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Review Article

NFKB: The Pre-Eminent Signaling System

Rosini Sergio[1], Rosini Stefano[2], Saviola Giannantonio[3], Molfetta Franceses[4] and Molfetta Luigi[4]*

[1]*Biomaterial Reserach Center, Livorno, Italy*

[2]*Smile-Restyle, Livorno, Italy*

[3]*Istituti Clinici Scientifici Maugeri, IRCCS Castel Goffredo, Castel Goffredo, Italy*

[4]*DISC Department, School of Medical and Pharmaceutical Sciences, University of Genoa, Research Center of Osteoporosis and Osteoarticular Pathologies, Italy*

***Corresponding Author:** Molfetta Luigi, DISC Department, School of Medical and Pharmaceutical Sciences, University of Genoa, Research Center of Osteoporosis and Osteoarticular Pathologies, Italy.

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Abstract

The ability of cells to respond to environmental changes is essential for the performance of their physiological function. The activation of a receptor initiates a cascade of biochemical transformations that connect it to downstream effectors, often to modify gene expression patterns. Subsequently, downstream effectors, such as transcription factors, transform specific dynamic signaling patterns into a specific cellular response. The Nuclear Factor Kappa-B (NF-kB), acronym of nuclear factor kappa-light-chain-enhancer of active B cells, and the proteins that regulate it, constitute a signaling system of primary importance in human physiology and in numerous pathologies where NFkB is required for adaptive changes in gene expression and tissue homeostasis. Furthermore, NF-kB is active in various steps of the immune system, such as in the differentiation of immune cells and lymphoid organs and during immune activation. NFkB is rapidly activated in response to various stimuli, including cytokines, infectious agents, free radicals, iNOS and COX-2 and increased expression of cartilage ECM degrading proteases.

Keyword: *NFkB; Gene Expression; Inflammation; Immune Activation*

Introduction

The ability of cells to respond to environmental changes is key to their function. A ligand binding to a receptor initiates a cascade of biochemical transformations of cellular kinases, phosphatase, and other enzymes that connect the receptor to downstream effectors, often to change gene expression patterns. Information about extracellular events undergoes multiple transformations. Initially, information on ligand identity and abundance is transformed, i.e. encoded, into a specific signaling activity pattern. Subsequently, downstream effectors such as transcription factors transform the specific dynamic signaling patterns to a specific cellular response.

The Nuclear Factor Kappa-B (NF-kB), and the proteins that are regulated, have emerged as a signaling system of pre-eminent importance in human physiology and in an increasing number of pathologies where NFkB is required for adaptive changes in gene expression and tissue homeostasis. Nuclear Factor Kappa B is a family of pleiotropic transcription factors which regulates expression of a large number of genes and is recognized as one of the main inflammatory pathways. NF-kB has been found to play roles during differentiation of immune

cells and development of lymphoid organs and during immune activation, regulates genes involved in inflammation and immunity, anti-apoptosis, cellular proliferation and it also adjusts the negative feed-back of itself Activated genes include those coding for cytokines (TNF-α, IL-1β, IL-6, IL-2, IL-12, IFN-γ, GM-CSF, vascular cellular adhesion molecules VCAM, intercellular adhesion molecules ICAM, chemokines and enzymes (COX-2, iNOS). Due to the ability of influencing the expression of numerous genes, NF-κB is regulated at multiple levels and one of the primary mechanism for regulating NF-κB is through inhibitory IκB proteins and kinase that phosphorylates IκBs, like the IκB kinase (IKK) complex. A number of post-translational modifications also modulate the activity of IκB and IKK proteins as well as NF-κB molecules themselves [1].

NFkB characteristics

NF-kB is the nuclear effector of signaling pathways emanating from many receptors, including those of the inflammatory tumor necrosis factor (TNF) and Toll-like receptor superfamilies. Members of the NF-κB transcription factor family orchestrate a wide range of stress-like inflammatory responses, regulate developmental programs and cellular differentiation and control the growth and survival of normal and malignant cells. Selectivity, as well as redundancy in NF-κB mediated transcriptional control, arises from the assembly of homodimers and heterodimers of 5 different NF-κB proteins (RelA/p65, RelB, c-Rel, NFκB1/p105 and NFκB2/p100) to NF-κB [2].

