A.T. Dolzhenko[1],

S. Sagalovsky[2]

Biomedical Research Unit, Institute of Molecular Medicine Martin-Luther University Halle-Wittenberg[1], Germany Department of Orthopedics Clinic Median[2], Bad Lausick, Germany

INHIBITION OF NUCLEAR FAKTOR - KB (NF-KB) SIGNALING AS A POTENTIAL THERAPEUTIC STRATEGY FOR RHEUMATOID ARTHRITIS

Abstract. *The family of nuclear factor-kappa B (NF-kB) transcription factors is intimately involved in the regulation of expression of numerous genes in the setting of the inflammatory response. Since inflammatory processes play a fundamental role in the damage of articular tissues, many in vitro and in vivo studies have examined the contribution of components of the NF-kB signaling pathways to the pathogenesis of various rheumatic diseases, in particular, of the rheumatoid arthritis. Inflammation, cartilage degradation, cell proliferation, angiogenesis and pannus formation are processes in which the role of NF-kB is prominent. Consequently, large efforts have been devoted to the study of the pharmacologic modulation of the NF-kB pathways. Understanding fundamental role of the NF-kB signaling pathway in the damage of articular tissues and progress rheumatoid arthritis allowed to reconsidering of the mechanisms employed currently available therapeutic agents including non-steroidal anti-inflammatory drugs, corticoids and disease-modifying anti-rheumatoid drugs, as well as novel small molecule inhibitors targeted to specific proteins of the NF-kB pathways. Noting the key role of the NF-kB signaling pathway molecules in the process development of the rheumatoid arthritis are interest as a target molecule to search them inhibitors for now drug treatment for rheumatoid arthritis.*

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease, primarily located in the synovial joints, leading to destruction of the cartilage and bone as a result of the chronic disease activity[13]. RA affects 0.5 - 1% of the population in the industrialized world is two to three times more frequent in women than men and can lead to disability and reduced quality of life.
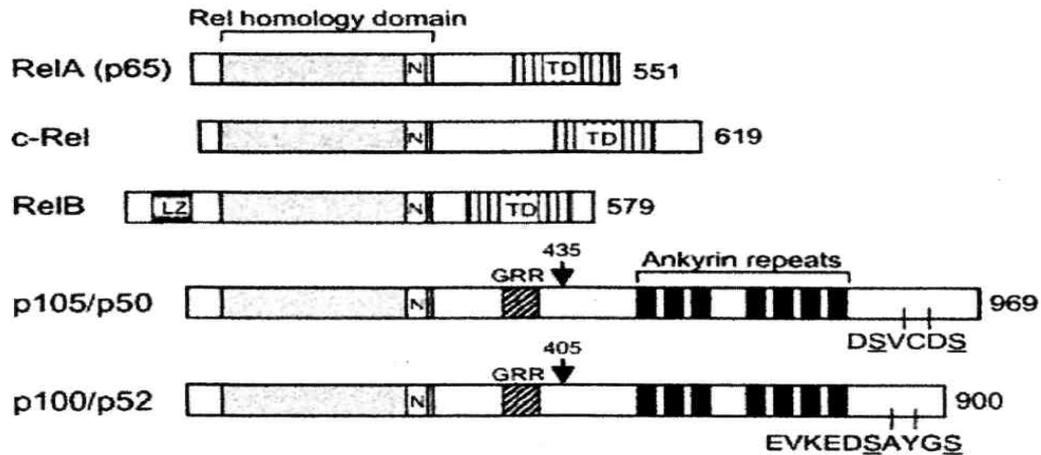
Chronic inflammation perpetuates and amplifies itself through the numerous autocrine and paracrine loops of cytokines, acting on the cells within the lesion. The vicious circle can be broken either by neutralizing the biological activities of extracellular inflammatory mediators or by inhibiting cytokine production. The pattern of gene expression is controlled by transcription factors, which relay into the nucleus signals emanating from the cytoplasmic membrane. In the nucleus, transcription factors selectively bind their cognate sites in the regulatory elements of targeted genes and activate or repress transcription. It appears that the complexity of inflammatory pathways is significantly reduced on the level of transcription factors. Whereas the cell within the inflammatory lesion is subjected to many dozens, perhaps hundreds, of extracellular stimuli, only a handful of inducible transcription factors, including AP-1 and NF-κB, appear to play a major role in the regulation of inflammatory genes. This suggests that neutralization of these transcription factors may provide an efficacious therapeutic strategy. A pivotal role for the transcription factor NF-κB in regulation of inflammation has been well recognized [9,12]. The present review focuses on the role of NF-kB in chronic inflammation, and to discuss the feasibility of therapeutic approaches based on the specific suppresion of the NF-kB pathway.

The NF-kB signaling pathway, function and its regulation

NF-kB comprises a family of transcription factors first described as B-lymphocyte-specific nuclear proteins, essential for transcription of immunoglobulin kappa (k) light chains. Mammalian cells contain five NF-kB subunits-relA (p65), relB, c-rel, p50 and p52- which form homo- and heterodimers and are characterized by the conserved N-terminal 'rel homology' domain (Figure 1, A, B). NF-kB is sequestered in the cytoplasm with members of the inhibitor of NF-B (IkB) family, which consists of IkBα, IkBβ, Ikγ and Bcl-3 [29].In the canonical activation pathway,
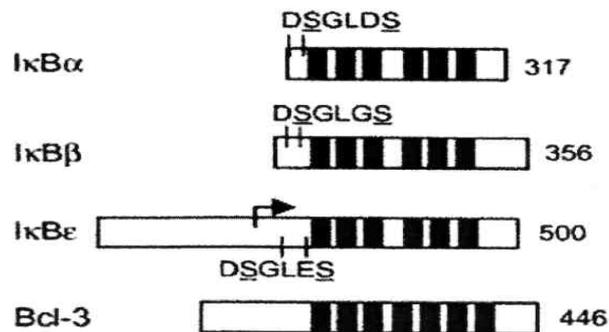
A) NF-κB family

B) IκB family

Figure 1. Mammalian NF-kB and IkB family members. (A). NF-kB family members possess a structurally conserved Rel-homology domain (RHD), which contains a nuclear localization domain (N), a dimerization motif, and a DNA-binding domain. RelA, c-Rel, and RelB also have a non-homologous transactivation domain (TD). RelB also contains a leucine-zipper motif (LZ). (B).The IkB family members, including p105 and p100, are characterized by ankyrin repeats. The amino-acid sequences of the phosphorylation sites triggering their degradation/processing are designated. The glycine-rich region (GRR), which is required for the processing of p105 and p100, is also indicated.
Abbreviations: cRel, proto-oncogene transcription factor; DNA, deoxyribonucleic acid; IkB, inhibitory kappa B; Rel A, transcription factor p65; RelB, transcription factor.

