (TLRs).

INTRODUCTION

Systemic lupus erythematosus (SLE) is autoimmune disease characterised by a myriad of immune system aberrations that involve B-cells, T-cells, and cells of the monocytic lineage, resulting in polyclonal B-cell activation, increased numbers of antibody producing cells, hypergammaglobulinaemia, autoantibody production, and immune complex formation. It appears that excessive and uncontrolled T-cell help in the differentiation and activation of autoantibody forming B-cells is probably a final common pathway.[1] B-cell activation is abnormal in patients with SLE. The number of B-cells at all stages of activation is increased in the peripheral blood of patients with active SLE.[2]

Abnormalities in T-cell function are also evident in patients with SLE. The total number of peripheral blood T-cells is usually reduced, probably because of the effects of antilymphocyte antibodies[3] there is a skewing of T-cell function towards B-cell help, leading to enhanced antibody production.[3] Experiments have shown that the early events of T-cell activation are defective in patients with SLE compared with controls.

The NF-κB/Rel family includes NF-κB1 (p50/p105), NF-κB2 (p52/p100), p65 (RelA), RelB, and c-Rel). Most members of this family (RelB being one exception) can homodimerize, as well as form heterodimers with each other. The most prevalent activated form of NF-κB is a heterodimer consisting of a p50 or p52 subunit and p65, which contains transactivation domains necessary for gene induction.[1] The NF-κB target genes are involved in different aspects of immune functions, ranging from the development, activation, and differentiation of lymphocytes to the maturation and inflammatory functions of innate immune cells. The NF-κB factors are normally sequestered in the cytoplasm *via* association with a family of inhibitory proteins, including inhibitor of κB-alpha (IκBα) and related ankyrin repeat-containing proteins. In addition,the IκB family also includes the precursor proteins of NF-κB1 and NF-κB2, p105 and p100, which contain a C-terminal IκB-like structure and inhibitthe nuclear translocation of specific NF-κB members.[2] Proteasome-mediated processing of p105 and p100 involves selective degradation of their C-terminal IκB-like structure, leading to the generation of re-

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spective mature NF-κB subunits, p50 and p52, and the nuclear translocation of sequestered NF-κB proteins. The latent NF-κB complexes can be activated by various immune stimuli, which involves two major signaling pathways: the canonical and non-canonical pathways.[2] Both the canonical and noncanonical NF-κB pathways play a critical role in regulating immune activation and tolerance. Recent studies have emphasized diverse.

NF-κB has been implicated in the pathogenesis of autoimmune disease, such as rheumatoid arthritis (RA), type I diabetes, multiple sclerosis and SLE. During the SLE pathogenesis nuclear NF-κB promotes the aviation of T and B-cells in SLE.[3,4] Multiple number of evidences point out the crucial role of NF-κB signaling for the proper maturation and development of lymphocytes and dendritic cells. Abnormal NF-κB signaling lead to the secretions of auto reactive T-cells, which have a critical role in SLE and promotes plasma cell development, linking linear ubiquitination to multiple autoimmune diseases.[5]

Innate immunity may have a great influence in autoimmunity through Toll-like receptors. (Figure 1) *TLR7* and *TLR9* are expressed in endosomal compartments ligation induce signal transduction *via* the myeloid differentiation primary-response protein 88 (*MyD88*).[6,7] A common adaptor protein, which interacts with *IRAK1/4* (Interleukin-1 receptor-associated kinase 1/4) and *TRAF6* (TNF receptor-associated factor 6) to form the *MyD88*/*IRAK1*/*IRAK4*/*TRAF6* complex. Subsequently, *IRAK1* and *TRAF6* dissociate from the receptor complex and interact with kinases IKKβ (Iκβ kinases) resulting in the activation of NF-κB (nuclear factor kappa-light-chain-enhancer of activated B-cells), permitting the expression of genes of proinflammatory cytokine and chemokines.[8] On the other hand, the transcription factor *IRF7* (Interferon regulatory factor 7) can bind to the *MyD88*/*IRAK1*/*IRAK4* complex, and its activation is dependent upon *TLR7* requiring the *TRAF3* (TNF receptor-associated factor 3) protein, which joins *IRAK1* and IKKα kinases to produce IFN-α. The activation of NF-κB is important for eliciting innate immune responses as well as for the subsequent development of adaptive immune responses.[9]

