# Comprehensive review on Nuclear Factor-κB (NF-κB) signaling and its role in autoimmune diseases.

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## ABSTRACT:

Nuclear factor-Kappa B (NF-kB) 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-kB family have been identified. There are two mechanisms for NF-kB activation: canonical and non-canonical signalling. NF-kB transcription factors are important regulators of both innate and adaptive immune responses, and abnormalities in NF-kB signalling lead to the development of immunological disorders. As a result of its activities during thymic selection, NF-kB 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-kB. The goal of this review is to discuss about molecular mechanism of NF-kB and how it implicated in the pathogenesis of human diseases.

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

## INTRODUCTION:

Nuclear factor-κB (NF-κB) was discovered in the nucleus of B cells by David Baltimore and colleagues in 1986 as a factor[1] that represents a family of inducible transcription factors, including NF-κB1 (also named p50), NF-κB2 (also named p52), RelA (also named p65), RelB and c-Rel, which mediates transcription of target genes by binding to a specific DNA element, κB enhancer, as various hetero- or homo-dimers[2] that located within promoters and enhancers of a large number of genes[3].

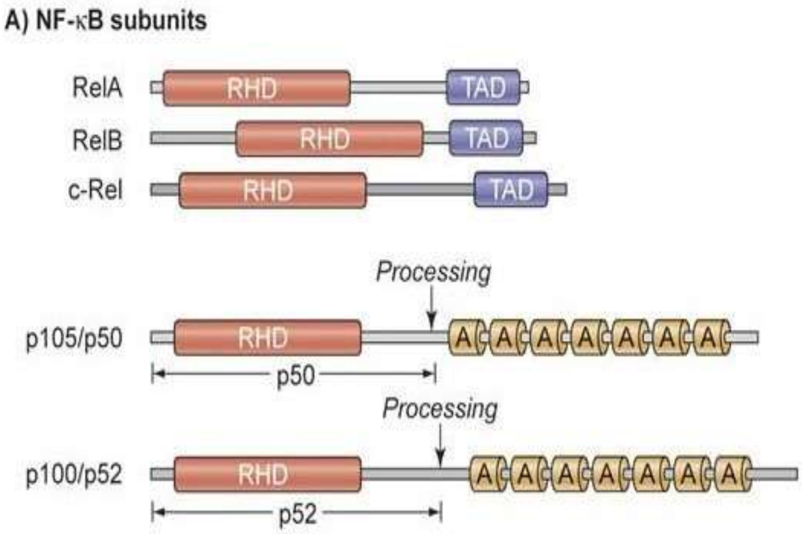

Figure 1: NF-κB subunits [4]

NF-κB 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 IκBs, and DNA binding[5]. NF-κB has also been linked to immune system dysfunction and autoinflammatory disorers[3]. NF-κB 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 types[6].

## NF-κB SIGNALLING:

NF-κB 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 presentation[7]. The NF-κB pathway is important for DC maturation, and unregulated NF-κB activation in DCs has been linked to the development of autoimmunity[8]. Mice lacking A20 (negative regulators of NF-κB) [3] specifically in DCs spontaneously demonstrated DC activation and T cells proliferation[9]. 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 animals[10]. Treg depletion causes inflammatory bowel disease, which is most likely caused by overactive immunological responses to commensal bacteria in the intestine[11]. Modulation of NF-κB has been observed for most coreceptor pathways, and thus the IκB kinase complex (IKK)/NF-κB signalling cascade is thought to play a critical role in integrating TCR and costimulatory signals[12]. 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 (PKCθ) in T cells and PKCβ 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-B activation has been identified as CARMA1, BCL10, and MALT1[13].

NF-κB signalling is primarily regulated by inhibitor κB (IκB) proteins and the IκB kinase complex via two major pathways: the canonical and non-canonical NF-κB pathways[14]. Individual IκB and IKK regulatory proteins play distinct roles in the canonical and noncanonical activation pathways, as well as in the activation of specific NF-κB dimers within these pathways[15]. Both canonical and noncanonical pathways play essential roles in modulating immunological activation and tolerance[8].

