

**PHARMACOLOGICAL REVIEWS**

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Nadezhdin S.V.<sup>2</sup>****NUCLEAR FACTOR KAPPA B AS A POTENTIAL TARGET FOR  
PHARMACOLOGICAL CORRECTION ENDOTHELIUM-ASSOCIATED  
PATHOLOGY**<sup>1</sup>Kursk State Medical University, 3, Karl Marx St., Kursk, 305041,<sup>2</sup>Belgorod State University, 85 Pobedy St., Belgorod, 308015, Russia. e-mail: kostina\_da@bsu.edu.ru

**Abstract.** The nuclear factor kappa B (NF- $\kappa$ B) is one of transcription factors. A high interest in studying the biological role of the signal system and its contribution to the development of cardiovascular, oncological and autoimmune diseases is obvious. A number of stimuli (pro-inflammatory cytokines: tumor necrosis factor  $\alpha$ , interleukin  $1\beta$ , ligand CD40 and others) trigger the canonical and non-canonical pathways of NF- $\kappa$ B signaling, which increase the expression of genes regulating synthesis of cytokines and chemokines, cell proliferation and differentiation, angiogenesis, immune reactions and apoptosis. However, pathological activation of NF- $\kappa$ B violates the balance of substances participating in the normal activity of the cardiovascular system. This leads to the development and progression of endothelium-associated pathology and comorbidity. Contribution of pathological activation the NF- $\kappa$ B signaling system in the formation of vicious circles in atherosclerosis, coronary heart disease, pulmonary hypertension, ischemic-reperfusion injury, is not subject to doubt. Thus, the search for new therapeutic targets and strategies for modulating the activity of the NF- $\kappa$ B signaling pathway is one of the key strategies for the development of experimental pharmacology. Another important aspect of studying the pharmacological activity of NF- $\kappa$ B activity modulators is the choice of a valid and easily reproducible way of assessing the activity of this system.

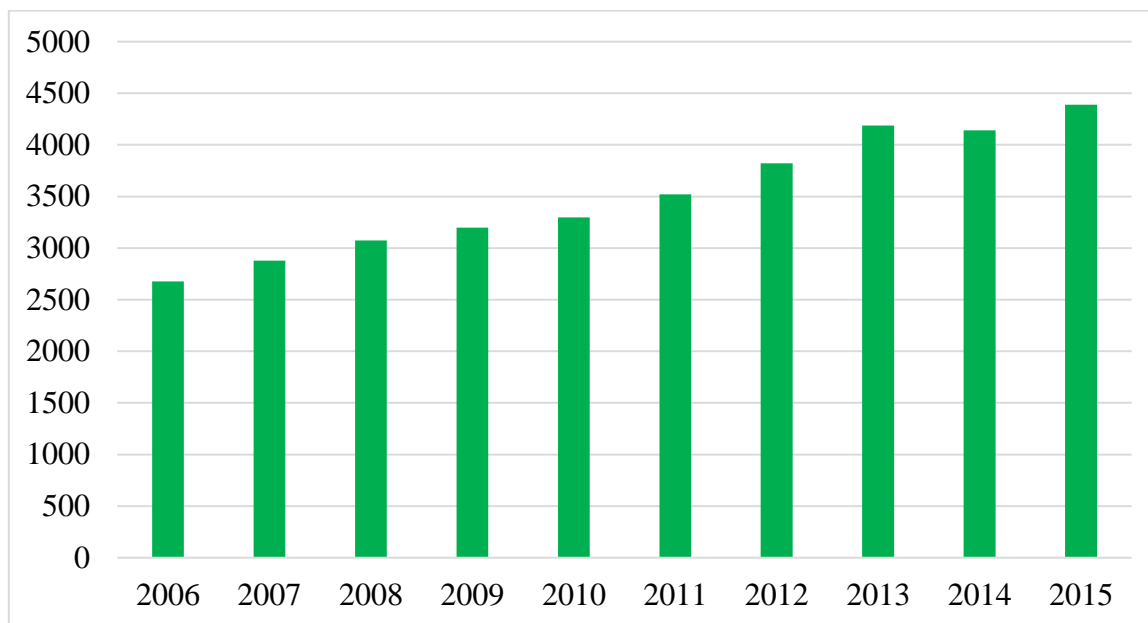
**Keywords:** nuclear factor kappa B, NF- $\kappa$ B, endothelial dysfunction, ischemia-reperfusion, pharmacological correction, comorbidity.