In its canonical signaling pathway NFkB is a heterodimer and, in unstimulated cells it is sequestered and bound in the cytoplasm with transcription activities blocked by one of three small inhibitory proteins (IκBα, IκBβ, IκBε). NFkB are rapidly activated in response to various stimuli, including cytokines, infectious agents, free radicals, iNOS and COX-2 and increased expression of cartilage ECM degrading proteases such as MMP-1, MMP-9, MMP-13, ADAMTS4, and ADAMTS5 [3]. Canonical NF-κB heterodimers are activated by site specific amino-terminal phosphorylation of IκBα by IKK (IkBkinase complex). The IKK complex consists of two serine-threonine kinases, IKKα and IKKβ, and NEMO/IKKγ, a regulatory or docking protein that facilitates IKK complex assembly and regulates the transmission of upstream activating signals to IKKα and IKKβ.

IKKβ is almost always represented by IκBα kinase that activates NF-κB-dependent immediate stress-like responses *in vivo*, although IKKα can also takes on this role in response to specific signaling pathways [4]. IKKα, not IKKβ, is specifically required for activation of the so-called non-canonical or alternate NF-κB pathway in response to several specific extracellular inducers. The resulting proteasomal degradation of IkB proteins liberates NF-kB-Transcription factors which translocate to the nucleus to drive expression of target genes. The two protein kinases IKKalpha and IKKβ represent a point for most signal transduction pathways leading NFkB activation [5].

NFκB appears to be also important in aging processes that are associated with inflammation during aging, the so-called inflammaging [6]. Inflammatory response is initiated by activation of NFκB in macrophages which aggravates much of age related metabolic disturbances. Several age-related metabolic disorders have been associated to increased NFkB signaling, which is a common event with the age [7]. In the late 1990th, a Receptor Activator of NFkB-ligand has been discovered and linked to bone resorption [8] which is common in RA and other bone and joint diseases by activation of the expression of an array of genes which induce destruction of articular joint, leading to osteoarthritis (OA) onset and progression [9].

NFkB in Osteoarthritis

Although chondrocytes are quiescent in normal cartilage, they may be activated by inflammatory mediators, mechanical stress, matrix degradation products and age-related advanced glycation end products (AGEs), leading to a phenotypic shift and to aberrant expression of inflammation-related genes that cause imbalance between catabolic and anabolic responses characteristic of OA chondrocytes [10]. Although NF-κB plays an essential beneficial role in normal physiology, inappropriate regulation of NF-κB activity has been implicated in the pathogenesis of several diseases including inflammatory and rheumatic diseases, rheumatoid arthritis (RA) and osteoarthritis (OA). NF-κB activation prior to the onset of clinical manifestations of arthritis has been found in both, murine type II collagen-induced arthritis and rat adjuvant-induced arthritis [11].

In addition to biomechanical and age-related alterations in chondrocyte function, inflammation and accompanying dysregulated cytokine activities probably contribute to disruption of the balance between anabolism and catabolism. The role of proinflammatory cytokines, particularly interleukin IL-1β and tumour necrosis factor (TNF-α) in cartilage pathology in rheumatoid arthritis and OA is well established based on *in vitro* and *in vivo* studies [12].