The transcription factor NF-κB is required for the initiation of immunological tolerance. Immune tolerance is made up of both central and peripheral mechanisms[8]. NF-κB 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 mTECs [16].

## CANONICAL PATHWAY:

The 'canonical' NF-κB pathway is the signalling mechanism through which cytokines regulate the degradation of IκBα to release p50/RelA and p50/c-Rel heterodimers[17]. Many agents, including microbial pathogens, pro-inflammatory cytokines, and T cell costimulation, activate the canonical pathway[12]. The classical pathway, which is regulated by RelA, c-Rel, and p50 nuclear translocation, is essential for activation, differentiation, and survival of immune cells[3]. Canonical pathway of NF-κB activation involves phosphorylation of IκBα by the IκB kinase (IKK) and subsequent IκBα degradation, which causes the nuclear translocation of NF-κB dimers[18]. Inhibitors of NF-κB Kinase (IKK) complex are made up of the catalytic subunits IKKα, IKKβ, and regulatory subunit NEMO, which is a component of the IKKα and β containing-complex[19], for NF-κB essential modulator, that also known as IKKγ in human[20]. 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].

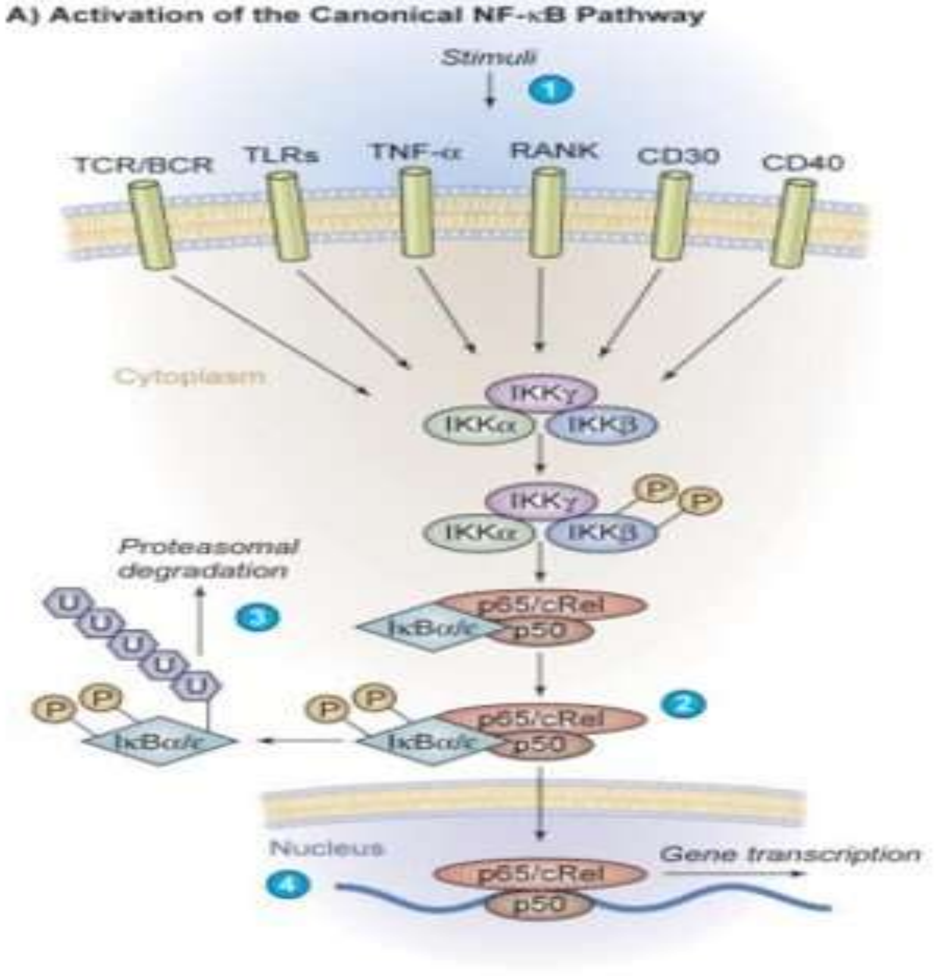

**Figure 2: Canonical NF-κB signaling pathways[4]**

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) agonists[16], and pattern recognition receptors (PRRs), can activate the canonical pathway rapidly and transiently[2]. TNF receptor activation causes a chain reaction of adaptor proteins with TRAF-binding domains to interact[23]. All TLRs