**Introduction**

There are more information about the intracellular processes that occur during the activation of this pathway, biological role, contribution to the pathogenesis of the disease and methods of modulating the activity of nuclear factor are appearing every year. Increasing interest in the

problem can be seen by analyzing the number of publications on request «NF kappa B», carried out in the PubMed system (fig. 1).

The role of signaling system nuclear factor kappa B in the development of various diseases, including the endothelium-associated [1, 2, 3, 4, 5, 6, 7] is presented in table 1.



**Figure 1.** Dynamics of the number of publications on the request «NF kappa B» in the PubMed system

Table 1

**The role of the signaling system of the nuclear factor kappa B in the development of diseases**

Disease	Dependence on the NF-κB activity	Reference
Atherosclerosis	Increased activity of NF-κB	B. Pamukcu et al., 2011 [8]; C. Monaco et al., 2004 [9]; W. Zhang et al., 2009 [1];
Acute myocardial infarction and ischemia-reperfusion	Increased activity of NF-κB	G. Valen et al., 2001 [11]; A. Kis et al., 2003 [12]; B. Zingarelli et al., 2002 [13];
Pulmonary hypertension	Increased activity of NF-κB	S. Hosokawa et al., 2013 [14];
Chronic renal failure	Increased activity of NF-κB	G. Rangan et al., 2009 [15];
Chronic obstructive pulmonary disease (COPD) and asthma	Increased activity of NF-κB	M.R. Edwards et al., 2009 [16]; M. Schuliga, 2015 [17];
Rheumatoid arthritis	Increased activity of NF-κB	M. Feldmann et al., 2002 [18]; R.E. Simmonds, et al., 2008 [19];
Diabetes mellitus and its complications	Increased activity of NF-κB	I.P. Kaydashev, 2011 [20]; S. Patel et al., 2009 [21];

**Signaling system nuclear factor kappa B**

Nuclear factor kappa B (NF-κB) is a transcription factor, discovered by Sen and Baltimore in 1980s [22], is widely expressed in many mammalian cells. NF-κB plays an important role in the innate immune system and stimulates the synthesis of proinflammatory mediators such as cytokines, in response to the activation of Toll-like receptors (TLR) by bacterial lipopolysaccharides.

