



Comprehensive review on Nuclear Factor- κ B (NF- κ B) signaling and its role in autoimmune diseases

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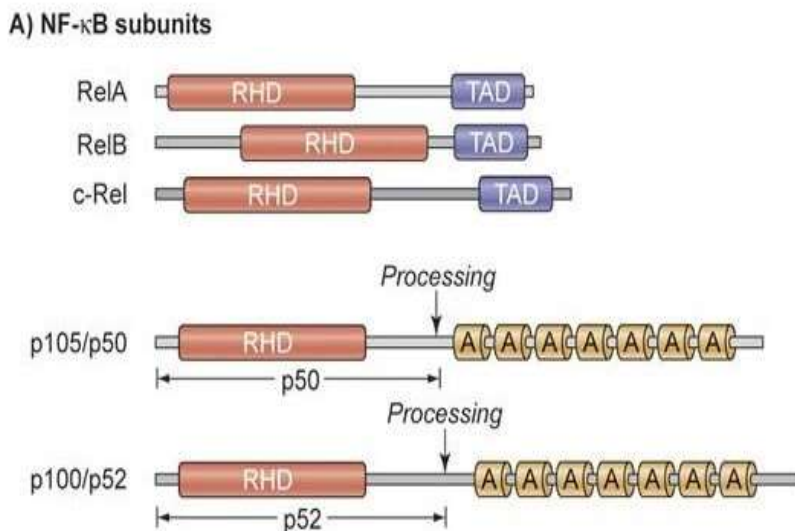
ABSTRACT:

Nuclear factor-Kappa B (NF- κ B) is an inactive transcription factor that became activated when translocate from cytoplasm to the nucleus, where it affects the expression of approximately 300 immunological, growth, and inflammatory genes. There are five members of the NF- κ B family have been identified. There are two mechanisms for NF- κ B activation: canonical and non-canonical signalling. NF- κ B transcription factors are important regulators of both innate and adaptive immune responses, and abnormalities in NF- κ B signalling lead to the development of immunological disorders. As a result of its activities during thymic selection, NF- κ B is critical for maintaining immunological tolerance, both for negative selection of autoreactive T cells and for the selection and maintenance of Tregs. Rheumatoid arthritis, multiple sclerosis, thyroid illness, diabetes, asthma, systemic lupus erythematosus, and inflammatory bowel disease have all been associated to NF- κ B. The goal of this review is to discuss about molecular mechanism of NF- κ B and how it implicated in the pathogenesis of human diseases.

KEYWORDS: Nuclear factor-Kappa B (NF- κ B), Signalling, Canonical, Non-canonical, Autoimmune diseases

INTRODUCTION:

Nuclear factor- κ B (NF- κ B) was discovered in the nucleus of B cells by David Baltimore and colleagues in 1986 as a factor¹ that represents a family of inducible transcription factors, including NF- κ B1 (also named p50), NF- κ B2 (also named p52), RelA (also named p65), RelB and c-Rel, which mediates transcription of target genes by binding to a specific DNA element, κ B enhancer, as various hetero- or homo-dimers² that located within promoters and enhancers of a large number of genes³.

Figure 1: NF- κ B subunits⁴

NF- κ B proteins are characterized by the presence of a conserved 300-amino acid Rel homology domain (RHD) that is located toward the N terminus of the protein, which is responsible for dimerization, interaction with I κ Bs, and DNA binding⁵. NF- κ B has also been linked to immune system dysfunction and autoinflammatory disorders³. NF- κ B was discovered in B cells due to its interaction with an 11-base pair sequence in the immunoglobulin light-chain enhancer, but it has been found in many different cell types⁶.

NF- κ B SIGNALLING:

NF- κ B either directly or indirectly promotes the activation of autoimmune T cells by altering the activity of dendritic cells (DCs). DCs are the most well-known accessory cells involved in the induction of cell-mediated immunity and antigen presentation⁷. The NF- κ B pathway is important for DC maturation, and unregulated NF- κ B activation in DCs has been linked to the development of autoimmunity⁸. Mice lacking A20 (negative regulators of NF- κ B) [3] specifically in DCs spontaneously demonstrated DC activation and T cells proliferation⁹. The normal immune system generates a population of T cells known as regulatory T cells (Tregs) that are trained to suppress the immune system. A disruption in Treg development or function is a primary cause of autoimmune and inflammatory diseases in humans and animals¹⁰. Treg depletion causes inflammatory bowel disease, which is most likely caused by overactive immunological responses to commensal bacteria in the intestine¹¹. Modulation of NF- κ B has been observed for most coreceptor pathways, and thus the I κ B kinase complex (IKK)/NF- κ B signalling cascade is thought to play a critical role in integrating TCR and costimulatory signals¹². Several genetic investigations have revealed signalling intermediates involved in the activation of the IKK complex by the BCR and TCR receptors. Protein kinase C θ (PKC θ) in T cells and PKC β in B cells act through these effectors to promote NEMO polyubiquitination and subsequent IKK and JNK activation via a trimolecular protein complex CARMA1 (also known as CARD11)-BCL10-MALT1 (referred to as the CBM complex). The antigen receptor (AgR)-induced signalling pathway that leads to NF- κ B activation has been identified as CARMA1, BCL10, and MALT1¹³.

NF- κ B signalling is primarily regulated by inhibitor κ B (I κ B) proteins and the I κ B kinase complex via two major pathways: the canonical and non-canonical NF- κ B pathways¹⁴. Individual I κ B and IKK regulatory proteins play distinct roles in the canonical and noncanonical activation pathways, as well as in the activation of specific NF- κ B dimers within these pathways¹⁵. Both canonical and noncanonical pathways play essential roles in modulating immunological activation and tolerance⁸.

The transcription factor NF- κ B is required for the initiation of immunological tolerance. Immune tolerance is made up of both central and peripheral mechanisms⁸. NF- κ B regulates three aspects of T-cell central tolerance: i) the development and function of medullary thymic epithelial cells (mTECs); (ii) the development of regulatory T cells (Tregs); and (iii) thymocyte negative selection. Noncanonical pathways play critical role in development of mTECs¹⁶.

