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Nf-k B as Target of Pharmacological Treatment

[1]G.A. Scardina, [1]A. Ruggieri, [2]F. Carini, [1]A. Cacioppo, [2]V. Valenza and [1]P. Messina
[1]Department of Oral Science,
[2]Department of Experimental Medicine, University of Palermo, Italy

Abstract: The Nuclear Factor Nf-k B (Nf-k B) is a Factor of Transcription (FT) ubiquitin preserved in the eukaryotic cells. Nf-k B is activated by numerous stimuli including viral and bacterial products, ultraviolet radiations, oxidant radicals, cytokines and various chemical substances. Once activated, Nf-k B directly checks, or with the cooperation of other factors of transcription, the activity of over 100 genes that produce cytokines, factors of growth, chemokines, molecules of adhesion, proteins of the acute phase. The transcriptional factor Nf-k B is implicated in the pathogenesis of chronic inflammatory disease of the vascular system and in the process of formation of atherosclerotic lesions. In fact, Nf-k B, in the activated state, is identified in situ in atherosclerotic human plates, while it's absent in vases exempted by atherosclerotic lesions. Recent study has shown that the infection by HSV-1 is able to activate Nf-k B in persistent way and to higher levels respect to the others deriving from subsequent exposure to inflammatory cytokines in various types of human cells. Moreover, the virus interferes with the self-regulating system of Nf-k B, with consequent exacerbation of the inflammatory state. For this reason, Nf-k B could represent an interesting target for new chemotherapic drugs with anti-viral action and anti-inflammatory in the herpetic infections. The biggest part of the anti-inflammatory actions of the Glucocorticoids (GC) depends by their ability to interfere with the functions of transcription factors, such as Nf-k B. Tissue lesions, cytokines, free radicals and oxidized damages induce the activation of the Nf-k B, whose action determines increase of the synthesis of COX2 and therefore of the production of some prostaglandins with pro-inflammatory function. Finally, the inhibition of the COX2 and Nf-k B operated by the FANSs has shown, in some cases, benefits anticancer effects. For all of these influences on many pathologic processes, Nf-k B can be considered as target of pharmacological treatment and object of continuous studies.

Key words: Nf-k B, Nfkb, anti-viral, HSV-1, glucocorticoids, FANS, anticancer

INTRODUCTION

The Nuclear Factor-k B (Nf-k B) is a Factor of Transcription (FT) ubiquitin preserved in the eukaryotic cells. Nf-k B is activated by numerous stimuli including viral and bacterial products, ultraviolet radiations, oxidant radicals, cytokines and various chemical substances (Karin and Ben-Neriah, 2000). Once activated, Nf-k B directly checks, or with the cooperation of other factors of transcription, the activity of over 100 genes that produce cytokines, factors of growth, chemokines, molecules of adhesion, proteins of the acute phase. The transcriptional factor Nf-kB is implicated in the pathogenesis of chronic inflammatory disease of the vascular system and in the process of formation of atherosclerotic lesions. In fact, Nf-k B, in the activated state, it's identified in situ in atherosclerotic human plates, while it's absent in vases exempted by atherosclerotic lesions. Recently study has shown that the infection by HSV-1 is able to activate Nf-k B in persistent way with consequent exacerbation of the inflammatory state. The major part of the anti-inflammatory actions of the Glucocorticoids (GC) depend from the ability to interfere with the functions of factors of transcription and just for this reason Nf-k B is remarkable. The activation of the Nf-k B determines the increase of the synthesis of COX2 and therefore of the production of some prostaglandins with pro-inflammatory function. Finally, the inhibition of the COX2 and Nf-k B operated by the FANSs has shown, in some cases, benefits anticancer effects. For all of these influences on many pathologic process Nf-k B can be considered as target of pharmacological treatment and object of continuous studies.

The Nf-k B is a protein that regulates the genic transcription. It is present in the cellular cytoplasm in inactive form because it is physically tied to a protein IkB that makes it inefficient. Inflammatory circulating stimuli

Corresponding Author: Scardina Giuseppe Alessandro, Department of Oral Science, University of Palermo, via Del Vespro, 129-90127 Palermo, Italy