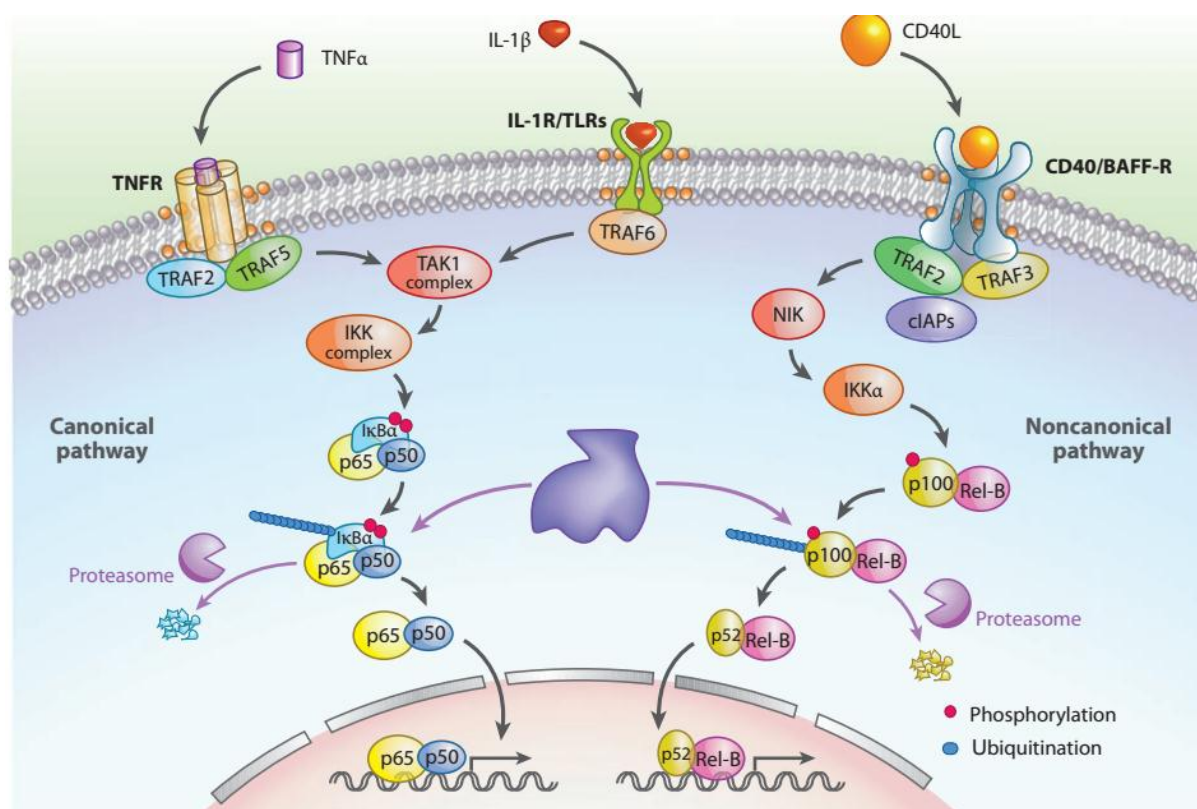
NF-κB complex consists of a family of dimeric transcription factors including RelA (p65), RelB, c-Rel, NFκB1 (p50) and NFκB2 (p52) [23]. They all

contain REL-homology domain (RHD), which is responsible for NF-κB intranuclear transport and DNA binding. In addition, p65, c-Rel and Rel-B contain transactivation domain (TAD), which is required for gene activation. P50 and p52 subunits are produced from precursors – p105 and p100, and subjected to dimerization with TAD-containing domain to activate transcription of genes. Thus, homodimers of p50 and p52 act as repressors of gene expression, whereas p65, c-Rel and Rel-B in any combination, including p50 and p52, transcription activators play a role.

In unstimulated cells, NF- $\kappa$ B dimers are united in the cytoplasm by RHDs with inhibitory proteins of NF- $\kappa$ B, called I $\kappa$ Bs. Stimulus-mediated activation of I $\kappa$ B-kinase (IKK) relates to I $\kappa$ Bs degradation to the release and activation of NF- $\kappa$ B [24]. I $\kappa$ B family includes I $\kappa$ B $\alpha$ , I $\kappa$ B $\beta$ , I $\kappa$ B $\gamma$  / p105, I $\kappa$ B $\delta$  / p100, I $\kappa$ B $\epsilon$  and B-cell lymphoma 3-encoded protein (Bcl-3). All of them have several ankyrin repeats (composed of 30-33 amino acids), binding with Rel-domain of NF- $\kappa$ B, maintaining nuclear factor in the cytoplasm [25, 26]. In activating of signaling pathway I $\kappa$ B exposed to phosphorylation and ubiquitination. It changes conformational structure of molecules, determining their recognition and destruction in the proteasome. I $\kappa$ B $\alpha$  is best understood. It is strongly associated with

the p65 subunit of NF- $\kappa$ B, inhibiting its activity. Stimulation of cells leads to the phosphorylation of I $\kappa$ B $\alpha$  (32 and 36 serine residues) and bonding (at 21 and 22 lysine residues), ubiquitin which is ATP-dependent proteolysis in a 26S-proteasome system complex [27, 28]. This leads to the release of NF- $\kappa$ B, which after further phosphorylation is able to migrate to the cell nucleus is the site of its action. The transcriptional activity of NF- $\kappa$ B appears within minutes after stimulation [25].