liberation of NF-kB from the inactive complex is initiated by phosphorylation of IkB on N-terminal serines. Phosphorylated IkBs are recognized by an E3 ubiquitin kinase complex and degraded by the 26S proteasome [5]. Amino acid residues Ser-32 and Ser-36 of IkBa were identified as essential for phosphorylation whereas Lys-21 and Lys-22 for the ubiquitination process. IkB degradation leads to the exposure of a nuclear translocation sequence of the NF-kB dimer, allowing it's nuclear translocation and DNA binding [49]. Central to the NF-kB cascade is the multi-subunit kinase IkB kinase (IKK) complex [20], which includes IKK-α (IKK-1) and -h (IKK-2) as well as regulatory subunits such as NEMO/IKK-g and IKAP. IKK-2 was shown to have a higher kinase activity for IkBα and to be the predominant kinase responsible for the phosphorylation of IkBα in response to tumor necrosis factor a (TNF-α), interleukin (IL)-1, lipopolysaccharide (LPS) and doublestranded RNA (Figure 2) [1,5,20,40,45]. IKK-2 knockout mice die as embryos and show massive liver degeneration due to hepatocyte apoptosis, a phenomenon similar to that of mice deficient in relA or IkBα. NF-kB activation by IL-1 or TNF-α is strongly impaired although not completely abolished. On the other hand, IKK-1 knockout mice have many morphogenetic abnormalities, including shorter limbs and skull, a fused tail, and die perinatally. They have hyperproliferative epidermal cells that do not differentiate, but IL-1- and TNFainduced NF-kB activation in embryonic fibroblasts is normal, as is IkB phosphorylation and degradation. This suggests that IKK-2 is crucial for NF-kB activation upon inflammatory stimuli, but also that IKK-1 or presently unknown kinases may contribute to this action. Activation of the IKK complex is thought to be mediated by phosphorylation of IKK-1 or IKK-2 by upstream kinases, including members of the mitogen-activated protein kinase kinase kinase family or NF-kB inducing kinase (NIK) [21]. NIK, in particular, has reported to play a major role in NF-kB activation [12]. However, recent studies in NIK-deficient mice and human primary cells have questioned its physiological role in NF-kB activation and have suggested that its
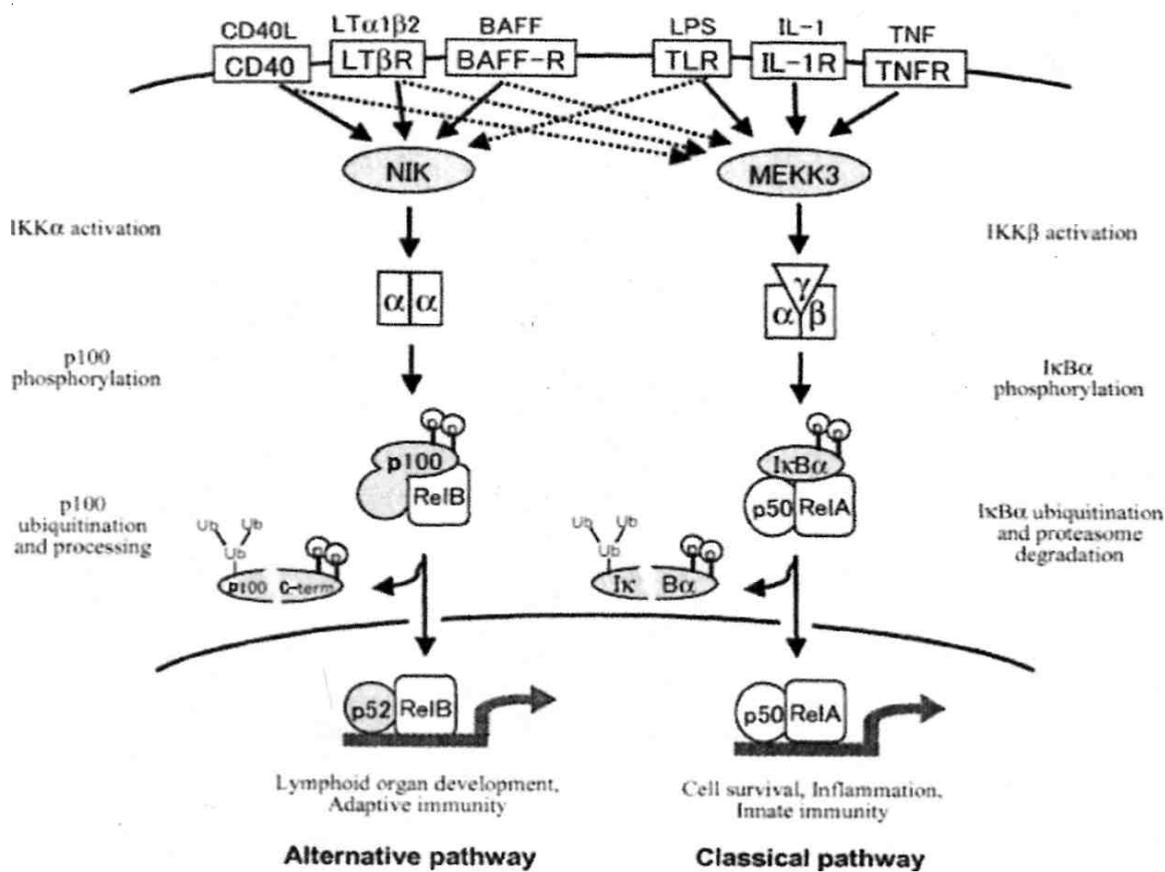
Figure 2. Classical and alternative NF-kB activation pathways.

Classical pathway of NF-κB activation via IκB degradation. Ligand engagement of specific membrane receptors triggers K63 polyubiquitination of TRAF2, TRAF6, RIP, MALT1, and NEMO. The TAK kinase complex is recruited through association of the polyubiquitin chains with TAB2 and TAB3. Activated TAK1 may phosphorylate and activate IKKβ, which then phosphorylates IκB bound to cytosolic NF-κB, triggering its β TrCP E3 ubiquitin ligase-mediated K48 polyubiquitination and proteasomal degradation. Free NF-κB then translocates to the nucleus and transactivates target genes. CYLD and A20 are deubiquitinating enzymes that may block NF-κB activation by removal of K63 ubiquitinated chains from activated TRAFs, RIP, and NEMO. A20 may also terminate TNF-α induced NF-κB activation by catalyzing the K48 ubiquitination of RIP, leading to its proteasomal degradation. In addition to promoting survival via NF-κB target genes, the TNF receptor (TNFR1) also stimulates competing apoptotic pathways. T cell (and B cell) antigen receptors (TCR and BCR, respectively [not shown]) may in some contexts enhance apoptotic pathways but usually they contribute to survival (see text). IκB, inhibitor of NF-κB; IKK, IκB kinase; MALT, mucosa-associated lymphoid tissue lymphoma translocation gene; NEMO, NF-κB essential modulator; NF-κB, nuclear factor-κB; RIP, receptor interacting protein; TAB, TAK1-binding protein; TAK, transforming growth factor β-activated kinase; TRAF, TNF receptor-associated factor.

Abbreviations: NF-kB, nuclear factor - kappa B, TRAF 2,6, TNF-receptor-associated factor 2 and 6; Rip, receptor interaction protein; MALT 1,mucosa-associated lymphoid tissue lymphoma transcription protein 1; NEMO, NF-kB essential modulator; TAK, transforming growth factor β-activated kinase;TAB, TAK1-binding protein; IkB, inhibitor kappa B;TNF-α, tumor necrosis factor-α; IKK, IkB kinase.

function may be restricted to signaling through the lymphotoxin B receptor [35]. Although many stimuli have the potential to activate the NF-kB pathway, the responses elicited are both cell and stimulus specific, suggesting that not all activators utilize the same signaling components and cascades. There are several levels of control and diversification. For instance, the spectrum of adaptor proteins and kinases differs between different stimuli and receptors-for example, adaptors activated via Toll-like receptors (TLR) and IL-1 receptors are distinct from those recruited by TNF receptors. IkB kinases are also an important level of control, in that IKK-1 regulates mostly morphogenetic events, whereas IKK-2 is involved in inflammatory signaling. Moreover, there is heterogeneity of requirement of IKK-2 in different cell types and in response to stimuli [4]. Novel IkB kinase complexes have been recently identified, including IKK-I (IKK-q) which shares 30% overall identity with IKK-1 or IKK-2. Differential binding by NF-kB dimers is another important level of control in this versatile pathway. NF-kB consensus binding sites are