as TNF, IL1, the protein LPS, produced by the pathogen bacteria and the RNA to double helix present during the viral infections, activate a group of tied up proteins which are called kinases complex Ikk (Senftleben *et al*., 2001; Verma *et al*., 1995). Such complex works tyng a phosphate group to the inhibiting IkB that is quickly degraded by the cell freeing therefore, the Nf-k B (Chariot *et al*., 2002). Recent studies have been elaborated about the IKK molecule. The IKK complex is constituted by two subunits with a kinase activity: IKKa and IKKb and by a third subunit which connect IKKa and IKKb: The NEMO protein. These studies have been shown that, if there's not NEMO protein, the formation of IKK is impossible, the phophorylation of IKKB doesn't occur, Nf-k B can't be released and the inflammatory response is interrupted (Rudolph *et al*., 2000; Smahi *et al*., 2000). The factor of transcript Nf-k B, released by the negative control, is free to move to the nucleus where it goes to activate the necessary genes to the cell for the answer to the inflammatory stimulus. The Nuclear Factor-k B (Nf-k B) is a Factor of Transcription (FT) ubiquitin preserved in the eukaryotic cells. Nf-k B is activated by numerous stimuli includig viral and bacterial products, ultraviolet radiations, oxidant radicals, cytokine, various chemical substances (Claudio *et al*., 2002). Once activated, Nf-k B directly checks, or with the cooperation of other factors of transcription, the activity of over 100 genes that produce cytokines, growth factors, chemokine, molecules of adhesion, proteins of the acute phase (Dejardin *et al*., 2002). Extended activation of Nf-k B can cause serious inflammatory conditions and even the death caused by an excessive production of cytokines. It's essential that Nf-k B is quickly activated non only during the infections, but also that its activation term quickly after the infectious/inflammatory stimulus has been taken off. For this reason, inside the cells there are mechanisms of control that limit the activation of Nf-k B. Examples of genes regulated by Nf-k B are: IL-1; TNF -α; IL-6; IL-8; Interferon-β of some anti-inflammatory drugs (for example the desametazone as prototype of the anti-inflammatory steroids, the indometacina as non selective COX-inhibitor and the rofecoxib as selective inhibitor of COX2), to modulate the activation of the factor of transcription Nf-k B and the liberation of TNF-α (Albensi and Maltson, 2000) from human monocytes stimulated by LPS or PMA. Evaluating the activation of NF-k B (EMSA and ELISA), it has been shown that the desametazone and the rofecoxib inhibit strongly the activation of Nf-k B induced both from PMA and from LPS, while the indometacina is much less active and it doesn't modify the activation induced by LPS. These observations contribute to determine better the therapeutic effectiveness of anti-inflammatory drugs (Gilmore, 2006). The transcriptional factor Nf-k B is implicated in the pathogenesis of many pathologies with different origin (Doffinger *et al*., 2001) in the chronic inflammatory disease of the vascular system and in the process of formation of atherosclerotic lesions. In fact, Nf-k B, in the activated state, it's identified in situ in atherosclerotic human plates, while it's absent in vases exempted by atherosclerotic lesions. Besides, many genes whose produced they have involved in the pathogenesis of the atherosclerotic process they are regulated by Nf-k B. Among these, those of greater importance are the molecules of adhesion VCAM-1, ICAM-1 and E-selectins and the chemokines MCP-1 and IL-8, that have an important role in the recruitment of monocytes circulating on the endothelium of the vases. Besides, other genes products target of Nf-k B, among which the ciclin D1 and the anti-apoptotic proteins cIAP-1, cIAP-2, XIAP and cFLIP, can stimulate the cellular proliferation or to induce survival in cells in the site of formation of the lesion. It's interesting to observe that under conditions of normal stimulation, Nf-k B, activates also the transcription of the gene for its inhibiting protein, IkBa, increasing therefore the intercellular levels of this protein and establishing a self-regulation loop that inhibits the transcription of the Nf-k B-dependent genes (Kayagaki *et al*., 2002). The system of self-regulation Nf-k B/IkBa guarantees the transiet activation of NF-k B in a physiological situation (Leonardi *et al*., 2000). It has been recently suggested that an activation not regulated of Nf-k B contributes to the change of the pattern of genic expression that is underlined in pathological situations and during the atherogenesis process (Fig. 1-3).