Canonical activation signaling pathway of nuclear factor kappa B induced by exposure to tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 $\beta$  (IL-1 $\beta$ ), or ligands Toll-like receptors (TLR) (bacterial lipopolysaccharide and others) (fig. 2).



**Figure 2.** The canonical and non-canonical pathway activation signaling pathway nuclear factor kappa B [29]

A common point of application for these incentives is I $\kappa$ B-kinase composed of two catalytic subunits, IKK $\alpha$  and IKK $\beta$ , and a regulatory subunit – NEMO, also known as IKK $\gamma$ . IKK phosphorylates I $\kappa$ B $\alpha$  at serine residues 32 and 36, resulting ubiquitination in 21 and 22 lysines and subsequent degradation by the 26S proteasome [29]. It means, that I $\kappa$ B $\alpha$  is rapidly degraded under the activation of canonical pathway NF- $\kappa$ B, which results as the release of a plurality of nuclear factor dimers system. The main target I $\kappa$ B $\alpha$  probably is the p65/p50 heterodimer. The crystal structure of I $\kappa$ B $\alpha$  bound

heterodimer with p65/p50 shows that protein I $\kappa$ B $\alpha$  masks the nuclear localization sequence (NLS) only in the p65, whereas p50 NLS in remains of exposed [30]. NLS was exposed in p50 in combination with the nuclear export sequence (NES) in I $\kappa$ B $\alpha$  and p65 regulate the circulation of I $\kappa$ B $\alpha$  / NF- $\kappa$ B complexes between the nucleus and cytoplasm, despite the almost exclusive cytosolic localization of the complex [30, 31]. Degradation of I $\kappa$ B $\alpha$  changes the dynamic balance between cytosolic and nuclear localization of NF- $\kappa$ B in favor of nuclear, allowing p50 / p65 to accumulate in the nucleus and activate

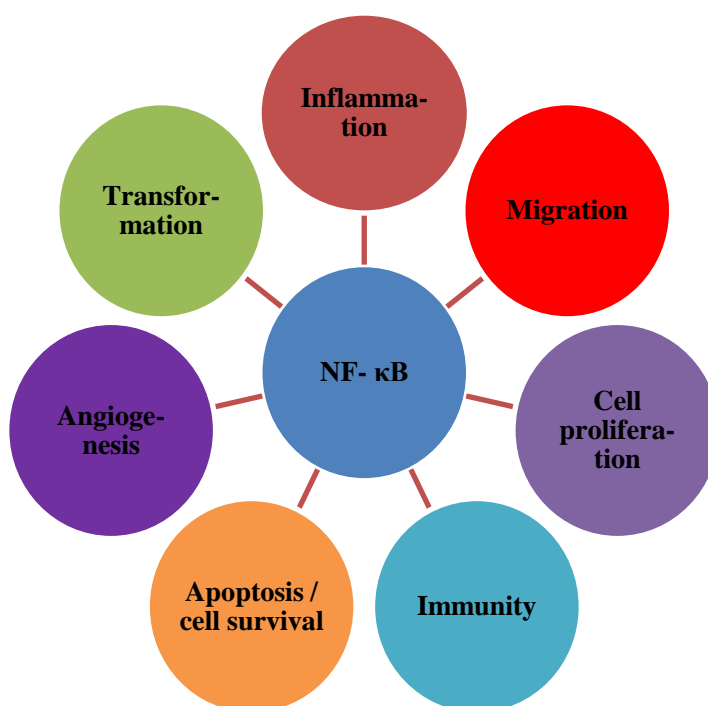
gene transcription. IκBα, which can enter the nucleus, NF-κB displaces from its association with the DNA, and transports it back to the cytoplasm releasing negative feedback [32].