TLRs represent an important link between innate and adaptive immune responses.[10,11] Several mechanisms have been proposed to explain the production of autoantibodies in diseased B-cells, including impaired survival or apoptosis signalling that may prevent negative selection, dysfunctional complement or inhibitory Fc-receptors, and the activation of TLR in response to the accumulation of apoptotic bodies. Studies have shown that abnormal stimulation of innate immunity may have a great influence on immunopathogenesis of SLE through Toll-like receptors.[12,13] So far, 11 human TLRs have been identified, and *TLR7* and *TLR9* has been associated with SLE in both human and mouse models.[14,15] Both receptors are found on endosomes of several immune cells, mainly antigen-presenting cells, such as dendritic and B-cells. The recognition and internalization, through the B-cell receptor, of nuclear self-antigens released as a consequence of apoptosis in SLE patients, can activate *TLR7* in endosomes of B-lymphocytes supporting its role in the production of autoantibodies.[16,17] RNA-containing complexes must access the interior of the plasmacytoid dendritic cells (pDCs), through the Fc-receptors, thus providing a route of entry for RNA to reach *TLR7*, with the resulting INF-α production. INF-α influences the development, progression, and pathogenesis of SLE.[18-19]

Several studies have pointed to a relationship between NF-κB and lupus pathogenesis. Wen Zhang et al demonstrated that CD40-induced NF-κB signaling was constitutively activated in B-cells from active lupus patients. Including increased

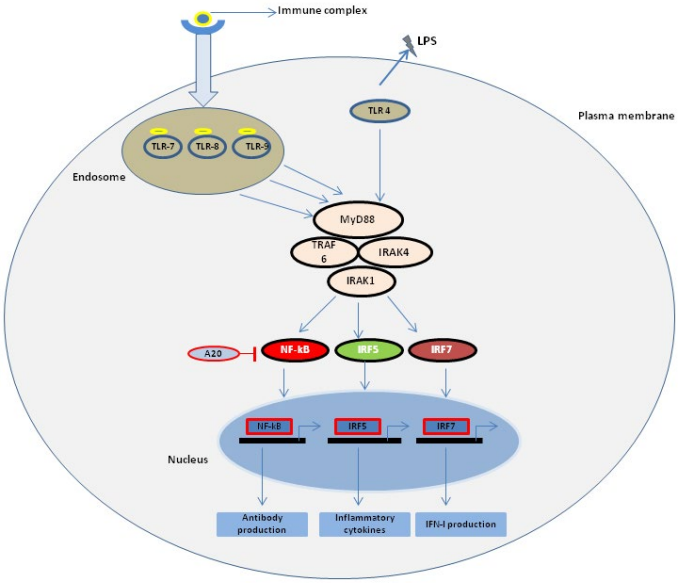

Figure 1: Overview of NF-κB signaling pathway.

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phosphorylation and degradation of IκB alpha, phosphorylation of P65 Aberrant CD40-Induced NF-κB Activation in Human Lupus B Lymphocytes.[20] Mayyan women are more suitable to get lupus disease. Pacheo et al[21] assess the role of *TLR7*, *MyD88*, and NF-κB p65 in B-lymphocytes of Mayan women with SLE and point out the increased expression of *TLR7*, *MyD88*, and NF-κB p65 in B-lymphocytes from Mayan women, which supports its role in the pathogenesis of SLE in this ethnic population of southeast of Mexico.[21]

Growing evidence suggests that recognition of nucleic acid motifs by Toll-like receptors may play a role in both the activation of antinuclear B-cells and in the subsequent disease progression after immune complex formation. TLRs expressed on various immune cells and upon detection of pathogens its trigger inflammation. For example, *TLR7* has been associated with SLE in both human and mouse models. This receptor is found on endosomes of several immune cells, mainly antigen-presenting cells, such as dendritic and B-cells. The recognition and internalization, through the B-cell receptor, of nuclear self-antigens released as a consequence of apoptosis in SLE patients, can activate *TLR7* in endosomes of B-lymphocytes supporting its role in the production of autoantibodies.[22]

Under basal conditions, NF-κB is maintained in the cytoplasm in an inactive state through inhibitors of κB (IκB). On activation, IκB rapidly undergoes phosphorylation and degradation, inducing nuclear translocation and gene expression. The A20-binding inhibitors of NF-κB (*ABINs1-3*) are suppressors of inflammation. Human polymorphisms in the gene encoding the *ABIN1* protein have been identified and are associated with a predisposition for autoimmune disease. *ABIN1*[D485N] knockin mice show significant expansion of myeloid cells in various organs and these mice show enhanced NF-κB and MAPK activation after TLR stimulation and display a SLE-like phenotype including expansion of myeloid cells, leukocyte infiltrations in different parenchymatous organs, activated T- and B-lymphocytes, elevated serum Ig levels, and the appearance of autoreactive antibodies. Kidneys develop glomerulonephritis and proteinuria, reflecting tissue injury.[23]

Inhibition of NF-κB reduced production of inflammatory cytokines IL-1 and TNFα in the RA model. NF-κB might also control B-cell function *via* BAFF and BAFF-R. This result would suggest that not only T-helper cells but also B-cells are connected by NF-κB pathways in SLE and RA. Excessive BAFF signaling through BAFF-R results in prolonged B-cell survival and costimulates B- and T-cells. Instead of blocking BAFF-R or decreasing BAFF, reduction of BAFF-R numbers would also, theoretically, reduce the effects of BAFF-BAFF-R signaling in inflammatory autoimmune diseases.

