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NF-κB — A Key Factor in Atherogenesis and Atheroprogression

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Abstract

Atherosclerosis is the major cause of cardiovascular diseases and it is responsible for a large proportion of mortality in the Western society.

Initially, atherosclerosis was thought to be a degenerative disease that was an inevitable consequence of aging. The recent research has shown that atherosclerosis is a slowly progressing inflammatory disease of the medium- and large-sized arteries, resulting in the formation of fatty and fibrous lesions.

Inflammatory processes mark all stages of atherogenesis: from early endothelial activation by modified lipids to eventual rupture of the atherosclerotic plaque. The inflammation of the vessel wall is a feature of this pathology, which is characterized by infiltration and oxidation of low-density lipoproteins (LDLs), increase in oxidative stress, with the consequent lipid accumulation in the vessel wall, and foam cells formation.

The extensive relation between the immune system and vessels induce the infiltration of immune cells into the vascular wall, the major pathogenic step in atherogenesis. At this aim, reactive oxygen species play a crucial role activating a number of redox-sensitive transcriptional factors such as nuclear factor kappa B (NF-κB), which is involved in transcription of many genes with an established role in atherosclerosis, such as cytokines, chemokines, adhesion molecules, acute phase proteins, regulators of apoptosis, and cell proliferation. Since its discovery in 1986, the transcription factor NF-κB has evoked large attention on the basis of its peculiar regulation, the abundance of activation stimuli, the different genes and biological responses controlled, the striking evolutionary conservation of structure and function among family members, and its role in different human diseases.

Recognition of the leading role of inflammation at all stages of pathogenesis focuses on the potential relationship between systemic inflammation and atherosclerosis and fuelled intense basic science, health, and clinical research.

The understanding of the inflammation involvement in atherogenesis, atheroprogression, and its complications confirm the importance of traditional risk factors in this disease, such as high LDL levels. Indeed, inflammatory process can be considered a pathway that,

from mechanistic and functional points of view, suggests a connection with the known risk factors and alterations to the vessel biology that drive to atheroprogression and its complications.

In this review, we discuss the transcription factor NF-κB and its potential role in atherogenesis and atheroprogression focusing on the major atherosclerotic factors regulated by NF-κB and how they may affect different steps in the atherosclerotic process.

Keywords: NF-κB, atherosclerosis, vessels

1. Introduction

Atherosclerosis is a disease of arteries with slow progression which induces the formation of lesions characterized by the accumulation of fatty and fibrous tissue in the vessel wall. It is one of the most important factor responsible for the mortality by cardiovascular diseases in developed countries, despite changes in lifestyle and the use of preventative pharmacological approaches. In the past years, after the understanding of the involvement of inflammation and immune response in the pathogenesis, atherosclerosis has been redefined as an inflammatory disease [1, 2].

The development of atherosclerotic lesions can be subdivided into initiation and expansion of fatty streaks. In the first step, activated vascular endothelium expresses inducible leukocyte adhesion molecules and chemokines. Once blood circulating leukocytes, in particular monocytes, adhere and enter into the artery wall, the cells differentiate into macrophages and, after lipidic phagocytosis, into foam cells. The macrophage and T-cell infiltration is a feature of the atherogenesis initiation called "fatty streaks formation" [3, 4].

After this step, there is production of cytokines and growth factors within lesions that may amplify monocyte recruitment, stimulate macrophage proliferation, and induce migration of smooth muscle cells into the intimal layer of the vessel, with consequent extracellular matrix proliferation and deposition, and "mature" plaques formation. This step of the atherosclerotic lesion is featured by the arrangement of a fibrous cap covering the lesion inside the internal elastic lamina constituted by fibrous tissue, with or without a lipidic core with foam cells and extracellular lipid deposits, determining a variable reduction of vascular lumen space [3].