Non-canonical pathway activation of the signaling pathway of the nuclear factor kappa B is mediated through receptors of the TNF family (TNFR) including B-cell activating factor (BAFF), CD40 ligand, etc., induces NF-κB activation through a different path -. NEMO-independent protein kinase NIK. It phosphorylates and activates IKKα [24, 26]. IKKα phosphorylates p100 on two serine residues at the C-end containing ankyrin repeats making RHD

domain (p52) intact. Then p52 dimerizes with its partner Rel-B, to induce a program of gene expression, which is necessary for the maturation and activation of B cells [23]. Moreover, in one study at knockout IKKα -/- mice, the ability of potential signaling pathway activated NF-κB to influence the normal epidermal differentiation and morphology of skeleton has been demonstrated [33].

**The biological role of NF-κB**

Signaling pathway NF-κB is involved in the transcriptional control of genes coding for the set of biological processes (fig. 3).



**Figure 3.** The biological role of the activation of the signaling pathway NF-κB

Most of the genes that are under the transcriptional control of NF-κB, encode the synthesis of biologically active substances involved in the immune response and inflammatory reactions [34, 35]. These biologically active substances include cytokines (TNF-α, IL-1β, IL-2, 3, 6, 12, granulocyte macrophage colony-stimulating factor (GM-CSF), acute phase proteins (C-reactive protein ), chemokines (monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein 1 (MIP-1), several β-chemokines), and adhesion molecules (inter-cellular adhesion molecule type 1 (ICAM-1), E-selectin and the vascular cell adhesion molecule (VCAM-1)) [36, 37, 38, 39, 40, 41].

Furthermore, NF-κB increases receptor (CD80 / 81, TLR-2) expression and proteins presenting

antigen (MHC class I and β2-microglobulin) on immune cells, which allows to properly implement the innate and adaptive immune responses [37, 41].

Other biological role of NF-κB is the regulation of apoptosis. Interestingly, NF-κB regulates the transcription of pro-apoptotic, (Bim, Bax, Fas and caspase 11) and anti-apoptotic (X-linked inhibitor of apoptosis protein (XIAP), Bcl-2, cFlip) gene [41, 42, 43]. Thus, with one hand activation of the signaling pathway protects cells from death in response to damage factors (radiation, viruses, bacteria etc.), and the other hand is prevent carcinogenesis limits the spread of infection.

Other genes category regulated NF-κB system includes growth factors such as nerve growth factor (NGF), vascular endothelial growth factor (VEGF),



insulin-like growth factor-binding protein (IGFBP), bone morphogenetic protein (BMP) and the fibroblast growth factor (FGF) [44, 45, 46].

### The role of NF- $\kappa$ B in the development of cardiovascular diseases

*Endothelial dysfunction.* Endothelial dysfunction is a marker and one of the early stages in the development of cardiovascular disease [47, 48, 49, 50, 51].

Some potential target genes under the transcriptional control of NF- $\kappa$ B, contribute to the development of "proatherogenic" phenotype endothelial dysfunction. These genes encode the synthesis of pro-inflammatory molecules such as IL-6, TNF- $\alpha$ , MCP-1, a receptor for advanced glycation end-products (RAGE) [52, 53]. On the other hand, the activation of NF- $\kappa$ B signaling pathway can lead to the development of oxidative stress with the formation of reactive oxygen species by enhancing NADPH oxidase activity [54].

Thus, in one pre-clinical trial in mice they confirmed hypothesis that increased expression of NF- $\kappa$ B results in a decrease in endothelium-independent vasorelaxation and development of endothelial dysfunction [55].

Involvement signaling pathway of NF- $\kappa$ B to the development of endothelial dysfunction also confirmed in clinical studies. So, in the elderly (n = 14) were identified violations of the processes of endothelium-dependent vasodilation, which, according to the authors was associated with increased nuclear translocation of NF- $\kappa$ B in the cells of the vascular endothelium. This increase in nuclear localization was associated with a decrease in the expression of I $\kappa$ B $\alpha$ . [56].

*Atherosclerosis.* One of the first stages of development of atherosclerosis is considered modification of low density lipoprotein (LDL) in the vessel wall, resulting in local inflammation, release of chemokines and increasing adhesion molecule expression on the endothelial cell surface [52]. NF- $\kappa$ B can be one of the inducers of these changes.