CANONICAL PATHWAY:

The 'canonical' NF- κ B pathway is the signalling mechanism through which cytokines regulate the degradation of I κ B α to release p50/RelA and p50/c-Rel heterodimers¹⁷. Many agents, including microbial pathogens, pro-inflammatory cytokines, and T cell costimulation, activate the canonical pathway¹². The classical pathway, which is regulated by RelA, c-Rel, and p50 nuclear translocation, is essential for activation, differentiation, and survival of immune cells³. Canonical pathway of NF- κ B activation involves phosphorylation of I κ B α by the I κ B kinase (IKK) and subsequent I κ B α degradation, which causes the nuclear translocation of NF- κ B dimers¹⁸. Inhibitors of NF- κ B Kinase (IKK) complex are made up of the catalytic subunits IKK α , IKK β , and regulatory subunit NEMO, which is a component of the IKK α and β containing-complex¹⁹, for NF- κ B essential modulator, that also known as IKK γ in human²⁰. NEMO mutations have been linked to anhidrotic ectodermal dysplasia with immunodeficiency (EDA ID). Ectodermal tissues such as the skin, hair, teeth, and sweat glands are abnormally developed in this disease^{21,22}.

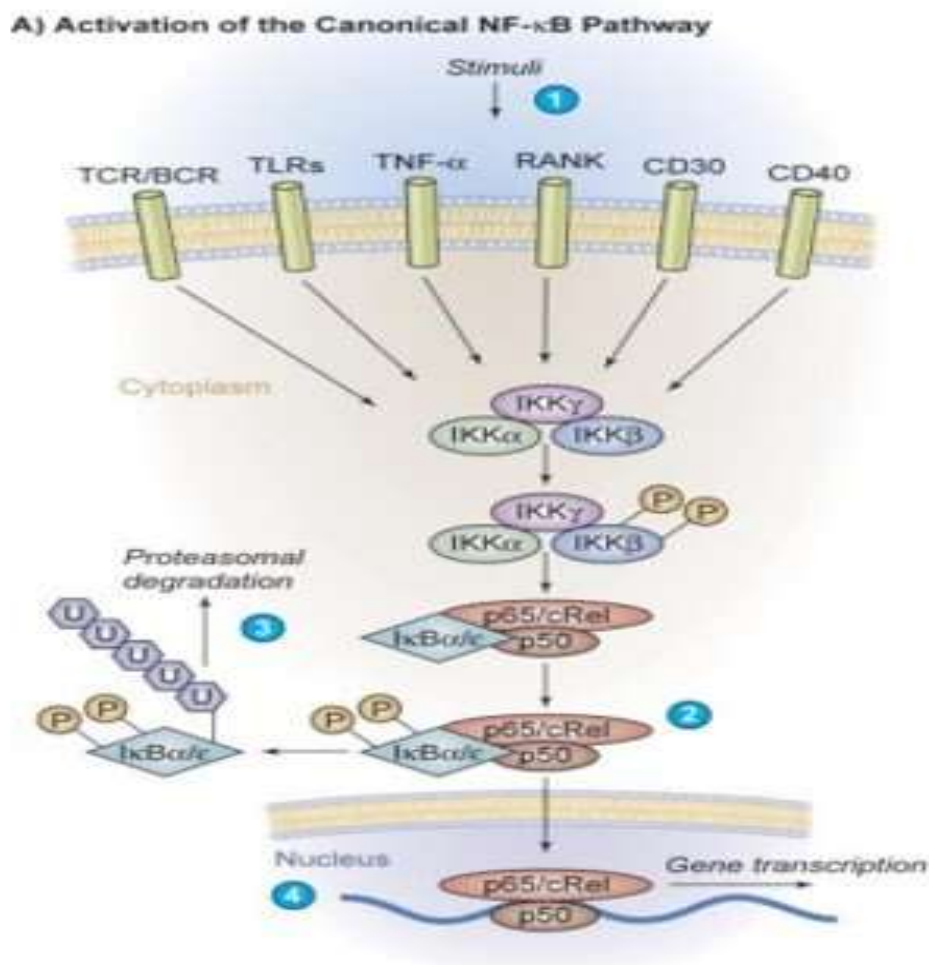


Figure 2: Canonical NF- κ B signaling pathways⁴

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A variety of stimuli, including Toll-like receptor (TLR) ligands, tumour necrosis factor- α (TNF- α) and IL-1, T-cell antigen receptor (TCR) and B-cell antigen receptor (BCR) agonists¹⁶, and pattern recognition receptors (PRRs), can activate the canonical pathway rapidly and transiently². TNF receptor activation causes a chain reaction of adaptor proteins with TRAF-binding domains to interact²³. All TLRs activate NF- κ B via the MyD88 (which is made up of a TIR domain and a death domain²⁴ or TRIF-dependent pathway, or both. TRIF activates NF- κ B via the RIP1/TRAF6-TAK1- IKK α / β pathway, whereas MyD88 activates NF- κ B via the IRAKs-TRAF6-TAK1- IKK α / β pathway²⁵. The canonical NF- κ B pathway is essential for T-cell activation⁸. In the Modification of canonical pathway, TNFAIP3 is increased in response to TNF receptor and TLR ligation, and A20 suppresses NF- κ B-dependent gene expression in the Modification of Canonical Pathway²⁶. Single nucleotide polymorphisms (SNPs) in the human A20 (encoded by TNFAIP3³ is a potent anti-inflammatory protein that utilizes de-ubiquitinating²⁶, locus (also known as TNFAIP3) have been associated with several human autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis, psoriasis, and celiac disease, implying that altered A20-dependent functions contribute to human autoimmunity⁹. The role of A20 in regulating NF- κ B activity and immunological responses was verified in A20-deficient mice²⁶. Human Crohn's disease (CD), an inflammatory bowel disease (IBD), may be linked to TNFAIP3 SNPs⁹. TRAF6 is a RING-domain E3 ubiquitin ligase that, along with E2, Ubc13, and Uev1A²⁵, is a member of the tumour necrosis factor receptor-associated factor (TNFR) family, which regulates the development, homeostasis, and activation of immune cells. Excessive activation of immune cells may be a cause of the development of autoimmune diseases²⁷.

NON-CANONICAL PATHWAY:

The noncanonical pathway is activated at a slower rate than the classical pathway¹⁵. Non-inflammatory stimuli, such as lymphotoxin signalling, CD40L, RANK ligand, and B-cell-activating factor (BAFF) of the tumor-necrosis factor family, frequently activate the non-canonical (or alternative) pathway¹⁶. NEMO- and IKK β -independent IKK α dimer complex mediates non-canonical signalling²⁰ via p52 and RelB nuclear translocation promotes lymphocyte maturation and survival, as well as lymphoid organogenesis³. The Noncanonical pathway results in NF- κ B2 processing and the selective activation of p52/RelB dimers¹².