decameric sequences of NF-kB (5V-GGGRNNYY CC-3V, where R indicates A or G, Y indicates C or T and N indicates any nucleotide), or kBlike motifs (5V-HGGARNYYCC-3Vwhere H indicates A, C or T, R indicates A or G, Y indicates C or T and N indicates any nucleotide) . Different NF-kB dimers exhibit different binding affinities for NF-kB or kB-like sites (reviewed in Refs. [22,33,34]). For example, the NF-kB sequence contained in some MMP genes allows predominantly binding of p50/ p65, while other NF-kB dimers (c-Rel/p50) are involved in regulation of other mediators (such as TF, whose promoter contains a kB-like site). In addition, while all five NF-kB subunits contain the 'rel homology' domain, only relA and c-Rel contain a transactivation domain. Indeed, there is growing evidence that the p50/p50 homodimer, lacking transactivating potential, may inhibit gene transcription. The major domain sensitive to phosphorylation is the transactivation domain located in the NF-kB C-terminal region [5]. Both stimulatory and inhibitory phosphorylations of relA have been reported. Phosphorylation of Ser- 927 within the p105 C-terminal PEST region by IKK has been reported to contribute to NF-kB activation [20]. Several upstream kinases have been implicated in the transactivating event, including phosphatidyl inositol 3-kinase, p38 mitogen-activated protein kinase (MAPK) and p42/44gen-activated protein kinase (MAPK) and p42/44 MAPK [21]. Hence, it is the differential expression of NF-kB components in tissues, cell types and possibly diseases, together with differential interactions with the transcription apparatus that contributes to coordinated regulation by NF-kB of complex cellular responses. Another mode of specificity in NF-kB-dependent gene activation lies in its ability to orchestrate gene expression in concert with other transcription factors. For instance, the organization of the cytokine-inducible element in the Eselectin promoter is remarkably similar to that of the interferon-γ gene, in that both require NF-kB, ATF-2 and HMGI(Y), whereas another adhesion molecule, vascular cell adhesion molecule-1 (VCAM-1), is induced through interactions of NF-kB with IRF-1 and HMG-I(Y) and also depends on constitutively present SP-1. The ability of NF-kB to interact with AP-1 is of particular importance, as many of the inflammatory genes require these two transcription factors working cooperatively, including VCAM-1, IL-8, cyclooxygenase (COX)-2, monocyte chemoattractant protein-1 (MCP-1) and MMP-13 [17,19]. A peculiarity of NF-kB is the rapid nature of its activation and downregulation. NF-kB activation induces IkBa, allowing switching off of the system. Hence, in physiological conditions, NF-kB activation is a transient phenomenon, which allows appropriate expression of immune and 'stress' genes. In contrast, prolonged or inappropriate activation of the NF-kB pathway is a feature of diseases such as rheumatoid arthritis.

NF-κB is activated in rheumatoid arthritis

The joints of patients with RA are characterised by an infiltration of an infiltration of immune cells into the synovium, leading to chronic inflammation, pannus formation and subsequent irreversible joint and cartilage damage. The RA synovium is known to comprise largely of macrophages (30-40%), T cells (~30%) and synovial fibroblasts, but also of B cells, dendritic cells, other immune cells and synovial cells such as endothelium [9,13]. RA synovial fluid has been shown to contain a wide range of effector molecules including proinflammatory cytokines (such as IL-1β, IL-6, TNFα and IL-18), chemokines (such as IL-8, IP-10, MCP-1, MIP-1, and RANTES), matrix metalloproteinases (MMPs, such as MMP-1, -3, -9 and -13) and metabolic proteins (such as Cox-1, Cox-2 and iNOS) [17,18]. These interact with one another in a complex manner that is thought to cause a vicious cycle of proinflammatory signals resulting in chronic and persistent inflammation. TNFα in particular is the prime inflammatory mediator and also induces apoptosis. Importantly, the genes encoding TNFα and many of the other factors mentioned above are now known to be under the control of NF-kB transcription factors, suggesting that NF-kB could be one of the master regulators of inflammatory cytokine production in RA. Indeed, the presence of activated NF-kB transcription factors have been demonstrated in cultured synovial fibroblasts [17], human arthritic joints and the joints of animals with experimentally induced RA. Immunohistochemistry has demonstrated the presence of both p50 and p65 in the nuclei cells lining the synovial membrane and macrophages [15,18]. Furthermore, nuclear extracts of cells have demonstrated an ability to bind to the NF-kB consensus sequence. New techniques such as in vivo imaging have also been used to demonstrate the activity of NF-kB in a mouse model that mimicked RA-like chronic inflammation. By placing the luciferase gene under the control of NF-κB, increased luminescence was observed in the joints of live mice [28]. These findings are supported by a study that investigated experimentally induced arthritis in mice that carried knockouts of the genes for the NF-kB family members p50 or c-Rel. The two experimental models used were collagen induced arthritis (CIA; a model of chronic RA where disease development involves both T and B cells) and an acute/destructive model induced by methylated BSA and IL-1 (involving exclusively T cells and not B cells). Lack of c-Rel had no influence on the acute

model and, whilst reducing the incidence of CIA, did not prevent a severe immunohistopathology in affected joints. In addition, c-Rel could not be found in the nuclei of cells explanted from the arthritic joints of wild-type mice, suggesting that this subunit of NF-kB is of limited importance in RA [15]. In contrast, lack of p50 caused a complete loss of a humoral response, severely impeded T cell proliferation and conferred resistance to both forms of arthritis [18]. This clearly demonstrates a central role for p50 (presumably p50/p65 heterodimers) in the inflammation that underlies RA.

Core principles of the 'canonical' NF-kB pathway

The molecular events that lead to activation of NF-kB transcription factors in the RA synovium are clearly of great interest and involve the so-called 'classical' or 'canonical' pathway. The three main players in the pathway, the IKK complex, IkBs and the NF-kB transcription factors will be discussed in turn.

The IKK complex

The high molecular weight IKK complex plays an extremely important role in the activation of NF-kB since it represents a convergence point for the signals that are transmitted from many different cellular stimuli, such as the bacterial endotoxin lipopolysaccharide (LPS) or cytokines such as TNFa and IL-1[50]. The function of the IKK complex in the canonical pathway is to phosphorylate IkBα and IkBβ and target them for degradation by the ubiquitin/proteasome pathway [5]. The canonical IKK complex consists of at least three subunits; IKK1 (also known as IKKα), IKK2 (also known as IKKβ) and NF-kB essential modulator (NEMO, also known as IKKγ). Additional, as yet unidentified, subunits are likely to be discovered. Both IKK1 and IKK2 have catalytic activity and IKK2 is generally considered to be the most relevant to RA, since it is indispensable for phosphorylation of IkBα by the IKK complex [1,19]. The role of IKK1 is less clear, but recent evidence points towards a negative regulatory role, acting as a 'checkpoint' in NF-kB activation to prevent uncontrolled stimulation of cells [33]. NEMO does not have kinase activity but is necessary for phosphorylation of IκBα/IkBβ by the IKK complex [21].

IkBα, IkBβ and IκBγ

IkBα is the prototypical member of the seven member IκB family (Figure 1, B) and was identified by its ability to render the common NF-kB p65/p50 dimer inactive in the cytosol of unstimulated cells. Both IkBα and IkBβ bind to NF-κB and mask the nuclear localisation sequence on the p50/p65 heterodimer thus inhibiting its entry into the nucleus. Following IkBα phosphorylation by the IKK complex

and degradation, the nuclear localisation signal is no longer masked and this causes translocation of the active dimer to the nucleus. One of the unique features of the canonical NF-kB pathway is its rapid yet transient activation, which prevents a persistent response that could result in pathological changes in affected cells. Down-regulation of NF-kB activity coincides with the reappearance of IkBα, which requires new protein synthesis. Indeed, the IkBα gene promoter contains NF-kB consensus sequences making it extremely responsive to NF-kB activation. Newly synthesised IkBα enters the nucleus, binds NF-kB dimers and returns them to the cytosol, thus dampening the response. If the stimulus is still present, these are again degraded and NF-kB activity rises again. Following LPS exposure, this results in a phenomenon known as 'rapid oscillatory activation'where the response gradually becomes dampened over time [40]. The NF-κB response is also negatively regulated by IκBγ, which is a target of NF-βB and is synthesised in anti-phase compared to IκBα [1]. In contrast to IkBα and IκBγ, IkBβ is not a genetic target of NF-kB and it is not rapidly resynthesised following NF-kB activation [37]. Therefore, situations in which IkBβ predominates have the potential to result in prolonged NF-kB activation [20]. However, the relevance of both IκBβ and IκBγ to RA is unclear, since IκBα is so dominant in the inactivation of NF-κB.