Thomas enzler et al,[24] examined which NF-κB pathway and which B-cell type are involved in development of SLE-like autoimmune disease in BAFF-Tg mice. In this study they have used genetic approach and found that both NF-κB signaling pathways contributed to disease development and possibility of controlling the amounts of BAFF-R and reducing the effects of BAFF-R signaling through NF-κB inhibition.

In other study conducted by Lee YH et al[25] determine whether polymorphisms of the Toll-like receptor (TLR) genes are associated with susceptibility to SLE and this study suggests that *TLR7*, *TLR8*, and *TLR9* polymorphisms are associated with the development of SLE in Caucasian, Asian, and African populations.[25]

Genetic approaches have gained much power and popularity in identifying the component mechanism(s) underlying the pathogenesis of common human diseases. (Table 1)

Gene	Function	Risk for disease
IRF5	Regulates type 1 IFN pathway	SLE, RA
IRF6	Regulates type 1 IFN pathway	SLE, RA
IRF7	Regulates type 1 IFN pathway	SLE, RA
STAT4	Regulates type 1 IFN pathway	SLE, RA
TRAF6	Regulates NF-κB pathway	SLE, RA
TNFAIP3	Regulates type 1 IFN pathway	SLE, RA
TNIP1	Regulates type 1 IFN pathway	SLE, RA
IRAK1	Innate immune signaling	SLE, RA
TLR7	Innate immune signaling	SLE, RA
TLR9	Innate immune signaling	SLE, RA
UBE2L3	Regulates NF-κB pathway	SLE, RA
SLC1514	Regulates NF-κB pathway	SLE, RA
PRKCB	Regulates NF-κB pathway	SLE, RA
TYK2	Regulates type 1 IFN pathway	SLE, RA

IFN: Interferon; NF-κB: Nuclear factor-κB; SLE: Systemic Lupus Erythematosus; TLR: Toll-like receptor. See text for complete gene names

Table 1: Pathway-associated SLE candidate genes.

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Genes that play a role in the NF-κB pathway downstream of TLR engagement have also been associated with increased SLE susceptibility. For example, both risk and protective haplotypes of *IRAK1* (interleukin-1 receptor-associated kinase 1) have been associated with SLE. The X-linked *IRAK1* gene encodes a kinase that acts as the *MyD88* complex on/off switch for activation of the NFκB inflammatory pathway. *TNFAIP3*, also associated with SLE and subphenotypes including renal disease, encodes A20, a deubiquitinating enzyme that inhibits NF-κB, leading to protein degradation and interactions that inhibit NF-κB activity and TNF-mediated programmed death. A dinucleotide polymorphism just downstream of the *TNFAIP3* promoter region was linked to the decreased expression of A20 in patients with SLE of Korean and European ancestry, and may be the risk haplotype functional variant. *TNIP1* (*TNFAIP3* interacting protein 1), encoding the A20-interacting protein, has also been associated with the risk of SLE. Additional genes within the NF-κB pathway associated with SLE susceptibility include: *SLC15A4* (solute carrier family 15, member 4) encoding a peptide transporter that participates in NOD1-dependent NF-κB signalling; *PRKCB* (protein kinase C, β), which is involved in B-cell receptor-mediated NF-κB activation and *UBE2L3* (ubiquitin-conjugating enzyme E2L 3), encoding the enzyme *UBCH7*, which participates in the ubiquitination of an NF-κB precursor, and may play a role in cell proliferation. A risk haplotype of *UBE2L3* confers increased *UBCH7* expression in patients with SLE; a variant contained in this haplotype has been associated with the presence of anti-dsDNA antibodies.[26] (Paragraph adapted from Ornella Josephine, Ann Rheum Dis 2012)

CONCLUSION

In this review, we have summarized that aberrant activation of NF-κB in lupus disease. It is worth to point out here that NF-κB may play even more roles than mentioned above in the development of SLE, as exemplified by multiples studies in both mice and human patients. The significance of NF-κB activation in SLE suggests that inhibition of this signaling pathway provides novel strategies for the prevention and treatment of disease. It is hopeful that as we increase our understanding of the regulation of the NF-κB pathways, insights into the better design of drugs that effectively target NF-κB will be gained that will ultimately lead to better prevention and treatment of the disease.

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