Firstly, under the transcriptional control of NF- $\kappa$ B is one of the important chemokines – MCP-1, which promotes primary migration of monocytes, are key cells in the early stage atherosclerotic plaque formation [8, 52]. Secondly, increased expression of adhesion molecules, including P-selectin, E-selectin, ICAM-1 and VCAM-1, which involved in process of atherogenesis [57]. Third, recently, much attention is paid to the activity of matrix metalloproteinases (MMPs) in atherosclerosis pathogenesis, that contribute to invasion of inflammatory cells into the

vessel wall, smooth muscle cell migration, and remodeling of an intercellular matrix involved in maintaining the oxidative stress [58].

NF- $\kappa$ B activation in endothelial cells during early atherogenesis stages is able to achieve by complex circuits of induction by many different stimuli. These agents include oxidized LDL, advanced glycation end-products [52], proinflammatory cytokines produced at the site of injury [8] or bacterial lipopolysaccharides [59].

One of the biological roles of signaling NF- $\kappa$ B is involved in the process of inflammation, which in the development of atherosclerosis has become an important pathogenetic link lies in increasing the synthesis of proinflammatory cytokines (TNF- $\alpha$ , IL-1, IL-6 et al.), and decreased production of inflammatory (IL-10). Violation of balance of biologically active substances, demonstrated in preclinical studies [60, 61, 62, 63], contributes to more rapid development and progression of atherosclerosis and endothelial dysfunction.

These data show that the early stages of atherosclerosis, such as lipoprotein modification, activation of chemotaxis, adhesion and oxidative stress, maintaining chronic inflammation may vary depending on the activity of NF- $\kappa$ B signaling pathway.

*Ischemia-reperfusion.* With the increasing prevalence of cardiovascular disease and diabetes, as well as the rapid development of cardiac surgery, more acutely the question arises about the pathogenesis and approaches to pharmacological correction of ischemia-reperfusion injury of the heart [64, 65], liver [66, 67], brain [68, 69], retina [70, 71], placenta [72, 73].

It is known that ischemia and ischemia / reperfusion results in activation of NF- $\kappa$ B in the cells of the coronary arteries. This in turn leads to increased synthesis of pro-inflammatory cytokines, adhesion molecules (ICAM-1, P-selectin), which promotes the migration of inflammatory cells into the damaged center [74]. This process has been documented in clinical trials [75]. Since inflammation causes tissue damage, NF- $\kappa$ B activity modulation during ischemia / reperfusion injury is one of the potential targets for reducing the volume and reduce the damage risk of complications.

**Methods for modulating the activity of a signaling pathway NF- $\kappa$ B.** Increased activity of the signaling pathway NF- $\kappa$ B in the pathogenesis of many diseases, forced scientists to search for drugs, the mechanism of action of which is directed to modulation of the activity of this factor.

One of the first drugs for which was demonstrated by the ability to inhibit NF- $\kappa$ B, were cytotoxic agents and steroids. Perhaps this is due to the significant contribution of this signaling pathway in the pathogenesis of malignancies. A potential pharmacodynamic effect of glucocorticoids and cytotoxic drugs is the induction of synthesis I $\kappa$ B $\alpha$  [76].

The ability to inhibit NF- $\kappa$ B for drugs that are widely used in clinical practice for the treatment of cardiovascular and metabolic diseases can be attributed pleiotropic properties.

One of the most studied drug-inhibitors NF- $\kappa$ B from the group of antiplatelet agents is acetylsalicylic acid (ASA). The mechanism of inhibition of ASA and sodium salicylate caused by binding and blocking ATP-site IKK $\beta$ . [77], thereby reducing the synthesis of proinflammatory cytokines and adhesion molecules [78] and the damaging effect of angiotensin II on potential target organs [79]. Thus, in one pre-clinical studies was demonstrated that low-dose aspirin suppress chronic inflammation and increased stability of atherosclerotic plaque, that is, exhibit antiatherogenic effects [80].