The NF-kB family of transcription factors

A crucial aspect of the NF-kB response is the make-up of the dimers that are bound to and inhibited by the IkBs. There is considerable variation in the combinations that have been observed [20]. The subunits that are present in the dimers influence their biological activity because the subunits have different functional domains. As mentioned above, all five members of the NF-?B transcription factor family contain a Rel-homology domain (RHD) that binds to DNA. In contrast, only three of the family (p65, RelB and c-Rel) contain transactivation domains (TADs) that interact with general transcription factors and co-activators, whereas p50 and p52 do not (Figure 1,A,B). This difference can influence whether a specific dimer has the potential to act as an activator or a repressor. For instance the common heterodimer of p50 and p65 is able to activate gene transcription due to the presence of a TAD in p65. Conversely, homodimers of p50 contain no TAD and they can therefore act as transcriptional repressors by competing for p50/p65 binding to the NF-kB consensus sequence. In addition, subtle differences in NF-kB consensus sequences have now been shown to demonstrate preferential binding to different NF-kB dimers [15]. This is exemplified by

the -863 C/A polymorphism in the human TNFα promoter. Here, the C allele can bind both p50/50 and p50/p65 dimers, whereas the A allele can bind only the inhibitory p50 homodimer [20] suggesting that the A allele should demonstrate a dampened TNFa response following NF-kB activation. Indeed, this polymorphism may influence the incidence of RA.Once activated, the ability of NF-kB to induce transcription can be further enhanced by post-translational phosphorylation and acetylation of the subunits [17]. For instance, serine phosphorylation of p65 can occur at different residues and is stimulus specific. Phosphorylated p65 can then be acetylated and this molecule has maximum activity. Acetylation of p65 is performed by CBP and p300, transcriptional coactivators that also recruit the transcriptional machinery. In addition, they have histone acetyltransferase activity, which helps to 'relax' the chromatin environment surrounding the activated genes and increase the efficiency of transactivation. Histone modification by NF-κB can lead to epigenic control of gene transcription, reviewed elsewhere [6,29].

The role of the canonical pathway in rheumatoid arthritis

The studies described above have been extremely important in establishing the molecular events that can occur in the canonical NF-kB pathway (Figure 2). However, their relevance to the activation of NF-kB seen in RA cannot be assumed. Important differences in immune cell function exist between humans and mice, and between transformed and non-transformed cells (dealt with in detail below). Research in primary human cells was hampered for many years because these non-dividing cells are resistant to conventional transfection techniques. Recently, this technological challenge was overcome by the use of adenoviral systems that efficiently infect primary cells and deliver exogenous expression constructs. Here, dominant negative (dn) variants of canonical pathway signalling components were expressed in cells that are relevant to RA, including primary synovial cell cultures (containing a mixture of cells) from patients undergoing knee replacement surgery, synovial fibroblasts derived from them, and primary M-CSF differentiated macrophages from normal human blood donors. In such studies, dnIKK1 was found not influence spontaneous cytokine production from primary synovial cell cultures, whereas dnIkBα and dnIKK2 profoundly inhibited IL-6, IL-8 and VEGF production [4]. Somewhat surprisingly dnIKK2 did not significantly inhibit spontaneous TNFα production. However, these findings generally support the hypothesis of an important role for the canonical pathway in RA and that IKK2 is the dominant kinase in the IKK complex. To extend these

studies, the dn proteins have also been tested in the different cells types present in the synovial cell cultures. Here, dnIKK2 was found to inhibit cytokine production from both TNFα and IL-1b stimulated macrophages and RA synovial fibroblasts. This same molecule could also block IL-6 and IL-8 production in LPS stimulated RA synovial fibroblasts. However, in stark contrast to findings in murine cells, it is interesting to note that dnIKK2 did not affect TNFα, IL-6 or IL-8 production following LPS stimulation of human macrophages [4]. This could have suggested that the canonical pathway is of low importance in LPS stimulated macrophages. However, dnIkBα effectively blocks expression of TNFα, IL-1b, IL-8 and IL-6 production in response to LPS [33]. This suggests that other (unidentified) IkB phosphorylating kinase(s) are present in these cells. It might also explain why the dnIKK2 could not affect spontaneous TNFα production from the synovial cell cultures, since the main source of TNFα here is macrophages. IkBα also has differential effects on the spontaneous production of different cytokines in primary RA synovial cultures. While IL-1β, IL-6, IL-8, MMP-1, -3 and -13 were all IkBα- dependent as expected, TNFα production was not affected [46].

These studies serve to highlight the complexities of the role that the NF-kB pathway plays in RA. Whilst the pathways activating NF-kB can be described in a straight forward way, in reality there is enormous variation in the molecular events that can occur between different cell types, in response to different cellular stimuli and for different genes that respond to NF-kB activation.

The 'non-canonical' pathway of NF-kB activation

An 'alternative' or 'non-canonical' pathway of NF-kB activation has been described that occurs specifically in B cells in response to small subset of stimuli (Figure 2) [35]. Here p100 itself, rather than an IκB, acts to sequester RelB in the cytosol. The processing of p100 is tightly regulated and virtually absent in unactivated cells. B cell stimulation with lymphotoxin results in p100 phosphorylation by a complex of IKK1 and NF-κB inducing kinase (NIK). It then undergoes limited proteolysis by the proteasome, giving rise to p52, and p52/RelB dimers are than able to activate transcription. Both NIK and IKK1 are indispensable for this activity. Recently p100 was shown to be a bona fide member of the IkB family and designated IkBε. However, as NIK is not required for NF-kB activation following TNFα or IL-1α stimulation in primary human macrophages or, fibroblasts, neither is it involved in the spontaneous TNFα production by RA synovial cell cultures [27] it will

not be considered further here.

Therapeutic strategies for NF-kB inhibition and clinical application

Several agents already safely used in clinical practice have been recently shown to have properties which go beyond their traditional pharmacological action. These 'pleiotropic' properties include NF-kB inhibition, at least in the in vitro setting (Figure 3). Many pharmaceutical companies have programmes to develop selective inhibitors of NF-kB, which include (1) directly targeting DNA binding activity of individual NF-kB proteins using small molecules or decoy oligonucleotides; (2) blocking the nuclear translocation of NF-kB dimers by inhibiting the nuclear import system; (3) stabilising IkBα protein by developing ubiquitination and proteasome inhibitors; (4) targeting signaling kinases such as IKK using small molecule inhibitors. All these therapeutic strategies are aimed at blocking NF-kB activity [11,43]. With increasing knowledge of signaling pathways leading to NF-kB activation, multiple targets can be identified for potential interaction with small molecules. From the upstream kinases, such as IKK1, IKK2, MEKK-3, and NIK, to their downstream effector IkB E3 protein, all represent attractive targets for novel drugs selectively regulating NF-kB function [11]. Other components of the TNFα and IL-1 signaling pathways including TRADD, RIP, TRAF2, and TRAF6 and IRAK, as well as PKC isoforms and phosphoinositide 3-kinase, may provide additional targets for yet to be discovered inhibitors of NF-kB [31]. Novel therapeutic strategies aimed at the specific inhibition of key elements in the NF-κB pathway activation are being developed, causing great expectation regarding their potential effects as arthritis treatments. For example, proteasome function inhibitors, decoy oligonucleotides, and peptides that inhibit nuclear localization of NF-κB have been utilized to inhibit NF-κB signaling in animal models