Though clinically significant complications of atherosclerosis, such as plaque ulceration, rupture, and thrombosis, occur in established or advanced atherosclerotic plaques, understanding the mechanisms of lesion formation offers the possibility of intervening to delay or prevent lesion progression and complications.

Numerous transcription factors may be critical in both the initiation and the expansion of lesions, as well as in protecting the vessel wall from the formation of atherosclerotic lesions. In this summary, we focus our attention on one transcription factor, nuclear factor-κB (NF-κB), which is considered to be a major transcription factor regulating many functions of the vessel wall.

In the context of the multifactor pathogenesis of atherosclerosis, different stimuli have the possibility to activate NF-κB, comprising local factors such as vascular injury, as well as modified low-density lipoproteins (LDLs), infectious agents, and cytokines, although it is not easy to determine which of them are responsible for the activation of NF-κB in vivo. Indeed, NF-κB, throughout the lifetime of an individual, may be a convergence point integrating these different stimuli [3, 5].

2. Atherosclerotic pathogenic process

The atherosclerotic pathogenic process is initiated early in life, during postnatal development and maturation and advances gradually throughout life [6]. Given the multifactorial and complex nature of atherosclerosis, further studies to clarify the understanding of the pathogenic process are needed to improve atherosclerosis diagnosis, management, prevention, and treatment [7]. The first step in the atherosclerotic lesion formation is endothelial activation or dysfunction and LDL-cholesterol deposition in the arterial wall, which are mediated by risk factors such as dyslipidemia, hypertension, diabetes mellitus, and smoking. After this step, the accumulated LDLs are oxidized and the resultant formation of oxidized LDLs (OxLDLs) has been suggested to be the critical event in deteriorating inflammation in vascular wall. After this, not only monocytes but also various types of leukocytes adhere to the activated endothelium, migrate into the arterial wall via upregulated adhesion molecules, and produce pro-inflammatory cytokines or chemokines. Subsequently, monocyte-derived macrophages take up OxLDLs via scavenger receptor, leading to the formation of lipid-laden foam cells. Following such steps, the initial fatty streaks contain lipids and numerous immune cells such as macrophages, dendritic cells (DCs), and T lymphocytes. After these phases progressed, atherosclerotic lesions involve the migrated smooth muscle cells, debris, apoptotic cells, and extracellular matrix such as collagen and proteoglycans [8]. Finally, such indolent progressed atherosclerotic plaques may suddenly rupture and induce life-threatening thrombosis. The notable features of unstable rupture-prone plaque are infiltration of many inflammatory cells, large lipid core, and thin fibrous cap [9–11].

3. NF-κB

The eukaryotic family of NF-κB transcription factors are involved in the expression of over 150 genes that regulate a variety of cellular processes [12,13, 14].

In this family there are p50, p52, p65 (RelA), c-Rel, and RelB, that form various homo- and hetero-dimers, where the most common active form is the p50/RelA or p52/RelA heterodimer. NF-κB subunits dimerization produces complexes with different DNA-binding specificities and transactivation potential [14, 15, 16]. The N-terminal region of each member of the NF-κB family is conserved and is called Rel-homology domain, which contains the dimerization, nuclear localization, and DNA-binding domains [14, 15, 17]. Most cell types

show inactive form of NF-κB complexes in the cytoplasm bound to inhibitory proteins known as IκBs and activated, by phosphorylation on conserved serine residues in the N-terminal portion of IκB, in response to multiple stimuli, including cytokines, infectious agents, and stress-inducing factors; this modification occurs at Ser-32 and Ser-36 in the case of IκBα [14, 18–21]. The degradation of the inhibitory subunit by the 26S proteasome by phosphorylation targets IκBα for ubiquitination by the Skp1/Cul-1/F-box ubiquitin ligase complex, which recognizes phosphorylated substrates, [14, 22, 23] activates NF-κB that translocates to the nucleus where it binds to its DNA-binding site (5'-GGGRNNYYCC-3') in the promoter or enhancer regions of specific genes. This activation is the last phase in the signal transduction pathway conducing from the cell surface to the nucleus. Phosphorylation of IκBs is a key event in the activation of NF-κB mediated by a multimeric complex, named as the IκB kinase (IKK) complex [14].