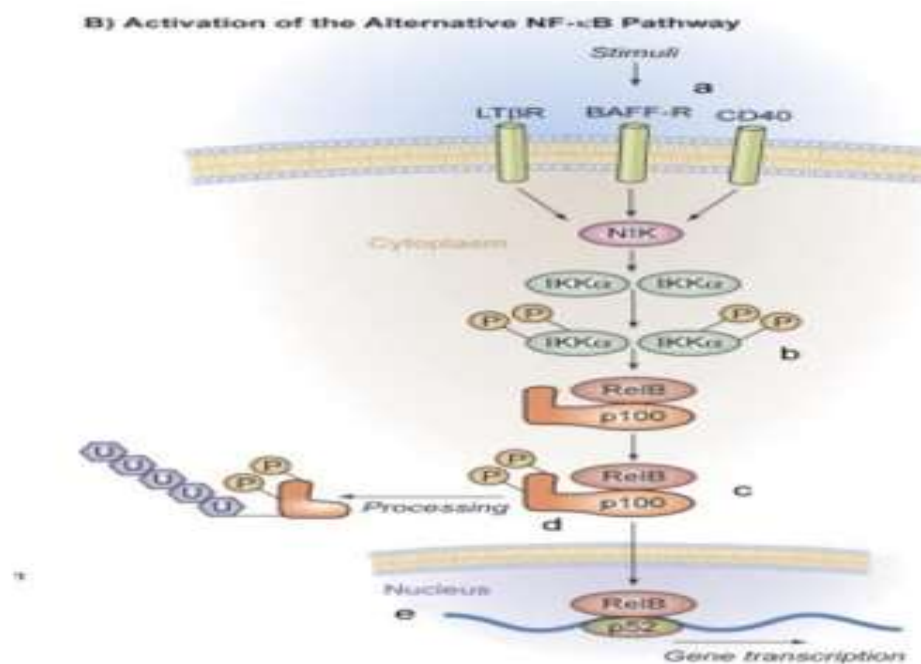


Figure 3: Non-canonical NF- κ B signaling pathways²⁸

The discovery of non-canonical NF- κ B signalling pathway came from the study of p100 processing²⁸, the precursor for p52, and this is independent of both IKK β and IKK γ ²⁹. Processing of p100 is a signal-induced and

posttranslational event³⁰ that serves to generate p52 as well as induce nuclear translocation of the RelB/p52 heterodimer²⁸. The only kinase capable of inducing productive p100 processing is the NF- κ B-inducing kinase (NIK)³¹. Overexpression of NIK in fibroblasts requires IKK1 expression to induce p100 processing to p52³². NF- κ B-inducing kinase (NIK) is a key signalling component of the noncanonical NF- κ B pathway that collaborates with a downstream kinase, initiate of NF- κ B kinase α (IKK α), to induce phosphorylation-dependent ubiquitination and processing of p100³⁰. NIK plays an important role in regulating DC maturation, which contributes to T-cell activation and autoimmunity. It has been proposed that NIK plays a role in the formation of Th17 cells, and its absence in Th cells renders them incapable of inducing autoimmune responses⁷. PELI1 can inhibit the NF- κ B pathway by ubiquitinating and destroying an NF- κ B-inducing kinase (NIK)³³. Activation of the noncanonical pathway is crucial for normal thymic structure and function, and consequently proper AIRE expression to maintain central tolerance. In the periphery, noncanonical NF- κ B signalling is essential for SLO development as well as for AIRE expression in eTACs³⁴. Mutations in the AIRE gene, which controls a rare step of polyglandular autoimmunity, suggest that the AIRE protein functions as an ubiquitin ligase, a working step required for NF- κ B activation³⁵. The alternative pathway appears to be the key signalling component in the growth and function of thymic stromal cells in the establishment of T-cell central tolerance, whereas the canonical pathway is more involved in autonomous T-cell selection¹⁶. Peli1 is unique in that it is expressed at high levels in lymphocytes and plays an important role in the negative regulation of T-cell activation and the maintenance of peripheral immune tolerance¹⁷. It has been linked to a number of autoimmune diseases, including systemic lupus erythematosus (SLE), multiple sclerosis (MS), and autoimmune encephalomyelitis³⁶.

NF- κ B AND ITS INVOLVEMENT IN AUTOIMMUNE DISEASES:

NF- κ B has been linked to the development of several autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, type I diabetes, multiple sclerosis, and inflammatory bowel disease⁸. NF- κ B has been linked to immune deficiencies and autoinflammatory diseases³. In mammals, there are five members of the NF- κ B family: RelA/p65, RelB, c-Rel, p50 (NF- κ B1) and p52 (NF- κ B2)³⁷. Syndromes caused by heterozygous mutations in NF- κ B1 include autoimmune manifestations of arthritis, lung inflammation, gut inflammation, and immune-mediated thrombocytopenic purpura (ITP)³, which can also lead to antibody deficiency³⁸, as well as a defect in Tregs, with a decrease in effector Tregs³⁹. Mutations in NF- κ B2 gene induce an antibody deficiency disease with varying B cell deficits⁴⁰.

Rheumatoid arthritis:

Rheumatoid arthritis (RA) is a diverse and complicated autoimmune inflammatory disease. A variety of cell types are involved in the pathogenesis of RA, including innate immune cells such as monocytes/macrophages, T cells, B cells, and synovial fibroblasts⁴⁰. In the pathophysiology of RA, fibroblast-like synoviocytes (FLSs) are important in disease progression by maintaining inflammation and promoting autoimmunity, resulting in joint destruction⁴¹. Th17 cells are one of the most critical subsets of T cells in the pathophysiology of RA. Deregulated NF- κ B activation also helps to the abnormal self-reactive B cells survival and the generation of autoantibodies, both of which play a role in the pathophysiology of RA². In RA, NF- κ B activation is critical in both in the beginning and continuation of chronic inflammation⁴². Immunohistochemical studies found nuclear RelA (p65) and NF-B1 (p50) primarily in RA endothelium and synovial lining⁴³ that is covered by two major cells, macrophages-like synovial cells (MLSs) and FLSs [42], particularly in CD14-positive cells, with no staining in normal synovium⁴³. TNF- α , IL-1, and IL-6 are inflammatory cytokines produced by CD4 + T cells activation, which stimulate synovial fibroblasts, monocytes, and macrophages⁴⁴. TNF- α and IL-1 β , IL-17 seems to be a critical pathogenic factor in RA and is released by both Th17 and mast cells within inflamed joints. Th1 immunity during RA is established through multiple experimental data and patients' observations, accumulating evidence points out the contribution of Th17 cells and IL-17 during disease progression⁴⁵. NF- κ B - inducing kinase is essential for production of Th1 and Th17 that is beneficial to the progression of RA⁴². It has been demonstrated that the interleukin 6 (IL-6) and interleukin 8 (IL-8) production by RA-FLSs has been induced by IL-17⁴⁶. Although RA was previously thought to be dependent on IFN-producing Th1 cells, new evidence suggests that Th17 cells play an important role in RA development⁴⁷. Survival, differentiation, and activation of T cells, B cells, and DCs are all significantly connected to NF- κ B pathway activity⁴². NOTCH activation has been demonstrated to activate p52 in osteoblasts and synoviocytes in individuals

with rheumatoid arthritis. Indeed, p52 activation has been shown to increase the production of pro-inflammatory cytokines and inhibiting osteoblast development, resulting in chronic inflammation, bone loss, and cartilage damage, all of which are characteristics of rheumatoid arthritis⁴⁸. The concentration of NF- κ B in the synovium increased, and its binding to DNA was found to be much stronger in RA.