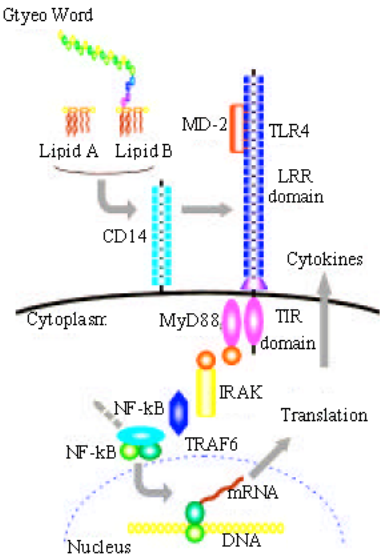

Fig. 1: Scheme of the inflammatory process Nf-k B acted

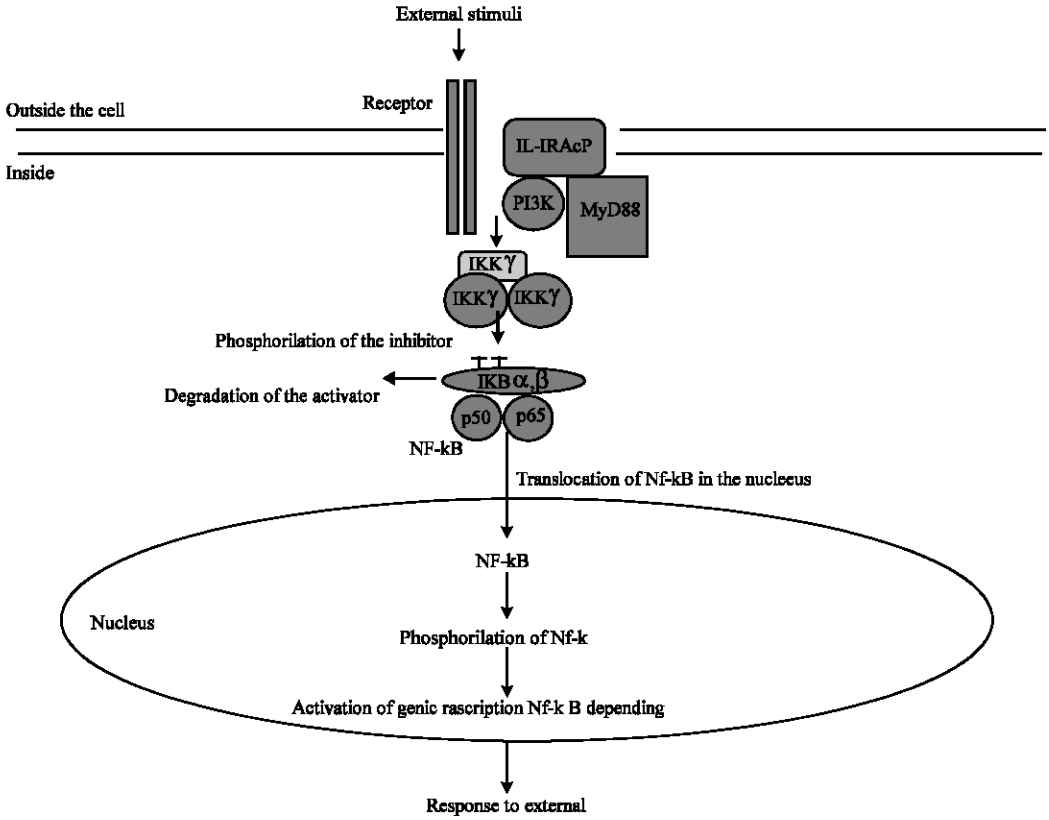

Fig. 2: Scheme of the Nf-k B activation

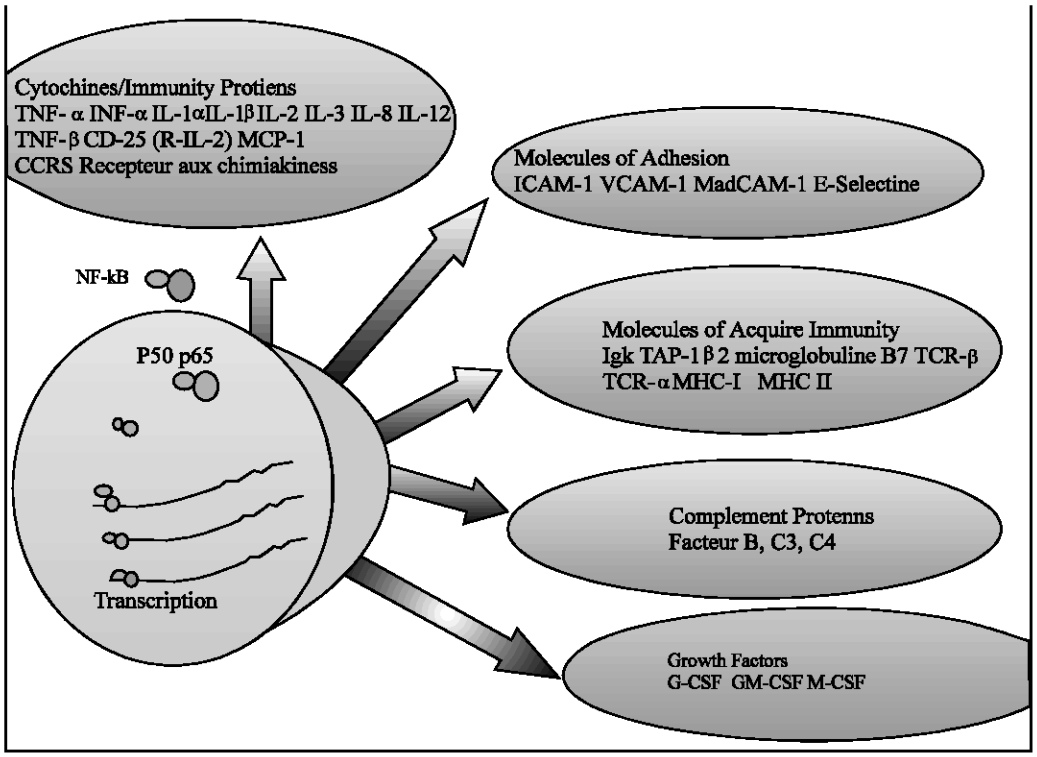

Fig. 3: Scheme of the molecules Nf-k B acted

Anti-viral drugs: Recent study has shown that the infection by HSV-1 is able to activate Nf-k B in persistent way and to higher levels respect to the others deriving from subsequent exposure to inflammatory cytokines in various types of human cells. The permanence of Nf-k B in a state activated binding the DNA for over 24 h after the infection, suggests that the virus interferes with the self-regulating system of Nf-k B, with consequent exacerbation of the inflammatory state. The virus HSV-1 is able to stimulate the kinase IKK and also to induce the activation of Nf-k B to higher levels in human endothelium cells. Analogous results have been gotten subsequently to infection of endothelium cells with the herpetic viruses HHV-6 and HHV-8. In the case of HSV-1, the activation of Nf-k B seems to be associated with an increase of the levels of transcription for the pro-inflammatory cytokines IL-6, IL-8 and TNF- á and for some molecules of adhesion. These preliminary results suggest the possibility that the induction of Nf-k B is involved in the activation of inflammatory process in the infection by Herpes virus. Nf-k B could represent an interesting target for new chemiotherapic drugs with anti-viral action and anti-inflammatory in the herpetic infections.

Glucocorticoids: The biggest part of the anti-inflammatory actions of the Glucocorticoids (GC) depend from the ability to interfere with the functions of factors of transcription and just for this reason Nf-k B is remarkable. Different pro-inflammatory stimuli induce the activation of enzymes (IkB chinase) that phosphorylate IkB (Harhaj *et al*., 2000; Hu *et al*., 2001; Karin and Ben-Neriah, 2000). IkB phosphorylated ties residual of ubiquitina that addresses itself to the proteasomis where it is degraded. Here Nf-k B free can move in the nucleus and to tie to the regions consent of a variety of genes implicated in the inflammatory and immunitary answers (Li and Verma, 2002). The GCs penetrate freely in the cytoplasm where they tie a Receptor (GR) activating it. The complex GC-GR interacts with Nf-k B holding it in the cytoplasm. Besides, GC-GR induces the synthesis of IkB that, produced in excess, inactivate Nf-k B. Finally, activated GR competes with NF-k B for the availability of co-activators. The activated GR can tie