NF-κB is peculiar for the characteristic to have a rapid activation and downregulation; the activation of this factor induces IκBα, permitting switching off of the system and for this reason NF-κB activation, in physiological conditions, is a transitory phenomenon, which induces a right expression of immune and "stress" genes. On the contrary, in diseases such as rheumatoid arthritis, asthma, or inflammatory bowel disease, there is a prolonged or inappropriate activation of the NF-κB pathway and this dysregulation induces the enhanced inflammatory response, feature of these pathologic conditions. NF-κB is also considered as an important key factor in the development and progression of cardiovascular diseases, such as atherosclerosis and acute coronary syndromes [3].

4. NF-κB in atherosclerosis

In humans, atherosclerotic plaques have been identified as the activated NF-κB form that is not detected in normal vessels [14, 24]. In atherosclerotic environment, there are different factors that induce the NF-κB activation in vitro. Furthermore, increased expression of numerous genes important in early atherosclerotic lesion formation is known to be regulated by NF-κB [14, 25]. NF-κB activation regulates the expression of some molecules that are involved in recruiting circulating mononuclear leukocytes to the arterial intima, an important step in atherosclerosis, like vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), and E-selectin, and chemokines interleukin 8 (IL-8) and monocyte chemoattractant protein 1 (MCP-1), [14, 26–28]. The activated NF-κB was detected in different areas of human atherosclerotic lesion and, also, in intimal cells found in coronary arteries of pigs placed on a hypercholesterolemic diet [14, 29, 30].

NF-κB is activated in intima and media tunica in models of arterial injury; moreover, animals treated with a statin, 3-hydroxy-3-methylglutaryl (HMG)-Co-A reductase inhibitor, demonstrated a greater decrease of NF-κB activity in circulating mononuclear cells and reduction in the extent of atherosclerosis. All these observations suggest an involvement of NF-κB activation in atherosclerotic pathology [14, 31].

5. NF-κB in early stages of atherosclerosis

The endothelium, thanks to its strategic position between the plasma and the underlying vascular tissue and its constitutive properties, has extensive biological activities that have key importance for body homeostasis [32, 33]. Endothelial cells (EC) regulate the transport of plasma molecules, in physiological conditions, by receptor-mediated and receptor-independent transcytosis and endocytosis; this traffic is bidirectional to monitor vascular tone and to synthesize and secrete a large variety of factors. Moreover, the endothelial layer has an important role in the regulation of hemostasis, inflammation, immunity, signal transduction, and lipidic homeostasis [32, 34, 35]. Under pathological conditions such as hyperlipidaemia and/or hyperglycemia, alterations in endothelial function precede the development of atherosclerotic plaques and contribute decisively to their perpetuation and to the clinical manifestations of vascular diseases [32]. Multiple upstream pathways might be responsible for activating NF-κB in endothelial cells promoting the development of atherosclerosis. Supporting the critical role of NF-κB in inflammation-dependent endothelial dysfunction is evidence that pharmacological inhibition of NF-κB signaling significantly reduces cytokines and enhances endothelial-dependent dilation in old mice and humans [36–38].