Multiple sclerosis:

NF- κ B pathways are altered in multiple sclerosis (MS), resulting in increased NF- κ B activation in cells. This could point to NF- κ B plays an important role in the MS pathogenesis⁴⁹. MS is thought to be caused by an autoimmune reaction mediated by T cells against oligodendrocytes and myelin. T cells are responsible for a wide range of immune responses, such as attacking foreign substances, enhancing the B cell response, and producing cytokines that direct responses and activities in other immune cells⁵⁰. MS is thought to develop in genetically susceptible people after they are exposed to an environmental trigger that causes myelin-specific T lymphocytes to become activated⁵¹. These myelin reactive T cells then cross the blood-brain barrier (BBB) and enter the CNS, causing inflammation and, eventually, demyelination and neurodegeneration⁵². The NF- κ B activation pathways, canonical and noncanonical signalling are both implicated in the pathogenesis of EAE². The animal model experimental autoimmune encephalomyelitis (EAE) has been extensively studied in the study of MS. EAE is induced by immunization with myelin-derived antigens in adjuvant or by the adoptive transfer of activated myelin-specific T cells⁵¹. In the peripheral blood, patients with multiple sclerosis and healthy people appear to have equal numbers of T cells that respond to myelin⁵³. Myelin-reactive T cells from MS patients generate cytokines that are more compatible with a Th1-mediated response, whereas myelin-reactive T cells in healthy people are more likely to produce cytokines that are more consistent with a Th2-mediated response⁵⁴. Other kinds of cells are believed to have a role in the multiple sclerosis pathogenesis. In patients with this disease, regulatory cells, such as CD4+/CD25+ and CD8+ regulatory T cells, appear to be deficient^{55,56}. In patients with this disease, regulatory cells, such as CD4+/CD25+ and CD8+ regulatory T cells, appear to be insufficient^{55,56}. TNF immunoreactivity has been reported in MS lesions in association with astrocytes and macrophages⁵⁷.

Thyroid:

Several studies have demonstrated that NF- κ B has been implicated in thyroid autoimmunity, thyroid cancer, and thyroid-specific gene regulation⁵⁸. Because of its ability to control the proliferative and anti-apoptotic signalling pathways of thyroid neoplastic cells, NF- κ B has recently been shown to play an important role in thyroid cancer. Thyroid carcinomas are classified into four types: papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), both of which are classified as differentiated thyroid carcinomas, medullary thyroid carcinoma (MTC), and undifferentiated anaplastic thyroid carcinoma (ATC)⁵⁹. Disruption of apoptosis has been linked to a variety of diseases, including cancer. NF- κ B is one of the key factors controlling anti-apoptotic responses among numerous molecules involved in various anti- or pro-apoptotic signalling pathways⁶⁰. The anti-apoptotic function of NF- κ B was mediated by the inhibition of JNK signaling⁶¹. Oncogenic proteins such as Ret/PTC, Ras, and BRAF can activate NF- κ B, which could be a promising treatment strategy for advanced thyroid cancer⁶⁰. The sodium-iodide symporter (NIS) is a member of the human solute carrier (SLC) family of transporters that mediates iodide transport across the basolateral membrane of thyroid cells⁶². It is essential for thyroid metabolism⁶³. The canonical NF- κ B pathway, which involves preferentially the heterodimer p65/p50 and is triggered in response to a variety of stimuli, including pro-inflammatory cytokines such as tumour necrosis factor (TNF-) and bacterial lipopolysaccharide, is one of the most important pathways for NF- κ B activation (LPS). TNF-, a genuine NF- κ B activator with a prominent function in thyroid autoimmunity⁶², has been shown to inhibit NIS expression.

Diabetes:

NF- κ B plays an important role in the pathogenesis of diabetic vascular complications. Inhibiting NF- κ B may be a viable treatment option for diabetic vascular complications. Increased levels of advanced glycation end products (AGEs), receptors for it (RAGE), oxidative stress, lipoproteins, and hyperlipidemia all increase nuclear factor- (NF- κ B) expression via different pathways⁶⁴. Proinflammatory cytokines activate the transcription factor nuclear factor (NF)- κ B, which is involved in beta cell death in type 1 diabetes⁶⁵. Type 1 diabetes mellitus (T1DM) is an organ-specific autoimmune disease characterized by inflammatory infiltration of the pancreatic islet and destruction of the

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pancreatic cells by autoreactive T cells. The genetic abnormality in humans with Type 1 diabetes differs from that of NOD mice, but the deficiency likewise decreases NF- κ B activity⁶⁶. The IKK complex, which includes NEMO and IKK, is critical for maintaining low baseline levels of NIK and inhibiting non-canonical NF- κ B signalling⁶⁷. IL-1 β mediates IKK β degradation in beta cells; leading to IKK α homodimer activation⁶⁸, IL-1 β -mediated IKK β reduction in beta cells contributes to higher NIK protein levels, contributes to the activation of the non-canonical pathway in beta cells⁶⁵. I κ B β is involved in the long-term activation of NF- κ B¹. Activation of the nuclear factor kappa B (NF- κ B) in adipose tissue has recently been linked to the development of insulin resistance. Celastrol, an NF- κ B inhibitor, that inhibition of the NF- κ B pathway may improve insulin resistance and renal function through the modulation of inflammatory processes in both adipose tissues and kidneys. Celastrol therapy reduced lipid accumulation and oxidative stress in a variety of tissues, including the liver and adipose tissue⁶⁹.