activate NF-κB via the MyD88 (which is made up of a TIR domain and a death domain[24] or TRIF-dependent pathway, or both. TRIF activates NF-κB via the RIP1/TRAF6–TAK1– IKKα/β pathway, whereas MyD88 activates NF-κB via the IRAKs–TRAF6–TAK1– IKKα/β pathway[25]. The canonical NF-κB pathway is essential for T-cell activation[8]. In the Modification of canonical pathway, TNFAIP3 is increased in response to TNF receptor and TLR ligation, and A20 suppresses NF-B-dependent gene expression in the Modification of Canonical Pathway[26]. Single nucleotide polymorphisms (SNPs) in the human A20 (encoded by TNFAIP3[3] is a potent anti-inflammatory protein that utilizes de-ubiquitinating [26], 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 autoimmunity[9]. The role of A20 in regulating NF-κB activity and immunological responses was verified in A20-deficient mice[26]. Human Crohn's disease (CD), an inflammatory bowel disease (IBD), may be linked to TNFAIP3 SNPs[9]. TRAF6 is a RING-domain E3 ubiquitin ligase that, along with E2, Ubc13, and Uev1A[25], 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 diseases[27].

## NON-CANONICAL PATHWAY:

The noncanonical pathway is activated at a slower rate than the classical pathway[15]. 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) pathway[16]. NEMO- and IKKβ-independent IKKα dimer complex mediates non-canonical signalling[20] via p52 and RelB nuclear translocation promotes lymphocyte maturation and survival, as well as lymphoid organogenesis[3]. The Noncanonical pathway results in NF-κB2 processing and the selective activation of p52/RelB dimers[12].