The demonstration of the role of inflammation in endothelial dysfunction is produced by researches in which exogenous administration of pro-inflammatory cytokines was shown to produce endothelial dysfunction or endothelial activation in endothelial cells or isolated arterial vessels [39–42]. The activation of NF-κB in endothelial cells, event involved in atherogenesis, is due to multiple upstream pathways. Previous studies have provided compelling evidence that inhibition of MyD88-dependent signaling downstream of Toll-like receptors (TLR) 2 and 4 led to a reduction in atherosclerosis through a decrease in chemokine levels and macrophage recruitment [43, 44]; other works suggested that the function in atherogenesis of TLR4 is induced by endogenous ligands and not by bacterial products, because CD14 deficiency did not have a protective effect. The expression of TLR2 was shown to be increased in intimal layer of vessel areas with disturbed blood flow, and the lack of TLR2 has a protective effect in vessels of hypercholesterolemic mice lacking the low-density lipoprotein receptor (LDL-R) [43, 45]. Several other studies suggested that activation of TLR pathways by oxidized LDL could contribute to the expression of proinflammatory mediators and plaque development in atherosclerotic lesions [46, 47]. Activation of TLR on vascular endothelial cells by oxidized LDL, inducing activation of NF-κB and proinflammatory cytokine and adhesion molecules synthesis by the intima tunica predisposing vessels to atherosclerotic disease, through the experiments directed to investigating the role of TLR signaling in atherosclerosis were performed using animal models [43, 44, 45, 48], but they could not clearly indicate the cellular specificity of TLR responses. Studies employing endothelial TLR signaling manipulation will provide important insights to approach in atherosclerosis about a specific role of endothelial cells for TLR-induced responses. NF-κB activation in lesion-prone sites of vessels could be also induced by fluid mechanical forces by integrin signaling [43, 49, 50], suggesting that NF-κB activation may function during the very early stages of atherogenesis by promoting monocyte recruitment and plaque formation in areas of disturbed blood flow [43, 48]. In addition to exacerbating inflammation downstream of NF-κB transcription of pro-inflamma-

tory cytokines, inflammatory signaling also stimulates O2− production and oxidative stress (and vice versa) through a number of mechanisms. These include increased NF-κB-mediated transcription of redox-sensitive genes like those encoding subunits of NADPH oxidase [51–53] that increase reactive oxygen species (ROS) bioavailability and further activation of IKK-NF-κB signaling. Thus, NF-κB lies at the center of a vicious cycle that can exacerbate oxidative stress and inflammation. Interestingly, endothelial NF-κB can impact the healthspan/lifespan beyond its effects on vascular function per se [42].

Indeed, recent researches showed that inhibition of endothelial cell-specific inhibition of NF-κB resulted in reduced development of atherosclerosis in vivo in atherosclerotic mouse models. These studies showed much evidence pointing the protective role of NF-κB signaling inhibition, in particular in endothelial cells, in atherosclerosis mouse models it has an athero-protective effect relevant to human disease. The specific NF-κB inhibition in endothelial cell induces a reduction in expression of adhesion molecules and other inflammatory mediators in vessel wall, so it prevents the recruitment of monocytes/macrophages into the first steps of atherosclerosis, resulting in disease prevention [43].

In atherogenesis, monocytes differentiate into macrophages, a protective event meant to eliminate accumulated, inflammatory components (i.e., oxidized LDL, oxLDL). Cholesterol is transported in the circulation by plasma lipoproteins, in particular, LDLs act as an exogenous source of cholesterol and other cellular nutrients for various tissues, including the hepatic ones, where it is taken up through endocytosis. Another possibility is that LDLs may be caught extracellularly in vessels, where they are subjected to an environment favorable to various enzymatic and chemical modifications. The generation of bioactive lipid peroxidative products occurs in early stages of arterial lipoprotein modification without change in cellular receptor recognition of the particles.