Blockade of NF-κB to DNA binding

The most direct strategy for blocking NF-κB activation is to block NF-κB from binding to specific κB sites on DNA [14,25]. Some sesquiterpene lactones (SLs) have been reported to inhibit NF-κB [14] by interacting with Cys-38 in the DNA-binding loop of RelA [37]. Most SLs can also inhibit DNA binding through an analogous Cys residue in the DNA-binding loops of p50 and c-Rel. Some SLs, including
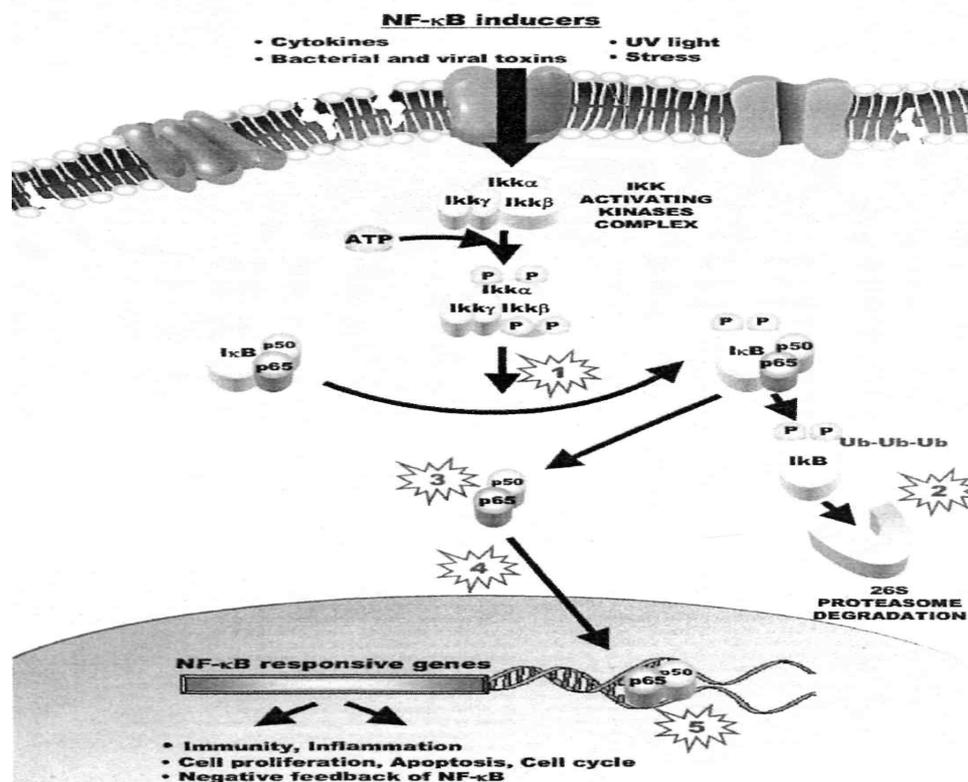

Figure 3. NF-kB signaling pathway. Many current therapeutic agents and future strategies block the NF-kB pathway in different steps:

(1) I-kB phosphorylation: NSAIDs (aspirin, salycilate, ibuprofen, sulindac), 5-aminosalicylic acid, SC-514.

(2) Protease activity of the 26S proteasome complex: Bortezomib, Cyclosporin A, sc-514, lactacystin.

(3) Disminution of levels of NF-kB subunits p65, p50, c-Rel and others: siRNA.

(4) Nuclear translocation of NF-kB subunits p65, p50, c-Rel and others: FK-506, BMS-205820, I-kB super repressor, Tat-srIkBa.

(5) NF-kB DNA binding: Glucocorticoids, NF-kB ODN, NF-kB morpholinos.

parthenolide, have been shown to inhibit IKKβ through the reactive Cys-179 in the kinase activation loop [14,26]. Thus, SLs, which target both IKK activity and NF-κB subunit DNA binding , have multistep inhibitory activity within the NF-κB signaling pathway. Blocking specific NF-κB-DNA binding can also be accomplished with decoy oligodeoxynucleotides (ODNs). These ODNs have κB sites and competes for NF-κB dimer binding to specific genomic promoters [38]. These oligonucleotides have modifications to increase their stability and their affinity for NF-κB in vivo. Decoy ODNs have been reported to have therapeutic potential in a number of animal models of inflammation including rheumatoid arthritis and atherosclerosis [36,41].

Peptides with nuclear localization sequences inhibit NF-kB activity

Translocation of the NF-kB heterodimer from the cytoplasm to the nucleus is a central program in the regulation of the NF-kB pathway [42]. Thus the development of inhibitors of NF-kB nuclear localization using recombinant peptides provides an approach that can mask the nuclear localisation sequence (NLS) of NF-kB family members. This approach utilizes cell-penetrating peptides consisting of the NLS of the p50 NF-kB subunit, designated as SN50. Introduction of SN50 into cell efficiently inhibits LPS - and TNFα-induced NF-kB nuclear translocation and reduces NF-kB DNA binding in cultured endothelial and monocytic cells [39]. Inflammatory articulation increases the release of cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), cytokines that play a key role in the development of RA. In chondrocytes, IL-1β activates extracellular signal-regulated kinase 1/2 (Erk1/2) and p38 mitogen-activated protein kinase (p38MAPK), and therefore induces the nuclear translocation of the nuclear factor-κB (NF-κB) and the activator protein-1 (AP-1) [10]. These transcription factors bind to consensus sequences of numerous pro-inflammatory genes, and initiate as well as maintain the inflammatory reaction in chondrocytes. As a result, IL-1κ increases the expression of matrix metalloprotease-3 (MMP-3) , phospholipase A2 (PLA2) and cyclooxygenase 2 (COX-2), IL-1β and TNF-α [10].Using chondrocytes stimulated by IL-1β as experimental model, it was demonstrated that chondroitin sulphate (natural glycosamineglican in the extracellular matrix and is formed by the 1 - 3 linkage of D-glucuronic acid to N-acetylgalactosamine) and glucosamine sulphate are diminishes IL-1β-induced NF-κB nuclear translocation. The effects of chondroitin sulphate and glucosamine are mediated by inhibition of p38MAPK and Erk1/2 phosphorylation. These data suggest that the anti-inflammatory activity

of chondroitin sulphate and glucosamine are associated with the reduction of Erk1/2 and p38MAPK phosphorylation and nuclear transactivation of NF-κB [7,30].

26S proteasome inhibitors prevent IkBα degradation and NF-kB activation

The activation of IKK and the subsequent phosphorylation and degradation of IkBα by the 26S proteasome is a key step in the nuclear translocation of NF-kB and subsequent NF-kB-regulated transcription. Given the fundamental role of the proteasome [5] in the regulation of the NF-kB pathway, it provides a variety of natural and synthetic proteasome inhibitors has been studied, including epoxomicin, which the first proteasome inhibitor to enter human trials for rehumatoid arthritis and atherosclerosis [44].The step before NF-κB leaves the cytoplasm involves the ubiquitination of IκB by the SCF-β-TrCP ubiquitin ligase complex followed by the rapid degradation of ubiquitinated IκB by the 26S proteasome. Because IκBα degradation is an important step in the NF-κB activation pathway, inhibiting the proteasomes that degrade IκBα may also serve as a tool for pharmacological intervention. Very specific and potent proteasome inhibitors have been engineered by coupling boronic acid to dipeptides. The dipeptide boronate, bortezomib, the most-studied proteasome inhibitor in clinical development, has been shown to inhibit proliferation and induce apoptosis in head and neck . Bortezomib's antitumor properties correlate in part with its ability to inhibit IκBα degradation [8] . Other well-known proteasome inhibitors include lactacystine, N-cbz-Leu-Leu-leucinal (MG132), MG115, and ubiquitin ligase inhibitors. In addition, recently identified a novel proteasome inhibitor, salinosporamide A (NPI-0052), which can suppress both constitutive and inducible NF-κB activation in a nanomolar range [2] .