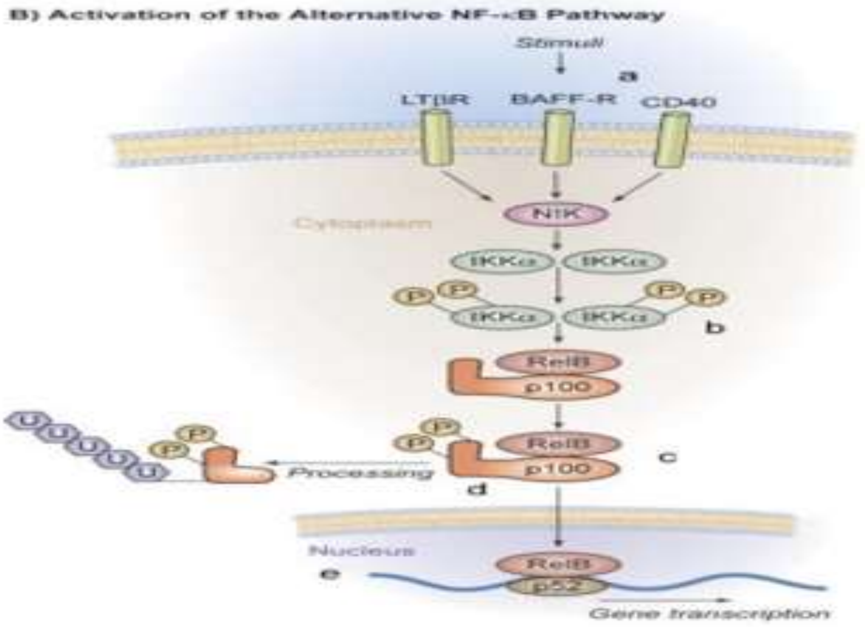

**Figure 3: Non-canonical NF-κB signaling pathways[28]**

The discovery of non-canonical NF-κB signalling pathway came from the study of p100 processing[28], the precursor for p52, and this is independent of both IKKβ and IKKγ[29]. Processing of p100 is a signal-induced and posttranslational event[30] that serves to generate p52 as well as induce nuclear translocation of the RelB/p52 heterodimer[28]. The only kinase capable of inducing productive p100 processing is the NF-κB-inducing kinase (NIK)[31]. Overexpression of NIK in fibroblasts requires IKK1 expression to induce p100 processing to p52[32]. NF-κB-inducing kinase (NIK) is a key signalling component of the noncanonical NF-κB pathway that collaborates with a downstream kinase, initiate of NF-κB kinase α (IKKα), to induce phosphorylation-dependent ubiquitination and processing of p100[30]. 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 responses[7]. PELI1 can inhibit the NF-κB pathway by ubiquitinating and destroying an NF-κB-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-κB signalling is essential for SLO development as well as for AIRE expression in eTACs[34]. 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-κB activation[35]. 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 selection[16]. 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 tolerance[17]. It has been linked to a number of autoimmune diseases, including systemic lupus erythematosus (SLE), multiple sclerosis (MS), and autoimmune encephalomyelitis[36].

## NF-κB AND ITS INVOLVEMENT IN AUTOIMMUNE DISEASES:

NF-κB has been linked to the development of several autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, type I diabetes, multiple sclerosis, and inflammatory bowel disease[8]. NF-κB has been linked to immune deficiencies and autoinflammatory diseases [3]. In mammals, there are five members of the NF-κB family: RelA/p65, RelB, c-Rel, p50 (NF-κB1) and p52 (NF-κB2)[37]. Syndromes caused by heterozygous mutations in NF-κB1 include autoimmune manifestations of arthritis, lung inflammation, gut inflammation, and immune-mediated thrombocytopenic purpura (ITP)[3], which can also lead to antibody deficiency[38], as well as a defect in Tregs, with a decrease in effector Tregs[39]. Mutations in NF-κB2 gene induce an antibody deficiency disease with varying B cell deficits[40].

### 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 fibroblasts[40]. In the pathophysiology of RA, fibroblast-like synoviocytes (FLSs) are important in disease progression by maintaining inflammation and promoting autoimmunity, resulting in joint destructio[41]. Th17 cells are one of the most critical subsets of T cells in the pathophysiology of RA. Deregulated NF-κB 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 RA[2]. In RA, NF-κB activation is critical in both in the beginning and continuation of chronic inflammation[42]. Immunohistochemical studies found nuclear RelA (p65) and NF-B1 (p50) primarily in RA endothelium and synovial lining[43] 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 synovium[43]. TNF-α, IL-1, and IL-6 are inflammatory cytokines produced by CD4 + T cells activation, which stimulate synovial fibroblasts, monocytes, and macrophages[44]. TNF-α and IL-1β, 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 progression[45]. NF-κB - inducing kinase is essential for production of Th1 and Th17that is beneficial to the progression of RA[42]. It has been demonstrated that the interleukin 6 (IL-6) and interleukin 8 (IL-8) production by

RA-FLSs has been induced by IL-17[46]. 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 development[47]. Survival, differentiation, and activation of T cells, B cells, and DCs are all significantly connected to NF-κB pathway activity[42]. 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 arthritis[48]. The concentration of NF-κB in the synovium increased, and its binding to DNA was found to be much stronger in RA.

**Multiple sclerosis:**

NF-κB pathways are altered in multiple sclerosis (MS), resulting in increased NF-κB activation in cells. This could point to NF-κB plays an important role in the MS pathogenesis[49]. 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 cells[50]. 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 activated[51]. These myelin reactive T cells then cross the blood-brain barrier (BBB) and enter the CNS, causing inflammation and, eventually, demyelination and neurodegeneration[52]. The NF-κB activation pathways, canonical and noncanonical signalling are both implicated in the pathogenesis of EAE[2]. 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 cells[51]. In the peripheral blood, patients with multiple sclerosis and healthy people appear to have equal numbers of T cells that respond to myelin[53]. 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 response[54]. 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 macrophages [57].