Cell surface receptors for LDL (LDL-R) as well as scavenger receptors for modified LDL (SR-A, CD36, CD68) are expressed in monocyte-derived macrophages in arteries. While LDL particles with a minimal level of oxidation carry bioactive molecules, they are physically indistinguishable from native plasma LDL [54]. Cellular signals that induce the generation of oxidized lipids are not determined, but after the oxidation the LDL can be phagocytosed by macrophages through the scavenger receptors on the cell surfaces. The macrophages perform an important protective function by removing of oxidized LDLs, so the effects of modified LDLs on endothelial cells and smooth muscle cells are reduced. The ingestion of oxidized LDL leads to the accumulation of lipid peroxides and to the store of the excess cholesterol as cholesteryl esters within the cytoplasm, resulting in the formation of foam cells. Some evidences suggest that elevated levels of LDLs, in both native and oxidized form, modulate vascular cell gene expression acting as pro-oxidant signals. The exposure of monocytes to oxidized LDL for short time activates NF-κB and upregulates the expression of target genes, while their longer exposure can downregulate these responses [55]. The native form of LDLs and minimally oxidized LDLs induce endothelial cells production of different NF-κB-dependent chemokines and adhesion molecules and, at the same time, components of oxidized LDL, such as lysophosphatidylcholine, induce expression of mononuclear leukocyte adhesion molecules and can activate NF-κB in the same cells [56, 57]. Production of these chemokines

may amplify inflammation through the stimulation of resident macrophages proliferation and the recruitment of new monocytes into lesion sites. Moreover, pro-inflammatory cytokines expression in lesions can induce an increase in LDL binding to endothelium and smooth muscle cells and upregulates the expression of the LDL receptor, leading to further inflammation [24].

For the study of LDL, local oxidation, and its effects in arterial wall, Calara et al. [58] injected human LDL particles into a rat model and showed that these lipoproteins underwent oxidative modification with an activation of the endothelial NF-κB pathway and expression of NF-κB-dependent genes [58]. Other studies demonstrated arterial activation of NF-κB by very low-density lipoprotein (VLDL) and the consequent increased expression of NF-κB-dependent genes [59]. All these studies suggest that both LDL and VLDL may induce atherosclerosis in vessels of animal models involving NF-κB activation [24].

Atherosclerotic lesion is characterized by the migration of muscle cells from the tunica media to the tunica intima and their proliferation [3]. Moreover, smooth muscle cell proliferation, termed "neointimal hyperplasia", after percutaneous interventions is a trademark of restenosis [3]. Because vascular injury is the major stimulus for NF-κB activation and smooth muscle cell proliferation, as described earlier, numerous experiments have been made to study the involvement of NF-κB in proliferation of this cell type. Numerous evidences suggest that in steps of atherosclerotic lesion formation, there are smooth muscle cell modifications, which changes from a contractile to a synthetic phenotype, these cells then displaying features similar to fibroblast and are the major source of connective tissue in this pathology [60, 61]. In cell cultures, smooth muscle cells in the synthetic state express genes that can be modulated by NF-κB, as tumor necrosis factor-α (TNF-α), interleukin 1 (IL-1), macrophage-colony stimulating factor (M-CSF), granulocyte macrophage-colony stimulating factor (GMCSF), or monocyte chemotactic protein–1 [60, 62–66].

The NF-κB involved in regulation of these genes may be activated by inflammatory cytokines or reactive oxygen intermediates, all of which can be produced by smooth muscle cells themselves as well as by monocyte/macrophages, endothelial cells, or lymphocytes [60, 62, 67–69]. Increased activation of NF-κB could even be triggered in an autocrine loop by NF-κB-induced TNF-α or IL-1 itself [62, 64]. Activated NF-κB has been identified in cultured smooth muscle cells using electrophoretic mobility shift assays. Additionally, two recent studies demonstrate NF-κB activation in cultured smooth muscle cells by fibronectin and thrombin [70, 71].