Inhibition of protein kinases

NF-κB activation requires the phosphorylation, polyubiquitination, and subsequent degradation of its inhibitory subunit, IκBα. Hence, inhibiting IκBα phosphorylation ultimately inhibits NF-κB's transcriptional activity [3]. IκBα phosphorylation is carried out by IKK, a serine/threonine protein kinase composed of three basic subunits: the kinases IKKα, IKKβ, and the regulatory subunit IKKγ (NEMO) [24,33]. The IKK activation is usually the first common step in the integration of many NF-κB-activating pathways; therefore, one strategy for inhibiting NF-κB activation is to block IKK activation. However, although more than 150 agents have been shown to inhibit NF-κB activation at the IKK step, few studies have investigated the mechanism by which a given agent can inhibit IKK or its activation [47]. The few

IKK inhibitors for which a mechanism of action is known can be divided into three general groups: adenosine triphosphate (ATP) analogs, which show some specificity for interacting with IKK; compounds that have allosteric effects on IKK structure; and compounds that interact with a specific cysteine residue (Cys-179) in the activation loop of IKKβ. ATP analogs include natural products such as β-carboline and synthetic compounds such as SC-839, which has an approximately 200-fold preference for IKKβ compared to IKKα [47]. Compounds that have allosteric effects on IKK structure include BMS-345541, a synthetic compound that binds to an allosteric site on both IKKα and IKKβ and has an approximately 10-fold greater inhibitory effect on IKKβ than on IKKα. Compounds that interact with Cys-179 IKKβ include thiol-reactive compounds such as parthenolide, arsenite, and certain epoxyquinoids [32]; these compounds' interactions with Cys-179 are believed to interfere with phosphorylation- induced IKK? activation because Cys-179 is located between Ser[177] and Ser[181], which are required for IKKβ activation in response to upstream signals such as tumor necrosis factor (TNF) and lipopolysaccharide (LPS). Gene-based inhibitors can also block IKK activation. Specifically, mutations at the ATP-binding site or in the kinase activation loop can create dominant-negative IKKα and IKKβ, which are capable of blocking NF-κB activation . Because of their distinct roles in the canonical and non-canonical NF-κB activation pathways, dominant-negative IKK mutants' can show stimulus-dependent inhibition . Adenoviral-mediated delivery of an IKKβ dominant-negative kinase has been shown to have therapeutic potential for airway inflammatory diseases such as asthma. NEMO can also serve as a target for inhibiting the IKK complex [24]. In particular, introducing a cell-permeable 10 amino-acid peptide that corresponds to the NEMO-binding domain of IKKβ can block the binding of NEMO to IKK in response to TNF in the canonical pathway. While activation of NF-κB by many stimuli depends on the phosphorylation of IκBs at N-terminal sites by the IKK complex, the mechanism of NF-κB activation by ultraviolet (UV) radiation involves the IKK-independent phosphorylation of IκBα at a cluster of C-terminal sites that are recognized by casein kinase II (CKII). CKII activity toward IκBα depends on p38 mitogen-activated protein kinase (MAPK) activation. CKII's role as a key survival signal that activates NF-κB and protects tumor cells from apoptosis suggests that CKII may be an attractive target for the treatment of diverse cancers [48]. Apigenin, a plant flavonoid, and emodin, a plant anthraquinone, are competitive inhibitors of CKII that directly in-

teract with the nucleotide-binding sites of CKII [23]. Besides phosphorylating and subsequently degrading the molecules that inhibit NF-κB, protein kinases can also target the functional domains of NF-κB proteins themselves to optimally activate NF-κB. NF-κB proteins can be phosphorylated in the cytoplasm or nucleus by such kinases as glycogen synthase kinase 3β (GSK3β), TRAF-associated NF-κB activator (TANK)-binding kinase 1 (TBK1), PKAc , mitogen- and stress-activated protein kinase-1 (MSK-1), MAP3K NIK, Tpl2, PKC-θ, PI3K, Akt, p38 MAPK, protein tyrosine kinase, PKC-δ, RHO-kinase 2, mitogen activated protein kinase kinase 3 (MEKK3) , and receptor tyrosine kinases such as epidermal growth factor receptor, human epidermal growth factor receptor 2 [46]. Antagonistic antibodies or kinase inhibitors that target these molecules may decrease NF-κB activation. Some kinase inhibitors that have the potential to inhibit NF-κB activation include SB203580 and PD0980589 (MAPK inhibitors); denbinobin (TAK1 inhibitor); tyrosine kinase inhibitors; rhein, (an MEKK inhibitor); TNAP, betaine (NIK inhibitors), epoxyquinol B (a TAK1 crosslinker); M2L (an extracellular signal-regulated kinase 2 inhibitor); CCK-8 (a p38 kinase kinase inhibitor), KSR2 (an MEKK3 inhibitor), golli BG21 (a PKC inhibitor) [14,16,39].

Conclusion
The NF-kB family of TFs plays a crucial role in the distinctive inflammatory processes characteristic of certain rheumatic disease, such as rheumatoid arthritis, leading to cartilage destruction and articular damage. NF-kB is abundant in rheumatoid synovium, however, its activation is higher in rheumatoid arthritis than in osteoarthritis. IKK, a key enzyme in the activation of the canonical NF-kB signaling pathway, is also abundantly expressed in rheumatoid arthritis fibroblast-like synoviocytes Animal models of arthritis, including murine type II collagen-induced arthritis and rat adjuvant arthritis, support the essential role of NF-kB, and of IKK in particular, on MMP gene expression and the development of inflammatory and histological changes of arthritis. In articular chondrocytes, NF-kB activation mediates the response to important proinflammatory cytokines, namely, IL-1β and TNF-α, as well as to fibronectin fragments and mechanical signals. NF-kB also participates in the RAGE signaling. Important NF-kB-mediated outcomes of the inflammatory response in human articular chondrocytes are the decrease in the expression of chondrocyte specific genes (collagen type II, link protein gene), and the increase in the expression of MMPs (MMP-1, MMP-3, MMP-13), cytokines (IL-6, IL-8) and chemokines. Interestingly,

NF-kB production is increased with donor aging and under hypoxic conditions in IL-1β-stimulated articular chondrocytes. NF-kB is also involved in the regulation of apoptosis in articular chondrocytes, exerting primarily anti-apoptotic effects. Therefore, NF-kB inhibition is a rational objective in the treatment of rheumatic disease such as rheumatoid arthritis. NSAIDs, glucocorticoids, natural products and certain disease-modifying anti-rheumatic drugs have been described to decrease NF-kB activation. Yet, novel therapeutic strategies targeting key elements in the NF-kB pathway including IKK, 26S proteasome, p65 and p50 subunits have been and continue being developed, and small molecule inhibitors, chimeric molecules, improved anti-sense therapy and RNA interference are part of the new approaches to block the NF-kB pathways. Thus, NF-kB appears as a very attractive target for treatment of rheumatoid arthritis; however, some concerns about the systemic and indiscriminate blockade of its numerous beneficial effects, as well as technical problems for local delivery of a potential agent through gene therapy still remain. Further in vivo studies will increase our understanding of the true significance of NF-kB and provide the foundations for the development of effective therapy for various joint diseases, including rheumatoid arthritis.