the sequences GRE in the promoting regions of some inflammatory genes and regulate directly the genic transcription. That has been shown for a limited number of genes, for example for the IL-1b, in which the bond of GC/GR with GRE directly inhibits the transcription of the cytokine. The mechanisms through which GR stops the functions of Nf-k B are multiple and studied more in detail: On the one hand, GR induces the transcription and the synthesis of IkBa, that it holds Nf-k B in the cytoplasm. On the other hand, the GR activated ties directly Nf-k B activated, imprisoning it in the cytoplasm. GR competes with Nf-k B for the availability of the co-activators CPB and SRC-1 (steroid receptor coactivator-1). Finally, GR can modify also the activity of the molecules S TAT (signal transducer and activator of transcription), a series of factors of transcription implicated in the trasduction of the signals baited by some citochines what IFN-g, IL-4, IL-5 and IL-10.

Fans: The COX1 has been identified as the isoform responsible of the maintenance of the homeostasis, while the COX2 as isoform inducible mainly involved in the production of great quantities of prostaglandins in inflammatory response and pathological stimuli. Tissue lesions, cytokines, free radicals and oxidized damages induce the activation of the Nf-k B, whose action determines increase of the synthesis of COX2 and therefore of the production of some prostaglandins with pro-inflammatory function (Fionda *et al*., 2007). The expression of the COX2 has been tied up, in some inflammatory chronic states (for instance of intestine in the man), to the mutation of the phenotype and the cellular genotype, through the activation of normally silent genes and the repression of normally expressed genes, predisposing to the onset of neoplastic lesions (Lee *et al*., 2007). The inhibition of the COX2 and Nf-k B operated by the FANSs has shown, in some cases, benefits anticancer effects; that referred, for example, to the case of some neoplasias of the intestine and of the bladder. The result of these recent discoveries on the COX2 has been primarily the synthesis of mixtures with action inhibiting COX2, theoretically able to eliminate the negative effects of the prostaglandins without influencing its function of maintenance of the homeostasis.

CONCLUSION

Nfk- B is a protein that has great influences in many pathological process and that, thanks to them, can be considered as target of pharmacological treatment and object of continuous studies.

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