Asthma:

Asthma is of particular importance since it is characterised by airway inflammation and infiltration of eosinophils, monocytes/macrophages, lymphocytes, and mast cells into the lungs⁷⁰. The pathogenesis of asthma involves persistent expression of a wide range of genes, which contain the κ B site for NF- κ B inside their promoters, suggesting that NF- κ B plays a pivotal role in the initiation and maintenance of allergic inflammation¹. Dendritic cells are Antigen-presenting cells (DCs) identify allergens and move to lymph nodes, where they offer antigens to naive CD4 T cells and stimulate development into distinct types of T helper (Th) cells (e.g. Th1, Th2, Th17). Th2 cells are linked to the development and progression of asthma. A variety of cytokines found in the environment affect the direction of T cell development by interacting with receptors and activating intracellular signalling cascades. In the asthma progression, TLRs and transcription factors such as NF- κ B serve an essential function. In allergen-specific Th2 cells activation, DCs perform a critical function. Toll-Like Receptors activate immune cells and pro-inflammatory cytokines by identifying pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) via unique structural domains⁷¹. NF- κ B controls the expression of large number of genes involved in immunological and inflammatory responses⁷². Furthermore, glucocorticoids (GCs), which block NF- κ B, are the most effective asthma treatment⁷³. GCs have been found to prevent the interaction of NF- κ B with DNA as well as the direct interaction of NF- κ B with the glucocorticoid receptor (GR). GC treatment has been proven in several investigations to inhibit NF- κ B activity in tissues *ex vivo*. The binding of GC with 2 agonists more effectively suppresses NF- κ B⁷⁰.

Systemic lupus erythematosus:

Systemic lupus erythematosus (SLE) is a chronic autoimmune illness characterised by multi-organ inflammation caused by a lack of tolerance to self-antigens and the development of anti-nuclear antibodies⁷⁴. Although the pathophysiology of SLE is unknown, various genetic, hormonal, and environmental variables are thought to play a role in its development. According to research, aberrant activation of innate immunity via Toll-like receptors (TLRs) may have a significant impact on the immunopathogenesis of SLE⁷⁵. Various TNF family members, including BAFF, TWEAK, CD40, and OX40, are involved in the systemic lupus erythematosus (SLE) pathophysiology. NIK promotes non-canonical NF- κ B signalling downstream of multiple TNF family members, including BAFF, TWEAK, CD40, and OX40⁷⁴. TWEAK is a novel member of the tumour necrosis factor ligand superfamily that is found in a variety of organs and is expressed in a variety of cell types, including lymphocytes, macrophages, natural killer cells, renal tubular epithelial cells, and glomerular mesangial cells. When TWEAK is combined with its receptor Fn14, it activates the NF- κ B signalling pathway, which plays a role in inflammation, angiogenesis, cell proliferation and apoptosis⁷⁶. During the pathophysiology of SLE, nuclear NF- κ B promotes T and B-cell activation. SLE patients have aberrant B-cell activation. In the peripheral blood of individuals with active SLE, the number of B-cells at all stages of activation is enhanced. T-cell function abnormalities are also seen in people with SLE. The total number of T-cells in the peripheral circulation is usually reduced, most likely due to the impact of antilymphocyte antibodies, which cause a skewing of T-cell function toward B-cell assistance, resulting in increased antibody production⁷⁷. In lupus, NF- κ B signalling activation is suppressed in T cells due to the lack of the p65 appearance in the nucleus, one of the NF- κ B subunits that bind to DNA⁷⁸. Abnormal NF- κ B signalling results in the

release of auto reactive T-cells, which play a vital role in SLE and promote plasma cell development, linking linear ubiquitination to a variety of autoimmune disorders⁷⁹

Inflammatory bowel disease:

Chronic inflammation of mucosal surface is caused by over activation of effector immune cells, which release high amounts of pro-inflammatory cytokines such as tumour necrosis factor- α , interleukin-6, and interferon- γ , causing colonic tissue damage in both IBD entities (This includes Crohn's disease and ulcerative colitis). Like macrophages and epithelial cells, lamina propria fibroblasts are thought to perform a pro-inflammatory role in IBD through the NF- κ B pathway⁸⁰. The intestinal lamina propria contains a complex population of immune cells that balance the luminal microbiota's requirement for immunological tolerance. Increased numbers and activation of innate immune cells (neutrophils, macrophages, dendritic cells, and natural killer T cells) and adaptive immune cells (B cells and T cells) in the intestinal mucosa in IBD patients raise local levels of tumour necrosis factor (TNF- α), interleukin-1 β , and interferon- γ ⁸¹. In addition to TNF- α , IL-1, and IL-6, NF- κ B can regulate the expression of IL-12 and IL-23, both of which are pro-inflammatory cytokines that are directly implicated in mucosal tissue destruction⁷⁹. IBD has also been linked to polymorphisms and mutations in the NFKB1 gene that encodes the I κ B-like protein p105 and its processing product p50². The IKK complex is made up of two catalytic subunits, IKK α and IKK β , and a regulatory protein called NF-kappaB essential modulator (NEMO)⁸⁰. I κ B- α , which is an inhibitor of Nf-kb, can enter the nucleus on its own and then facilitates the inhibition of DNA-binding of NF- κ B and promotes the nuclear export of NF- κ B⁸².

REFERENCES:

1. Mamatha Serasanambati, Shanmuga Reddy Chilakapati. Function of Nuclear Factor kappa B (NF- κ B) in human diseases-A Review. South Indian Journal of Biological Sciences, 2016; 2(4): 368-87.
2. Liu, T., Zhang, L., Joo, D. et al. NF- κ B signaling in inflammation. Sig Transduct Target Ther 2, 17023 (2017). <https://doi.org/10.1038/sigtrans.2017.23>
3. Miraghazadeh B and Cook MC. Nuclear Factor-kappaB in Autoimmunity: Man and Mouse. Front. Immunol. 2018; 9: 613. <https://doi.org/10.3389/fimmu.2018.00613>
4. Philipp J. Jost and Jurgen Ruland. Aberrant NF-B signaling in lymphoma: mechanisms, consequences, and therapeutic implications. Blood, 2007; 109 (7): 2700–7. <https://doi.org/10.1182/blood-2006-07-025809>
5. Hayden MS, Ghosh S. Signalling to NF-kappaB. Genes Dev. 2004; 18:2195–224. doi:10.1101/gad.1228704
6. Patel S., Santani D. Role of NF- κ B in the pathogenesis of diabetes and its associated complications. Pharmacol. Rep. 2009; 61595–603. [https://doi.org/10.1016/S1734-1140\(09\)70111-2](https://doi.org/10.1016/S1734-1140(09)70111-2)
7. Janin Hofmann, Florian Mair, Melanie Greter, Marc Schmidt-Supprian and Burkhard Becher. NIK signalling in dendritic cells but not in T cells is required for the development of effector T cells and cell-mediated immune responses. J. Exp. Med. 2011 Aug 29; 208(9): 1917–29. doi: 10.1084/jem.20110128
8. Sun SC, Chang JH, Jin J. Regulation of nuclear factor- κ B in autoimmunity. Trends Immunol. 2013; 34(6): 282-9. doi: 10.1016/j.it.2013.01.004
9. Hammer GE, Turer EE, Taylor KE, Fang CJ, Advincula R, Oshima S, Barrera J, et al. Expression of A20 by dendritic cells preserves immune homeostasis and prevents colitis and spondyloarthritis. Nat Immunol. Dec 2011; 12(12):1184-93. DOI:10.1038/ni.2135
10. Shimon Sakaguchi, Tomoyuki Yamaguchi, Takashi Nomura, Masahiro Ono. Regulatory T cells and immune tolerance. Cell, 30 May 2008; 133(5): 775–87. <https://doi.org/10.1016/j.cell.2008.05.009>
11. B. Singh, S. Read, C. Asseman, V. Malmstrom, C. Mottet, L.A. Stephens, R. Stepankova, H. Tlaskalova, F. Powrie. Control of intestinal inflammation by regulatory T cells Immunol. Rev., 2001; 182: 2190-200.
12. Schmitz, M., Krappmann, D. Controlling NF- κ B activation in T cells by costimulatory receptors. Cell Death Differ 2006; 13: 834–42. doi:10.1038/sj.cdd.4401845
13. Jan Schulze-Luehrmann, Sankar Ghosh. Antigen-Receptor Signaling to Nuclear Factor κ B. Immunity. November 2006; 25(5): 701-15. <https://doi.org/10.1016/j.immuni.2006.10.010>
14. Gilmore, T. Introduction to NF- κ B: players, pathways, perspectives. Oncogene. Published: 30 October 2006; 25(51): 6680–4.
15. Felicity D. Herrington, Ruaidhri J. Carmody, and Carl S. Goodyear. Modulation of NF- κ B signaling as a Therapeutic Target in Autoimmunity. Journal of Biomolecular Screening 2016, Vol. 21(3) 223–42.
16. Mingzhao Zhu and Yangxin Fu. The complicated role of NF- κ B in T-cell selection. Cell Mol Immunol, published online 2010 Mar 1; 7: 89–93. doi: 10.1038/cmi.2009.112
17. Beinke S, Ley SC. Functions of NF-kappaB1 and NF-kappaB2 in immune cell biology. Biochem J. 2004 Aug 24; 382(Pt 2): 393-409. doi: 10.1042/BJ20040544
18. Chang M, Jin W, Chang JH, et al. The ubiquitin ligase Peli1 negatively regulates T cell activation and prevents autoimmunity. Nat Immunol. 2011; 12(10): 1002-9. doi:10.1038/ni.2090

19. Rothwarf DM, Zandi E, Natoli G, Karin M. IKK-Gamma Is an Essential Regulatory Subunit of the I κ B Kinase Complex. *Nature*, 1998; 395: 297–300. <https://doi.org/10.1038/26261>
20. Barnabei Laura, Laplantine Emmanuel, Mbongo William, Rieux-Laucat Frédéric, Weil Robert. NF- κ B: At the Borders of Autoimmunity and Inflammation. *Frontiers in Immunology*. 2021 Aug 9; 12: 716469. doi: 10.3389/fimmu.2021.716469
21. Doffinger R, Smahi A, Bessia C, Geissmann F, Feinberg J, Durandy A, et al. X-Linked Anhidrotic Ectodermal Dysplasia With Immunodeficiency is Caused by Impaired NF- κ B Signaling. *Nat Genet*, 2001 Mar; 27(3): 277-85. DOI:10.1038/85837
22. Zonana J, Elder ME, Schneider LC, Orlov SJ, Moss C, Golabi M, et al. A Novel X-Linked Disorder of Immune Deficiency and Hypohidrotic Ectodermal Dysplasia Is Allelic to Incontinentia Pigmenti and Due to Mutations in IKK-gamma (NEMO). *Am J Hum Genet*, 2000 Dec; 67(6): 1555–62. doi: 10.1086/316914
23. Chen N-J, Chio IIC, Lin W-J, Duncan G, Chau H, Katz D, et al. Beyond tumor necrosis factor receptor: TRADD signaling in toll-like receptors. *Proc Natl Acad Sci U S A*, Published online 2008 Aug 21; 105(34): 12429–34.
24. West A.P. et al. Recognition and signaling by toll-like receptors. *Annu. Rev. Cell Dev. Biol.* November 2006; 22: 409-37.
25. Kawai T, Akira S. Signaling of NF- κ B by Toll-like Receptors. *Trends Mol Med.* November 1, 2017; 13(11): 460-9. doi:10.1016/j.molmed.2007.09.002
26. Lee EG, Boone DL, Chai S, Libby SL, Chien M, Lodolce JP, et al. Failure to regulate TNF-induced NF- κ B and cell death responses in A20-deficient mice. *Science*, 2000 Sep 29; 289(5488): 2350–4.