References. 1.Adli M. IKKα and IKKβ each function to regulate NF-kB activation in the THF-induced/canonical pathway / M.Adli, E.Merkhofer, P. Cogswell, AS Baldwin // PLoS ONE. - 2010. - Vol.5, N2. -P. a9428. 2.Ahn K, Salinosporamide A (NPI-0052) potentiates apoptosis, suppresses osteoclastogenesis, and inhibits invasion through down-modulation of NF-kB-regulated gene products / K.Ahn, G. Sethi, TH. Chao [et al.] // Blood. - 2007. - Vol.110, N7. - P.2286-2295. 3.Anchoori RK. Inhibition of IkB kinase and NF-kB by a novel synthetic compound SK 2009 / RK. Anchoori, KB. Harikumar, VR.Batchu [et al.] //Bioorg. Med. Chem. - 2010. - Vol.18, N1. - P. 229-239. 4.Andreakos E. Heterogeneous requirement of IkB kinase 2 for inflammatory cytokine and matrix metalloproteinase production in rheumatoid arthritis / E.Andreakos, C.Smith, S. Kiriakidis [et al.] // Arthritis Rheumatism. - 2003. - Vol.48, N7. - 1901-1912. 5.Asano S. Proteasomes: a molecular census of 26 S proteasomes in intact neurons / S.Asano, Y. Fukuda, F.Beck [et al.] // Science. - 2015. - Vol.347, N5. -P.439-442. 6.Bhatt D. Regulation of the NF-kB-mediated transcription of inflammatory genes /D.Bhatt, S.Ghosh // Front Immunol. - 2014. - Vol.5, N1. - P.71-79. 7.Campo GM. Chondroitin-4-sulfate inhibits NF-kB translocation and caspase activation in collagen-induced arthritis in mice / GM.Campo, A.Avenso, S.Campo [et al.] // Osteoarthritis Cartilage. - 2008. -Vol.16, N12. - P. 1474-1483. 8.Chen D. Bortezomib as the first proteasome inhibitor anticancer drug: current status and future perspective / D.Chen, M. Frezza, S. Schmitt [et al.] // Curr. Cancer Drug Targets. - 2011. - Vol.11, N3. P.239-253. 9.Choy E. Understanding the dynamics: pathways involved in the pathogenesis of rheumatoid arthritis / E.Choy// Rheumatol. - 2012 - Vol.51, N5. -P.3-11. 10.Domagala F. Inhibition of interleulin-1β-induced activation of MEK/ERK pathway and DNA binding of Nf-kappa B and AP-1: potential mechanism for Diacerein effects in osteoarthritis / F. Domagala, G.Martin; P. Bogdanowicz [et al.] // Biorheology. - 2006. - Vol.43, N3-4 - P.577-587. 11.Fishman P. Rheumatoid arthritis: history, molecular mechanisms and therapeutic application / P.Fishman, S.Bar-Yehuda // In: Adenosine receptors from cell biology to pharmacology and therapeutic. Borea PA., ed. Springer Sci., N.Y. - 2010. - P.291-

298. 12.Ganesan N. Signal transduction pathway in rheumatoid arthritis / N.Ganesan, V. Pallinti, G. Rajasekhar// SRJM - 2010 - Vol.3, N1. -P.18-21. 13.Gibofsky A. Overview of epidemiology, pathophysiology, and diagnosis of rheumatoid arthritis /A.Gibovsky // Am. J. Manag. Care - 2012. - Vol.18, N13. - P.295-302. 14.Gilmore TD. Inhibition of NF-kB signaling: 785 and counting / TD. Gilmore, M.Herscovitch // Oncogene. - 2006. - Vol.25, N51. - P.6887-6899. 15.Giopanou I. Metadherin, p50, and p65 expression in epithelial ovarion neoplasms: an immunohistochemical study / I. Giopanou, V. Bravou, P. Papanastasopoulos [et al.] // BioMed Res. Int. - 2014. - Vol.2014. - P. ID 178410. 16.Gupta SC. Inhibiting NF-kB activation by small molecules as a therapeutic strategy / SC.Gupta, C. Sundaram, S.Renter [et al.] // Biochem. Biophys. Acta. - 2010. - Vol.1799, N10-12. - P.775-787. 17.Hayden MS. NF-kB in immunobiology /MS.Hayden, S. Ghosh // Cell Res. - 2011. - Vol.21, N2. - P.223-244. 18.Herkenham M. Cautionary notes on the use of NF-kB p65 and p50 antibodies for CNS studies /M. Herkenham, P.Rathore, P.Brown, SJ.Listwak // J. Neuroinflam. - 2011. - Vol.8, N2. - P.141-155. 19.Hoesel B. The complexity of NF-kB signaling in inflammatory and cancer / B. Hoesel, JA Schmid // Mol.Cancer. - 2013. - Vol.12, N1. - P.86-94. 20.Israel A. The IKK complex, a control regulator of NF-kB activation / A.Israel // Cold Spring Harb Perspect Biol. - 2010. - Vol.2, N4. -P. a158. 21.Karin M. Mitogen activated protein kinases as target for development of nivel anti-inflammatory drugs / M.Karin // Ann. Rheum. Dis. -2004. - Vol.63, N1. -P. 62-64. 22.Karin M. Role for IKK2 in muscle: waste not, want not / M. Karin // J. Clin. Invest. - 2006. - Vol.116, N11. - P. 2866-2868.23.Kroonen J. Casein kinase II inhibition modulates the DNA damage response but fails to radiosensitze malignant glioma cells / J.Kroonen, M.Artesi, V.Capraro [et al.] // Int. J. Oncol. - 2012. - Vol.41, N2. - P. 776-782. 24. Lee SH. Novel phosphorylation of IKKγ/NEMO/ SH. Lee, LY. Wong, K. Brulois [et al.] // Clin. Microbiol. Portal. - 2012. - Vol.3, N6. - P.e411-412. 25.Leung CH. Novel mechanism of inhibition of nuclear factor-kB DNA-binding activity by diterpenoids isolated from isodan rubescens / CH.Leung, SP.Grill, W.Lam [et al.] // Mol.Pharmacol. - 2005. - Vol.68, N2. - P.286-297. 26. Liu L. A sesquiterpene lactone from a medical herb inhibits proinflammatory activity of TNF-α by inhibiting ubiquitin-conjugation enzyme UbcH5 / L. Liu, Y.Hua., D.Wang [et al.]// Chem.Biol. - 2014. - Vol.21, N10. - P.1341-1350. 27.Lowe JM. P53 and NF-kB coregulate proinflammatory gene responses in human macrophages /JM.Lowe, D. Menendez, P. Bushel [et al.] // Cancer Res. - 2014. - Vol.74, N8. - P. 2182-2192. 28.Mann DA. The NF-kB luciferase mouse: a new toolfor real time measurement of NF-kB activation in the whole animal /DA Mann // Gut. - 2002. - Vol.51, N6. -P.769-770. 29.Oeckinghaus A. The NF-kB family of transcription factors and its regulation / A.Oeckinghaus, S. Chosh // Cold Spring Harb Perspect Biol. - 2009. - Vol.1, N4 - P. a34. 30. Reginster JY. Role of glucosamine in the treatment for osteoarthritis / JY. Reginster, A. Neuprez, MP. Leeart [et al.] / / Rheumatol. Int. - 2012. - Vol.32, N10. - P.2959-2967. 31.Royuela M. TNF-alpha /IL-1/NF-kB-transduction pathway in human cancer prostate / M. Royuela, G.Rodriguez-Berriguete, B.Frail, R.Paniagua // Nistol. Histopathol. - 2008. - Vol.23, N10. - P. 1279-1290. 32.Saadane A. Parthenolide inhibits I kappa B kinase, NF-kappa B activation, and inflammatory response in cystic fibrosis cells and mice / A. Saadane, S.Masters, J.DiDonato [et al.] // Am. J. Respir. Cell Mol. Biol. - 2007. - Vol.36, N6. - P. 728-736. 33.Solt LA. NEMO-binding domains of both IKKα and IKKβ regulate I kappa B kinase complex assembly and classical NF-kappaB activation / LA Solt, LA Madge, MJ May // J. Biol. Chem. - 2009. -Vol.284, N40. -P.27596-27608. 34.Solt LA. The I kappa B kinase complex: master regulator of NF-kB signaling / LA Solt, MJ May// Immunol. Res. - 2008. - Vol.42, N1-3. -P.3-18. 35.Sun SC. Non-cannonical NF-kB signaling pathway / SC. Sun // Cell Res. - 2011. - Vol.21, N1. - P. 71-85. 36.Tandon VR. Gene therapy in rheumatoid arthritis: a novel therapeutic approach / VR. Tandon, A. Mahajan, JB. Singh // J.Indian Rheumatol. - 2005. - Vol.13, N1. - P.98-102. 37.Tang JR. The NF-kB inhibitory proteins IkBα and IkBβ mediate disparate responses to inflammation in fetal pulmonary endothelial cells /JR. Tang, KA.Micharlis, E. Nozik-Grayck [et al.] // J.Immunol. - 2013. -Vol.190, N6. - P. 2913-2923. 38.Tas SW. Gene therapy targeting nuclear factor -kappa B: towards clinical application in inflammatory diseases and cancer / SW.Tas, MJBM.