Because NF-κB has been considered a potential therapeutic target of vascular diseases, many studies were performed to examine the effects of NF-κB inhibition on neointima formation following vascular injury. For example, adenovirus-mediated transfer of IκB super-repressor inhibited the development of intimal hyperplasia after vascular injury in rats in vivo. Likewise, double-stranded decoy oligonucleotides that bind NF-κB and keep it localized in the cytoplasm decreased injury-induced neointima formation in rats and pigs, [72, 73] as well as in-stent restenosis in hypercholesterolemic rabbits [74]. Moreover, antisense oligonucleotides that decrease p65 synthesis reduced neointima formation following carotid injury in rats [75]. Most recently, the NF-κB essential modulator-binding domain peptide, which can block the

activation of the IκB kinase complex and therefore inhibit NF-κB activation, was also able to reduce injury-induced neointima formation in rats and in apolipoprotein E-deficient mice [76]. Although results of these studies suggest that NF-κB inhibition is an effective therapeutic approach for vascular diseases, the target cell types had been unclear because of the global inhibition of NF-κB activity in these studies. In this regard, results of the study of Yoshida et al. (2005) [77] provide compelling evidence that NF-κB activation within smooth muscle cells is critical for injury-induced SMC phenotypic switching and neointima formation, although they do not negate a possibility that paracrine factors secreted by endothelial cells and/or monocytes/macrophages also affect the characteristics of smooth muscle cells. In fact, NF-κB inhibition in endothelial cells and macrophages has also been shown to decrease the formation of atherosclerosis [78]. Probably, NF-κB activation in multiple cell types including smooth muscle cells would simultaneously enhance lesion formation [79].

6. NF-κB in advanced lesions

In later stages of atherosclerosis, cell death became an important point. Death of lipid-laden cells is considered as an important step in the determination of the stability of the lesion and the formation of the necrotic core. Macrophage death by apoptosis, a prominent feature of atherosclerotic plaques, occurs in all stages of atherosclerosis and has a critical role in athero-genesis and atheroprogression [80]. Macrophage apoptosis in early lesions, coupled with rapid phagocytic clearance of dead cells (efferocytosis), reduces macrophage burden and slows lesion progression. Whereas in late lesions, macrophage apoptosis, accompanied by defective efferocytosis, promotes the enlargement of lipid core and results in inflammation, necrosis, and even plaque rupture, which are identified as the causative processes in the small percent-age of atherosclerotic lesions that cause acute vascular events such as stroke, acute myocardial infarction, and sudden coronary death [81–84].

In atherosclerosis, NF-κB pathway regulates cell survival signaling by the inhibition of programmed cell death induced via TNF-receptors and several other triggers. The contribution of NF-κB to apoptosis is mediated through regulation of ROS production and a control of sustained activation of the c-Jun NH2-terminal kinases (JNK)-mitogen-activated protein kinases (MAPK) cascade [85, 86]. Generally, NF-κB pathway, by interfering with induction of ROS and JNK signaling, inhibits the apoptotic response and promotes cell survival, while its blockade induces oxidative stress and activation of JNK-MAPK cascade that results in cell death, via apoptosis or necrosis [87, 88].

The pro-survival activity of NF-κB is mediated by the phosphorylation and degradation of the inhibitory IκBα proteins through IκB kinase (IKK) [15, 87]. Ottonello et al. showed that a long-acting nonsteroidal anti-inflammatory drug, oxaprozin, is able to inhibit the activation of kinase Akt in human monocytes, mediated by immune complexes, and prevents the activation of NF-κB mediated by IKK. This inhibition leads to cell programmed cell death by the reduction of the production of the anti-apoptotic molecule X-linked mammalian inhibitor of apoptosis protein in monocytes [87, 89]. These antiapoptotic effects of NF-κB are sustained by a positive

feedback regulation with TNFα, and are important in the pathogenesis of chronic inflammatory diseases (i.e., rheumatoid arthritis, inflammatory bowel disease) [14, 87, 90, 91]. Other evidences indicate that an aberrant NF-κB mediated inhibition of programmed cell death may be involved in the initiation of type-II diabetes and atherosclerosis [14, 87, 92, 93]. Anyhow, there are studies suggesting pro-apoptotic properties of NF-κB. It has been established that the activation of NF-κB increases expression of Fas ligand; the death factor Fas (CD95) is noted to contributing in cell apoptosis induced by DNA damage and other stresses. Thus, we can conclude that NF-κB is able to exert both pro- and anti-apoptotic properties depending upon the context of the various activating stimuli [87, 94].