27. Jingjing Wang, Xinjie Wu, Mengyu Jiang, Guixiang Tai. Mechanism by which TRAF6 Participates in the Immune Regulation of Autoimmune Diseases and Cancer. *BioMed Research International*, Published online 2020 Nov 26; 2020: 4607197. doi: 10.1155/2020/4607197
28. Sun SC. Non-canonical NF- κ B signaling pathway. *Cell Res.* 2011; 21: 71-85. Published: 21 December 2010.
29. Lawrence T. The nuclear factor NF- κ B pathway in inflammation. *Cold Spring Harb Perspect Biol.* 2009 Dec; 1(6): a001651. Doi: 10.1101/cshperspect.a001651
30. Sun S. C. The noncanonical NF- κ B pathway. *Immunological reviews*, 2012 Mar; 246(1): 125–140. doi:10.1111/j.1600-065X.2011.01088.x
31. Gutian Xiao, Edward W. Harhaj and Shao-Cong Sun. NF- κ B-Inducing Kinase Regulates the Processing of NF- κ B2 p100. *Mol Cell*, Feb 1, 2001; 7: 401–409.
32. Senftleben U., Cao Y., Xiao G., Greten F. R., Krahn G., Bonizzi G., Chen Y., Hu Y., Fong A., Sun S.-C., Karin M. Activation by IKK α of a second evolutionary conserved, NF- κ B signaling pathway. *Science*. 2001; 293: 1495–9.
33. Roy E, Byrareddy SN, Reid SP. Role of MicroRNAs in Bone Pathology during Chikungunya Virus Infection. *Viruses*, Published online 2020 Oct 23; 12(11): 1207. doi: 10.3390/v12111207
34. Myrthe A. M. van Delft, Leonie F. A. Huitema and Sander W. Tas. The contribution of NF- κ B signalling to immune regulation and tolerance. *European Journal of Clinical Investigation*, 2015; 45(5): 529-39. <https://doi.org/10.1111/eci.12430>
35. Heino M, Peterson P, Sillanpaa N, Guerin S, Wu L, Anderson G, Scott HS, Antonarakis SE, Kudoh J, Shimizu N, Jenkinson EJ, Naquet P, and Krohn KJ. RNA and protein expression of the murine autoimmune regulator gene (Aire) in normal, RelB-deficient and in NOD mouse. *Eur J Immunol*, 25 August 2000; 30: 1884–93. [https://doi.org/10.1002/1521-4141\(200007\)30:7<1884::AID-IMMU1884>3.0.CO;2-P](https://doi.org/10.1002/1521-4141(200007)30:7<1884::AID-IMMU1884>3.0.CO;2-P)
36. Li, Xinran & Xie, Jiaxin & Wang, Qingru & Cai, Huihua & Xie, Chuhai & Fu, Xiafei. miR-21 and Pellino-1 Expression Profiling in Autoimmune Premature Ovarian Insufficiency. *Journal of Immunology Research*. 2020 Apr 13; 2020: 3582648.
37. Matthew s.Hayden & Sankar Ghosh. NF- κ B, the first quarter-century: remarkable progress and outstanding questions. *Genes Dev.* 2012 Feb 1; 26(3): 203–34. Doi: 10.1101/gad.183434.111
38. Fliegau M, Bryant VL, Frede N, Slade C, Woon S-T, Lehnert K, et al. Haploinsufficiency of the NF- κ B1 subunit p50 in common variable immunodeficiency. *Am J Hum Genet*, 2015 Sep 3; 97(3): 389–403. doi: 10.1016/j.ajhg.2015.07.008
39. Vasanthakumar A, Liao Y, Teh P, Pascutti MF, Oja AE, Garnham AL, et al. The TNF receptor superfamily-NF- κ B axis is critical to maintain effector regulatory T cells in lymphoid and non-lymphoid tissues. *Cell Rep*, September 19, 2017; 20(12): 2906–20. <https://doi.org/10.1016/j.celrep.2017.08.068>
40. Lee CE, Fulcher DA, Whittle B, Chand R, Fewings N, Field M, et al. Autosomal-dominant B-cell deficiency with alopecia due to a mutation in NFKB2 that results in nonprocessable p100. *Blood*, 2014 Nov 6; 124(19): 2964–72. doi: 10.1182/blood-2014-06-578542
41. Feldmann M, Maini RN. Anti-TNF alpha therapy of rheumatoid arthritis: what have we learned? *Annu Rev Immunol* 2001; 19: 163–96.
42. Nejatbakhsh Samimi L, Farhadi E, Tahmasebi MN, Jamshidi A, Sharafat Vaziri A, Mahmoudi M. NF- κ B signaling in rheumatoid arthritis with focus on fibroblast-like synoviocytes. *Auto Immun Highlights*. Published: 8 Aug 2020; 11: 11.
43. Makarov SS. NF- κ B in rheumatoid arthritis: a pivotal regulator of inflammation, hyperplasia, and tissue destruction. *Arthritis Res*. Published online 2001 Mar 26; 3(4): 200-6. Doi: 10.1186/ar300
44. Isler P, Vey E, Zhang JH, Dayer JM. Cell surface glycoproteins expressed on activated human T cells induce production of interleukin-1 beta by monocytic cells: a possible role of CD69. *Eur Cytokine Netw.* 1993; 4(1): 15-23.
45. Boniface K, Moynet D, Mossalayi MD. Role of Th17 cells in the pathogenesis of rheumatoid arthritis. *World J Rheumatol* 2013; 3(3): 25-31 [DOI: 10.5499/wjr.v3.i3.25]
46. Hwang S-Y, Kim J-Y, Kim K-W, Park M-K, Moon Y, Kim W-U, et al. IL-17 induces production of IL-6 and IL-8 in rheumatoid arthritis synovial fibroblasts via NF- κ B-and PI3-kinase/Akt-dependent pathways. *Arthritis Res Ther.* 2004; 6: R120-28.
47. Mellado M, Martínez-Muñoz L, Cascio G, Lucas P, Pablos JL, Rodríguez-Frade JM. T cell Migration in Rheumatoid Arthritis. *Front Immunol.* 2015 Jul 27; 6: 384. doi: 10.3389/fimmu.2015.00384
48. Cildir G, Low KC, Tergaonkar V. Noncanonical NF- κ B signaling in health and disease. *Trends Mol Med.* 2016; 22: 414–29.
49. Leibowitz SM, Yan J. NF- κ B Pathways in the Pathogenesis of Multiple Sclerosis and the Therapeutic Implications. *Front Mol Neurosci.* 2016 Sep 15; 9: 84. doi: 10.3389/fnmol.2016.00084