The chondrocyte is the cellular target of cytokine action in cartilage, and IL-1β and TNF-α can inhibit the synthesis of type II collagen by chondrocytes by suppressing gene transcription and also stimulate the synthesis of prostaglandin E2, which feedback-regulates collagen type II α1 chain (COL2A1) transcription [13]. Injurious mechanical stress and cartilage matrix degradation products can stimulate the same signaling pathways as those induced by IL1-β and TGF-α (it remains controversial whether inflammatory cytokines are primary or secondary regulators of cartilage damage and defective repair mechanisms in OA). However, physiological loading on cartilage may protect against cartilage loss by inhibiting IKKβ activity in the canonical NF-κB cascade and attenuating NF-κB transcriptional activity while high magnitude stress induce proinflammatory gene expression via the same translocation. Furthermore, mechanical overload induces similar intracellular events to those generated by proinflammatory cytokines in arthritis [14]. The degradation of IκBα and IκBβ allows phosphorylation of NF-κB at multiple sites in a stimulant-dependent manner and its transmigration to the nucleus. NF-κB binding to its consensus sequences leads to transcription of a plethora of genes including proinflammatory cytokines and mediators, as well as several of the molecules required for the activation of NF-κB signaling cascade. Although this classical model of NF-κB activation by TNF-α or IL-1β is well documented, its complexity evolves from its regulation at multiple intracellular levels, in a cell as well as stimulus-dependent manner.

Some experiences on transgenic animals expressing Luciferin have allowed to evaluate the degree, induction times and activity of NFkB upon stimulation of various stressors [15], this work shows that the induction of chronic inflammatory processes resembling rheumatoid arthritis produce strong NFkB activity in affected joints while Vitamin A feeding is able to modulate NFkB activity. Although NFkB plays a fundamental role in normal physiology as a defense against aggressive agents, inappropriate activation results in a series of pathogenetic events characterized by inflammatory and rheumatic-type reactions [10].

It is well established [16] that NFkB (p50 and p65) are highly expressed in osteoarthritic synovitis and particularly activated in rheumatoid arthritis. Synovial tissues of individuals with RA and spondylopathies have far greater numbers of cells expressing NFkB at the pannus-cartilage junction than in other areas. Animal models of inflammatory arthritis support the concept that NFkB plays a key role in development and progression of arthritis [17]. In other animal models it has also been observed that NFkB activation occurs before clinical manifestations of arthritis, while its expression correlates with collagenase-3 (MMP-13) and stromelysin-1 (MMP-3) [18]; a localization of NFkB in chondrocytes was also observed during initial cartilage degradation [19].

Further studies have highlighted a potent activation of NFkB on joint chondrocytes following stimulation with IL-1β, TNF-α and other cytokines that play a role in cartilage catabolism [20] and it is still NFkB that mediates the expression of MMP-1, MMP-3 and MMP-13 induced by the same cytokines on chondrocytes of patients with osteoarthritis [21].

A different effect is exerted by NFkB on human chondrocytes as a result of mechanical stimuli, in fact, while low mechanical stresses prevent the nuclear translation of NFkB with a consequent inhibition of the expression of proinflammatory cytokines, the opposite occurs due to mechanical overloads; similarly in certain conditions an anti-apoptotic activity also occurs [22].

NFkB and Inflammation

Research on targets relevant to OA disease has focused on exogenous insults that trigger chondrocyte de-regulation and the endogenous factors that lead to the expression of inflammatory and hypertrophic-like factors in OA chondrocytes, including: IL-1 receptor, c-Jun

N-terminal kinase (JNK) and Mitogen-activated protein kinase (MAPK) dependent cytokine signaling, MMPs expression and activities and pro-inflammatory NF-κB signaling, amongst other pathways [23]. Because NF-κB signaling pathway responds to most injurious stimuli that affect cartilage to trigger OA and thereby brings about chondrocyte pro-inflammatory and phenotypic changes in affected cartilage tissue, targeting NF-κB signaling in OA disease is of paramount importance. Several approaches have been done to suppress on a long term the NFkB pathway by pharmacological agents but at the cost of a number of side effects. There is ongoing research to discover interventions which may influence NFkB and immune diseases, with a special attention to RA, OA and the expression of inflammatory response genes.