Vervoordeldonk, PP. Tak [et al.] // Curr. Gene Ther. - 2009. - Vol.9,N3. - P.160-170. 39.Tergaonkar V. Inhibitors of NF-kB activity / V. Tergaonkar, Q.Li, IM. Verma// In. NF-kB 7Rel transcription factor family. Liou HC. Ed. Springer Sci., N.Y., 2006. - P.162-178. 40.Thangjam GS. Novel mechanism of attenuation of LPS-insused NF-kB activation by the heat shock protein 90 inhibitor, 17-N- allylamino-17-demetho-xygeldanamycin, in human lung microvascular endothelial cells / GS Thangjam, C.Dimitropoulou, AD Joshi [et al.] // Am. J. Respir. Cell Mol Biol. - 2014 - Vol.50,N5. - P.942-952. 41.Tomita T. Application of NF-kappa B inhibitor for arthritis / T.Tomito, Y. Kunugiza, K. Nomura [et al.] // Nichon Rinsho Meneki Gakkai Kaishi. - 2009. - Vol.32,N2. - P.71-76. 42.Trask JO. Nuclear factor kappa B (NF-kB) translocation assay development and validation for high content screening / JO.Trask// In: Assay Guidance Manual. Sittampalam S., ed. - Eli Lilly. Co., N.Y., 2012 - P.1-22. 43.Verma IM. Nuclear factor (NF)-kB proteins:therapeutic targets /IM.Verma // Ann. Rheum. Dis. - 2004. - Vol.63,N2. - P.57-61. 44.Wang H. The proteasome inhibitor lactacystin exerts ist therapeutic effects on glioma via apoptosis: an in vitro and in vivo study / H.Wang, S.Zhang, J. Zhong [et al] // Int. Med. Res. - 2013. - Vol.13,N1. - P.1-10. 45. Weber A. Interleukin-1 (IL-1) pathway / A.Weber, P. Wasiliew, M. Kracht // Science Signal. - 2010. - Vol.3,N105. - P.1-6. 46. Xu X.Activation of epidermal growth factor receptor is required for NTHi-induced NF-kB dependent inflammation / X.Xu, RR.Steere, CA.Fedorchuk [et al.] //PLoS ONE. - 2011. - Vol.6,N11. - P.e28216. 47.Yoon JW. β-Carboline alkaloid suppresse NF-kB transcriptional activity through inhibition of IKK signaling pathway / JW Yoon, IK Kang, KR Lee [et al.] // J. Toxicol.Environ. Health A. - 2005. - Vol.68,N 23-24. - P.2005-2017. 48.Yu M. Protein kinase casein kinase 2 mediates inhibitor-kappaB kinase and aberrant nuclear factor-kappa B activation by serum factor(s) in head and neck squamous carcinoma cells / M.Yu, J. Yeh, C. Van Waes // Cancer Res.- 2006. - Vol.66,N13. - P.6722-6731. 49.Zamanian-Daryoush M. NF-kB activation by double-stranded-DNA-activated protein kinase (PKR) in mediated through NF-kB-inducing kinase and IkB kinase / M.Zamanian-Daryoush, TH Mogensen, JA DiDonato, BRG Williams // Mol. Cell. Biol. - 2010 - Vol.20,N4. - P. 1278-1290. 50.Zhang JM. Cytokines, inflammation and pain /JM.Zhang, J.An// Int. Anesthesiol. Clin. - 2007. - Vol.45,N2. - P.27-37.

ПРИГНІЧЕННЯ СИГНАЛЬНОГО ШЛЯХУ ЯДЕРНОГО ФАКТОРА - КВ (NF-KB) ЯК ПОТЕНЦІЙНА СТРАТЕГІЯ ЛІКУВАННЯ РЕВМАТОЇДНОГО АРТРИТУ

А.Т.Долженко, С. Сагаловські

Резюме. Ядерний фактор - кВ (NF-kB) є одним із головних транскрипційних факторів, які приймають участь у розвитку запальних реакцій і видіграючих основну роль у пошкодженні сіновіальної тканини і патогенезу різних ревматоїдних захворювань, у тому числі, ревматоїдного артриту. NF-kB видіграє важну роль не тільки у розвитку запалення, але і у порушенні хрящевої тканини, клітинної діференціації, проліферації, ангіогенезу і подавлення апоптозу. У результаті встановлення важної ролі NF-kB сигнального шляху в деградації суглобового хрящу і прогресуванні ревматоїдного артриту, дозволило перег-лянути механізми дії звісних протиревматичних середовищ, таких як кортикостероїди, нестероїдні протизапальні препарати. Розуміння значності ролі NF-kB сигнального каскаду в патогенезі ревматоїдного артриту сприяло виникненню ідеї пошуку середовищ, інгібуючих/моди-фікуючих активність молекул сигнального шляху, розробку та впровадження в практику нових препаратів для ліку-вання захворювання.

Ключові слова: NF-kB сигнальний шлях, фактори транскрипції, запалення, ревматоїдний артрит.

УГНЕТЕНИЕ СИГНАЛЬНОГО ПУТИ ЯДЕРНОГО ФАКТОРА - КВ (NF- KB) КАК ПОТЕНЦИАЛЬНАЯ СТРАТЕГИЯ ЛЕЧЕНИЯ РЕВМАТОИДНОГО АРТРИТА

А.Т.Долженко, С. Сагаловски

Резюме. Ядерный фактор - кВ (NF-kB) является одним из главных транскрипционных факторов, участвующих в развитии воспалительных реакций и играющих основную роль в повреждении синовиальной ткани и патогенезе различных ревматоидных заболеваний, в частности, ревма-тоидного артрита. NF-kB играет важную роль не только в развитии процесса воспаления, но и разрушении хрящевой ткани, клеточной дифференциации, пролиферации, ангио-генезе и подавлении апоптоза. В результате выяснения важной роли NF-kB сигнального пути в деградации сустав-ного хряща и прогрессировании ревматоидного артрита, пересмотрены механизмы действия известных противорев-матических средств (кортикостероидов, нестероидных противовоспалительных препаратов). Понимание значимости роли NF-kB сигнального каскада в патогенезе ревматоидного артрита позволило предложить идею поиска средств, игибирующих/модулирующих активность молекул сиг-нального пути, разработку и внедрение в практику новых препаратов для лечения заболевания.

Ключевые слова: NF-kB сигнальный путь, факторы транскрипции, воспаление, ревматоидный артрит.

Отдел биохимических научных исследований, Институт молекулярной медицины университета Мартина-Лютера, Галле-Выттенберг, Германия

Кафедра ортопедии центральной клиники, Бад Лаузик, Германия

———————————