Another pharmaceutical group with numerous pleiotropic effects are inhibitors of HMG-CoA reductase inhibitors (statins). One potential explanation for the presence of their pleiotropic effects is their inhibitory effect on NF- $\kappa$ B, associated with the induction and stabilization of the endogenous inhibitor – I $\kappa$ B $\alpha$  [81]. At present time, much attention is paid to the effects of statin-related effects on receptors, peroxisome proliferators-activated (PPAR). PPARs play an important role in energy homeostasis and in the regulation of inflammatory responses [8]. It has been shown that statins (such as agonists, PPAR $\gamma$ ) inhibit LPS-induced production of TNF- $\alpha$ , VCAM-1, MCP-1 by inhibiting the transcriptional activity of NF- $\kappa$ B [82]. Perhaps, PPARs agonists, exercise their effects by binding to RelA domain signaling pathway [83]. Another group of lipid-lowering drugs, realizing their pleiotropic effects through PPARs, are fibrates [84]. Thus, some groups of hypolipidemic agents realize their effects through direct inhibition of NF- $\kappa$ B, or by acting on PPARs, which reduces production of proinflammatory cytokines (TNF- $\alpha$ , IL-1, IL-6), chemokines and growth factors and slow the progression of endothelial dysfunction and cardiovascular diseases.

In addition, certain polyunsaturated fatty acids (PUFAs) may exhibit anti-inflammatory effects by selectively inhibiting I $\kappa$ B kinase, which allows their use as anti-inflammatory agents in the treatment of atherosclerosis therapy [8].

Antioxidants have been suggested as possible inhibitors of NF- $\kappa$ B many years ago [85]. One possible mechanism of action is the inhibition of the growth activity of NF- $\kappa$ B in response to various stimuli (IL-1, LPS, TNF- $\alpha$ ) [86]. On the other hand, the antioxidants can inhibit IKK, minimizing the degradation of I $\kappa$ B $\alpha$  [85]. For compounds of phenolic nature inhibitory activity described in the signaling pathway is realized through the reduction of NF- $\kappa$ B binding to DNA through RHD [87]. Promising pharmacological agents of the antioxidant properties of the group with inhibitors NF- $\kappa$ B, in our opinion, are the derivatives of cinnamic acid [88, 89].

However, the decrease in activity of NF- $\kappa$ B, can be dangerous because of the involvement of the signaling system in the regulation of immunity and its antiapoptotic role.

For determining the activity of NF- $\kappa$ B currently there are different approaches, among which you can choose the best for your study, and sometimes the activity understand the common expression of NF- $\kappa$ B. So P. Fraunberger et al. [90] were determined the common expression of the p50 NF- $\kappa$ B in the liver cells of Guinea pigs by immunohistochemical method at the light microscope. But more often they determine the expression of p65 NF- $\kappa$ B and its translocation into the nucleus of the cell, which along with light microscopy using immunohistochemical method with a fluorescent tag, and the expression of messenger RNA of NF- $\kappa$ B-dependent proteins in the cytoplasm of tumor cells by polymerase chain reaction with reverse transcriptase [91]. Another widely used method to determine p65 NF- $\kappa$ B and other components of the NF- $\kappa$ B network, associated with its activation, is the Western blot [92]. Moreover, despite the absence of direct criteria of activity definition immunohistochemical or Western blot sections, software for morphometric or densitometric analysis, for example, the program ImageJ, allows quantitative assessment of prote expression and statistical processing of the obtained results [93]. Finally, test systems exist for enzyme-linked immunosorbent assay determination of p65 NF- $\kappa$ B, which are also used in scientific research [94, 95].

Thus, modulation of the activity of the signaling pathway nuclear factor kappa B and methods of the activity evaluation, requires further study for the creation of new, effective and safe group of drugs for the prevention and treatment of endothelium-associated pathology.

### Conclusion

Signaling system NF- $\kappa$ B is a significant contributor to the development of endothelium -

associated disease by altering the expression of genes responsible for the persistence of inflammation, proliferation, cell migration and apoptosis. This can be attributed to the system of nuclear factor kappa B to a potential target for the creation of innovative-targeted therapies to reduce mortality from socially significant diseases.

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