50. Yue Y, Stone S, Lin W. Role of nuclear factor κ B in multiple sclerosis and experimental autoimmune encephalomyelitis. *Neural Regen Res*. 2018 Sep; 13(9): 1507–1515. doi: 10.4103/1673-5374.237109
51. Goverman J. Autoimmune T cell responses in the central nervous system. *Nat Rev Immunol* 2009 Jun; 9(6): 393–407. doi: 10.1038/nri2550
52. Dendrou CA, Fugger L, Friese MA. Immunopathology of multiple sclerosis. *Nat Rev Immunol*. 2015 Aug; 15(9). DOI:10.1038/nri3871
53. Frohman EM, Racke MK, Raine CS. Multiple sclerosis--the plaque and its pathogenesis. *N Engl J Med*. 2006; 354: 942–55.
54. Crawford MP, Yan SX, Ortega SB, et al. High prevalence of autoreactive, neuroantigen-specific CD8+ T cells in multiple sclerosis revealed by novel flow cytometric assay. *Blood* 2004; 103(11): 4222-31. <https://doi.org/10.1182/blood-2003-11-4025>
55. Viglietta V, Baecher-Allan C, Weiner HL, Hafler DA. Loss of functional suppression by CD4+CD25+ regulatory T cells in patients with multiple sclerosis. *J Exp Med*, May 2004; 199(7): 971-9. DOI:10.1084/jem.20031579
56. Balashov KE, Khoury SJ, Hafler DA, Weiner HL. Inhibition of T cell responses by activated human CD8+ T cells is mediated by interferon-gamma and is defective in chronic progressive multiple sclerosis. *J Clin Invest* 1995; 95(6): 2711-9. 10.1172/JCI117973
57. Selmaj KW, Raine CS, Cannella B, Brosnan CF. Identification of lymphotoxin and tumor necrosis factor in multiple sclerosis lesions. *J Clin Invest*, 1991 Mar; 87(3): 949-54. doi: 10.1172/JCI115102
58. Giuliani C, Bucci I, Napolitano G. The Role of the Transcription Factor Nuclear Factor-kappa B in Thyroid Autoimmunity and Cancer. *Front Endocrinol (Lausanne)*. Aug 21 2018; 9: 471. doi: 10.3389/fendo.2018.00471
59. Pacifico F, Leonardi A. Role of NF- κ B in thyroid cancer. *Mol Cell Endocrinol*. 2010; 321: 29–35.
60. Namba, Saenko & Yamashita. Nuclear Factor- κ B in Thyroid Carcinogenesis and Progression: a Novel Therapeutic Target for Advanced Thyroid Cancer. *Arq Bras Endocrinol Metab*, July 2007; 51 (5). <https://doi.org/10.1590/S0004-27302007000500023>
61. Francesco Pacifico et al. Oncogenic and Anti-apoptotic Activity of NF-B in Human Thyroid Carcinomas. *THE JOURNAL OF BIOLOGICAL CHEMISTRY*, December 2004; 279(52): P54610-9. DOI: <https://doi.org/10.1074/jbc.M403492200>
62. Faria M, Domingues R, Paixão F, Bugalho MJ, Matos P, Silva AL. TNF α -mediated activation of NF- κ B downregulates sodium-iodide symporter expression in thyroid cells. *PLoS ONE*, Published: February 12, 2020; 15(2): e0228794. <https://doi.org/10.1371/journal.pone.0228794>
63. Tavares C, Coelho MJ, Eloy C, et al. NIS expression in thyroid tumors, relation with prognosis clinicopathological and molecular features. *Endocr Connect*. 2018 Jan; 7(1):78-90. doi: 10.1530/EC-17-0302
64. Suryavanshi, Sachin v, yogesh a kulkarni. NF- κ B: A Potential Target in the Management of Vascular Complications of Diabetes. *frontier in pharmacology*, 2017; 8: 798. doi: 10.3389/fphar.2017.00798
65. Kira Meyerovich, Makiko Fukaya, Leticia F. Terra, Fernanda Ortis, Decio L. Eizirik & Alessandra K. Cardozo. The non-canonical NF- κ B pathway is induced by cytokines in pancreatic beta cells and contributes to cell death and proinflammatory responses in vitro. *Diabetologia*, 2016 Mar; 59(3): 512-21. DOI: 10.1007/s00125-015-3817-z
66. Elizabeth Dale, Miriam Davis, Denise L. Faustman. A role for transcription factor NF- κ B in autoimmunity: possible interactions of genes, sex, and the immune response. *Advances in Physiology Education*. 2006; 30: 152-8. <https://doi.org/10.1152/advan.00065.2006>
67. Gray CM, Remouchamps C, McCorkell KA, et al. Noncanonical NF- κ B signalling is limited by classical NF- κ B activity. *Sci Signal*, 2014 Feb 4; 7(311): ra13. doi: 10.1126/scisignal.2004557
68. Ortis F, Miani M, Colli ML, et al. Differential usage of NF- κ B activating signals by IL-1 β and TNF- α in pancreatic beta cells. *FEBS Lett*, 22 February 2012; 586(7): 984–9. <https://doi.org/10.1016/j.febslet.2012.02.021>
69. Kim JE, Lee MH, Nam DH, Song HK, Kang YS, et al. Celastrol, an NF- κ B Inhibitor, Improves Insulin Resistance and Attenuates Renal Injury in db/db Mice. *PLoS ONE*, Published online 2013 Apr 26; 8(4): e62068. doi: 10.1371/journal.pone.0062068
70. Guadalupe Rico-Rosillo, Gloria Bertha Vega-Robledo. The involvement of NF- κ B Transcription factor in asthma. *Rev Alergia Mex* 2011; 58(2): 107-111.
71. Vikas Mishra, Jaspreet Banga, and Patricia Silveyra. Oxidative stress and cellular pathways of asthma and inflammation: Therapeutic strategies and pharmacological targets. *Pharmacol Ther*. 2018 January; 181: 169–82. doi: 10.1016/j.pharmthera.2017.08.011
72. Barnes PJ, Karin M. Nuclear factor- κ B: a pivotal transcription factor in chronic inflammatory disease. *N Engl J Med*, May 1997; 336(15): 1066-71. DOI: 10.1056/NEJM199704103361506
73. Sheinman RI, Gualberto A, Jewell CM, et al. Characterization of mechanisms involved in trans-repression of NF- κ B by activated glucocorticoid receptors. *Mol Cell Biol*, Feb 1995; 15(2): 943-53. DOI: 10.1128/MCB.15.2.943
74. Hans D. Brightbill et al. NF- κ B inducing kinase is a therapeutic target for systemic lupus erythematosus. 2018 Jan 12; 9(1): 179. DOI: 10.1038/s41467-017-02672-0
75. Pacheco GV et al. Expression of TLR-7, MyD88, NF- κ B, and INF- α in B Lymphocytes of Mayan Women with Systemic Lupus Erythematosus in Mexico. *Front. Immunol*. 2016; 7: 22. doi: 10.3389/fimmu.2016.00022
76. Fang sun, Jian teng, Pengfei yu, Wenshuang li, Jing chang and Honglei xu. Involvement of TWEAK and the NF- κ B signalling pathway in lupus nephritis. *EXPERIMENTAL AND THERAPEUTIC MEDICINE*, 2018; 15: 2611-9.
77. Rakesh K. Mishra. Involvement of NF- κ B Signalling Pathway in the Pathogenesis of Systemic Lupus Erythematosus. *Nephrol Open J*. 2016; 2(1): 9-13. <http://dx.doi.org/10.17140/NPOJ-2-112>
78. Wong HK, Kammer GM, Dennis G, and Tsokos GC. Abnormal NF-kappa B activity in T lymphocytes from patients with systemic lupus erythematosus is associated with decreased p65-RelA protein expression. *J Immunol*, 1999 Aug 1; 163(3): 1682–9.
79. Lewis MJ, Simon Vyse, Adrian M. Shields, Sebastian Boeltz, et al. UBE2L3 polymorphism amplifies NF- κ B activation and promotes plasma cell development, linking linear ubiquitination to multiple autoimmune diseases. *Am J Hum Genet*. 2015 Feb 5; 96(2): 221-34. Doi: 10.1016/j.ajhg.2014.12.024
80. I. Atreya, R. Atreya, M. F. Neurath. NF- κ B in inflammatory bowel disease. *Journal of internal medicine*, June 2008; 263(6): 591-6. <https://doi.org/10.1111/j.1365-2796.2008.01953.x>
81. Clara Abraham¹, Judy H Cho. Inflammatory bowel disease. *N Engl J Med*. 2009 Nov 19; 361(21): 2066-78. DOI: 10.1056/NEJMra0804647

82. Siebenlist U, Brown K, Claudio E. Control of lymphocyte development by nuclear factor-kappaB. *Nat Rev Immunol.* 2005 Jun; 5(6): 435-45. DOI: 10.1038/nri1629