NF-kB has a major role in homeostatic function of managing appropriate immune response and regulation of cell cycle, which may be impaired by non-discriminative suppression [24]. 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-κB signaling pathways to the pathogenesis of some rheumatic diseases, in particular, of osteoarthritis (OA) and rheumatoid arthritis (RA). Inflammation, cartilage degradation, cell proliferation, angiogenesis and pannus formation are processes in which the role of NF-κB is prominent. Consequently, large efforts have been devoted to the study of the pharmacologic modulation of the NF-κB pathways. These studies have employed currently available therapeutic agents including non-steroidal anti-inflammatory drugs, corticosteroids, nutraceuticals and disease-modifying anti-rheumatic drugs, monoclonal antibodies, as well as novel small molecule inhibitors targeted to specific proteins of NF-κB pathways. In addition, promising strategies such as improved antisense DNA therapy and RNA interference have been examined. However, since NF-κB also plays a crucial beneficial role in normal physiology, technical problems for effective gene therapy still remain; further research will be needed before NF-κB-aimed strategies become an effective therapy for joint diseases, such as OA and RA [25].

NFkB and therapeutic strategies

Glucocorticoids are potent inhibitors of the NF-κB pathway through several proposed mechanisms. Glucocorticoids induce expression of IκB, causing an increased cytosolic retention of NF-κB and may also inhibit the NF-κB DNA-binding activity through direct interaction between the glucocorticoid receptor and components of the NF-κB binding sites in various gene promoters [26]. The activated glucocorticoid receptor can also interact with NF-κB by direct protein–protein binding, preventing the activation of the NF-κB pathway in certain types of cells. A competition can occur between the glucocorticoid receptor and NF-κB.

Some nonsteroidal anti-inflammatory drugs (NSAIDs) such as sodium salicylate, sulindac, ibuprofen, and flurbiprofen cause anti-inflammatory and antiproliferative effects independent of cyclooxygenase activity and prostaglandin synthesis inhibition. These effects are mediated through inhibition of certain transcription factors such as NF-kB and activator protein-1 (AP-1), probably mediated through alterations of the activity of cellular kinases such as IKKβ. These effects apparently are not shared by all NSAIDs, since indomethacin failed to inhibit NF-kB and AP-1 activation. In contrast, indomethacin was able to activate PPAR-γ which was not affected by sodium salicylate or aspirin. The differences in cyclooxygenase-independent mechanisms may have consequences for the specific use of these drugs in individual patients because additional effects may either enhance efficacy or reduce toxicity of the respective compounds.

TNF-α induced nuclear translocation of NF-kB is also prevented by sulfasalazine through inhibition of IkB degradation demonstrating that sulfasalazine is a potent and specific inhibitor of NF-kB activation, and thus may explain some of the known biological properties of sulfasalazine probably owing to the effects of its anti-inflammatory metabolite, 5-aminosalicylic acid. Immunosuppressive agents as Cyclosporin A and Tacrolimus also inhibit the NFkB pathway by preventing IκBα degradation or blocking the translocation from cytoplasm to the nucleus.

Several other agents have also been described to inhibit NF-κB including vitamin C, vitamin E, curcumin, flavonoids, lactacystin, thalidomide, leflunomide, pyrrolidine dithiocarbamate, glucosamine and diacehrein as well as some Bisphosphonates like Clodronate for its anti-macrophage and stabilizing activity of the macrophage IkB factor.

These compounds are intracellular inhibitors of NFkB activation by preventing in different ways the activation of IKKβ kinase, starting from IKK-mediated phosphorylation of IκBs in the cytoplasm to transcriptional induction of direct NF-κB target genes in the nucleus, with the aim of modulating nuclear transfer of NFkB.

Among already known and used drugs, it worths mentioning Vitamin D3 which, through its active metabolite, Calcitriol, has the ability to modulate the immune system and consequently inflammatory processes through the interaction with the VDRs on the antigen-presenting cells.

The inhibitory activity on the expression of cytokines is induced by regulation of MAKP-1 (mitogen activated protein kinase phosphatase-1), inhibition of the p38 protein and NFkB activation.

Other compounds aimed to intervene on the kinases (IKKβ), which involve inactivation of the IkB factor allowing the migration of NFkB towards the nucleus, have been investigated. Among these the BMS-345541 has shown efficacy on animal models with collagen arthritis and with both preventive and therapeutic regimens, blocking inflammation and cartilage degradation. Other therapeutic strategies are under investigation using chimeric molecules and antisense therapies.