**Thyroid:**

Several studies have demonstrated that NF-kB has been implicated in thyroid autoimmunity, thyroid cancer, and thyroid-specific gene regulation[58]. Because of its ability to control the proliferative and anti-apoptotic signalling pathways of thyroid neoplastic cells, NF-kB 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-kB is one of the key factors controlling anti-apoptotic responses among numerous molecules involved in various anti- or pro-apoptotic signalling pathways [60]. The anti-apoptotic function of NF-kB was mediated by the inhibition of JNK signaling[61]. Oncogenic proteins such as Ret/PTC, Ras, and BRAF can activate NF-kB, which could be a promising treatment strategy for advanced thyroid cancer[60]. 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 cells[62]. It is essential for thyroid metabolism[63]. The canonical NF-κB 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-κB activation (LPS). TNF-, a genuine NF-κB activator with a prominent function in thyroid autoimmunity[62], has been shown to inhibit NIS expression.

**Diabetes:**

NF-kB plays an important role in the pathogenesis of diabetic vascular complications. Inhibiting NF-kB 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-kB) expression via different pathways [64]. Proinflammatory cytokines activate the transcription factor nuclear factor (NF)-kB, which is involved in beta cell death in type 1 diabetes[65]. Type 1 diabetes mellitus (T1DM) is an organ-specific autoimmune disease characterized by inflammatory infiltration of the pancreatic islet and destruction of the 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-κB activity[66]. The IKK complex, which includes NEMO and IKK, is critical for maintaining low baseline levels of NIK and inhibiting non-canonical NF-κB signalling[67]. IL-1β mediates IKKβ degradation in beta cells; leading to IKKα homodimer activation[68], IL-1β-mediated IKKβ reduction in beta cells contributes to higher NIK protein levels, contributes to the activation of the non-canonical pathway in beta cells[65]. IkBβ is involved in the long-term activation of NF-kB[1]. Activation of the nuclear factor kappa B (NF-kB) in adipose tissue has recently been linked to the development of insulin resistance. Celastrol, an NF-kB inhibitor, that inhibition of the NF-kB 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 tissue[69].

**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 lungs[70]. The pathogenesis of asthma involves persistent expression of a wide range of genes, which contain the kB site for NF-kB inside their promoters, suggesting that NF-kB plays a pivotal role in the initiation and maintenance of allergic inflammation[1]. 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-κB 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 domains[71]. NF-kB controls the expression of large number of genes involved in immunological and inflammatory responses[72]. Furthermore, glucocorticoids (GCs), which block NF-B, are the most effective asthma treatment[73]. GCs have been found to prevent the interaction of NF-kB with DNA as well as the direct interaction of NF-kB with the glucocorticoid receptor (GR). GC treatment has been proven in several investigations to inhibit NF-kB activity in tissues ex vivo. The binding of GC with 2 agonists more effectively suppresses NF-kB[70].

**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 antibodies[74]. 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 SLE[75]. Various TNF family members, including BAFF, TWEAK, CD40, and OX40, are involved in the systemic lupus erythematosus (SLE) pathophysiology. NIK promotes non-canonical NF-κB signalling downstream of multiple TNF family members, including BAFF, TWEAK, CD40, and OX40[74]. 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-κB signalling pathway, which plays a role in inflammation, angiogenesis, cell proliferation and apoptosis[76]. During the pathophysiology of SLE, nuclear NF-κB 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 production[77]. In lupus, NF-κB signalling activation is suppressed in T cells due to the lack of the p65 appearance in the nucleus, one of the NF-κB subunits that bind to DNA[78]. Abnormal NF-κB 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 disorders[79].

**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-a, interleukin-6, and interferon-c, 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-kB pathway[80]. 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-a, IL-1, and IL-6, NF-kB can regulate the expression of IL-12 and IL-23, both of which are pro-inflammatory cytokines that are directly implicated in mucosal tissue destruction[79]. IBD has also been linked to polymorphisms and mutations in the NFKB1 gene that encodes the IκB-like protein p105 and its processing product p50[2]. The IKK complex is made up of two catalytic subunits, IKKa and IKKb, and a regulatory protein called NF-kappaB essential modulator (NEMO)[80]. IkB- 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-kB and promotes the nuclear export of NF-kB[82].

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