However, it is surprising how in the research of efficient NFkB nuclear migration inhibitors, it has been omitted to examine the activity of an endogenous neuropeptide such as α-melanocyte-stimulating hormone (α-MSH) deriving from pro-opiomelanocortin (POMC). Alfa-MSH in addition to intervening in numerous physiological processes also has an important role in energy homeostasis and in modulating inflammatory reactions [27].

The physiological activities of α-MSH are mediated by binding to 5 different receptors (MC1-2-3-4-5) and its anti-inflammatory action is mainly due to the interaction with MC1 and MC3 widely expressed on the cells of immune system; activation of these receptors has been shown to provide protection against various inflammatory diseases such as rheumatoid arthritis or colitis [28], but also vascular inflammation [29]. Animal experiments have shown that α-MSH and its tripeptide sequence COOH-terminal, are able to inhibit the inflammatory reaction, induced by intradermal injections of IL-1, IL-6, TNF- α, due to an anti-inflammatory neurogenic signal [30]. Alfa-MSH or the terminal sequence (Lis, Pro, Val) by systemic or intracerebro-ventricular injection inhibits inflammation induced by peripheral injection of several cytokines [31]; otherwise, some pro-inflammatory agents, induced by endotoxins, increase in concentration after a central block of the. α-MSH. Besides its central influence α-MSH reduces chemotaxis of human neutrophils as well as the production of TNF-α, neopterin and NO by monocytes. In septic patients, the release of cytokines in isolated blood samples was also inhibited [32]. The inhibitory effects of α-MSH on production of cytokines and other mediators of inflammation observed in blood cells was confirmed in monocyte/macrophage and microglial cell lines.

What is highlighted by the scientific literature presents α-MSH as a modulator of all forms of inflammation by acting on peripheral inflammatory cells, glial cells and receptors in the CNS through the activation of an anti-inflammatory descending neural response exerted primarily by modulating the activation of the NFkB factor [33].

Similar results were obtained in experiments on human glioma cells and whole mouse brains stimulated with lipopolysaccharide. α-MSH, and its C-terminal tripeptide KPV, modulated brain inflammation by inhibiting NF-kB activation [34]. In both models of central nervous system inflammation, the evidence was consistent with α-MSH-induced modulation of NF-kB activation by limiting IkB

degradation. Furthermore, α-MSH modulates activation of NF-kB in human dermal fibroblasts [35], endothelial cells [36], keratinocytes [37], melanocytes, and melanoma cells [38].

As a further demonstration of the central action of α-MSH, it may be interesting to observe its relevant antipyretic action estimated to be about 20,000 times higher than that of paracetamol after intravenous administration [39].

However, it must be recognized that although NFkB represents an attractive target for the treatment of RA, OA and other pathologies, some doubts remain about the safety of an indiscriminate systemic block that would also negatively influence the beneficial effects related to the NFkB factor.

It is thought to be a more appropriate strategy to achieve a reduction in NFkB signaling rather than its complete inhibition. Each intervention on a physiological function always gives rise to a reaction, not always the expected one and not always the desired one (Also in Biology each medal has its reverse side).

Conclusions

NFkB is a ubiquitous transcription factor with varied roles within mammalian cell and well known for its regulation of inflammation and role in the innate immune response. As such, NFkB is a transcriptional activator of inflammatory mediators such as cytokines besides an influence on complex behaviors. NF-kB proteins can regulate expression of hundreds gene which regulate important physiological processes; one of the major activities of NF-kB proteins is controlling the inflammation process modulating the body's complex defense mechanisms under inflammatory conditions. This is performed by positively and negatively regulating expressions of many important genes and the expression of chemokines and pro-inflammatory cytokines. In addition, NF-κB also contributes to the resolution of inflammation. Since NF-kB activity is spontaneously regulated by a number of different stimuli, NF-kB proteins can be considered as regulators of cellular homeostasis which makes any attempt to modify its activity very complex and risky.

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