Thrombosis associated with plaque rupture or erosion is the most acute complication of atherosclerosis and is an important mechanism in cardiovascular diseases, such as unstable angina and acute myocardial infarction. Several molecules have emerged as leading pathophysiological contributors, including thrombogenic tissue factor (TF), which is considered as the main initiator of coagulation and thrombus formation. In the last steps of atherosclerosis, the TF expression leads to activation of matrix metalloproteinase (MMP), which induces the loss of fibrous cap integrity, by collagen fibrils degradation, and infiltration and activation of inflammatory cells by pro-inflammatory cytokines. The expression of these mediators is regulated by transcription factors, such as NF-κB. TF, member of the cytokine receptor superfamily activates the coagulation cascade, forming a complex which cleaves factors IX and X, and thereby acts as an essential co-factor for factor VII/VIIa [3, 95, 96]. In human atherosclerotic vessels, different cells express TF, such as macrophages, smooth muscle cells, and endothelial cells that cover the plaque, but this factor is also present in the extracellular matrix. The TF promoter region presents a non-consensus NF-κB-binding site, which differs from the consensus sequence for one base [3, 97]. Lipopolysaccharide-mediated activation of TF transcription is inhibited by protease inhibitors of the chloromethylketone class in human monocytic cells, possibly preventing degradation of IκB [3, 98]. An inhibitor of the NF-κB pathway, the pyrrolidine dithiocarbamate, has the same effect on TF synthesis in endothelial cells modulated by different inducers [99]. TF is also inhibited in endothelial cells by the overexpression of IκBα or a dominant negative form of IKK-2 [100]. Recently, in fish, it has been demonstrated that in monocytes/macrophages the intracellular signaling pathways regulating TF is modulated by NF-κB [101].

Macrophages present in atherosclerotic plaques constitutively express MMP-1, -3, and -9, so the induction of these matrix-degrading enzymes is an important step inducing loss of fibrous cap integrity by the reduction of collagen protein [3, 102]. The release of MMP is regulated by NF-κB, but this may depend on the cell type and stimulus involved [103–105]. However, spontaneous secretion of MMP-9 by human macrophages does not appear to involve NF-κB, although Chase et al. demonstrated that NF-κB is a key factor in macrophage-derived MMP-1 and MMP-3 secretion. Inhibition of NF-κB dramatically reduced MMP-1 secretion from healthy human macrophages in response to CD40 ligation, a surface molecule in which ligation leads to this cells activation. Moreover, NF-κB was necessary for the pathology-related upregulation of MMP-1 and MMP-3 in foam cells elicited during atherosclerosis formation in vivo, thereby giving an indirect indication of the likely impact of NF-κB inhibition in vivo

[106]. Moreover, oxLDL, typical of atherosclerosis, has been found to increase macrophage MMP-9, associated with increased nuclear binding of NF-κB and activator protein-1 [13, 104].

7. Conclusions

Atherosclerosis and its complications are the major causes of mortality and morbidity around the world; for this reason, interventions aimed to prevent and treat these diseases are still a clinical challenge. Several researches suggest that the biology of the plaque is the first responsible for clinical manifestations of atherosclerosis. Current evidence supports a central role for inflammatory signaling pathways in all phases of the disease. Substantial biological data implicate NF-κB inflammatory pathways in early atherogenesis, in the progression of lesions, and finally in the thrombotic complications of this disease (Figure 1). This new insight into the role of NF-κB and of inflammation in the pathogenesis of atherosclerosis has initiated important new areas of direct clinical relevance. Future researches will be useful as guides to the development of inhibitors specific for the NF-κB pathway. Because the inhibitors now available lack of specificity for counteracting NF-κB activation eviting side effects, there is a need to identify appropriate therapeutic targets in the pathway for obtaining specific inhibition.
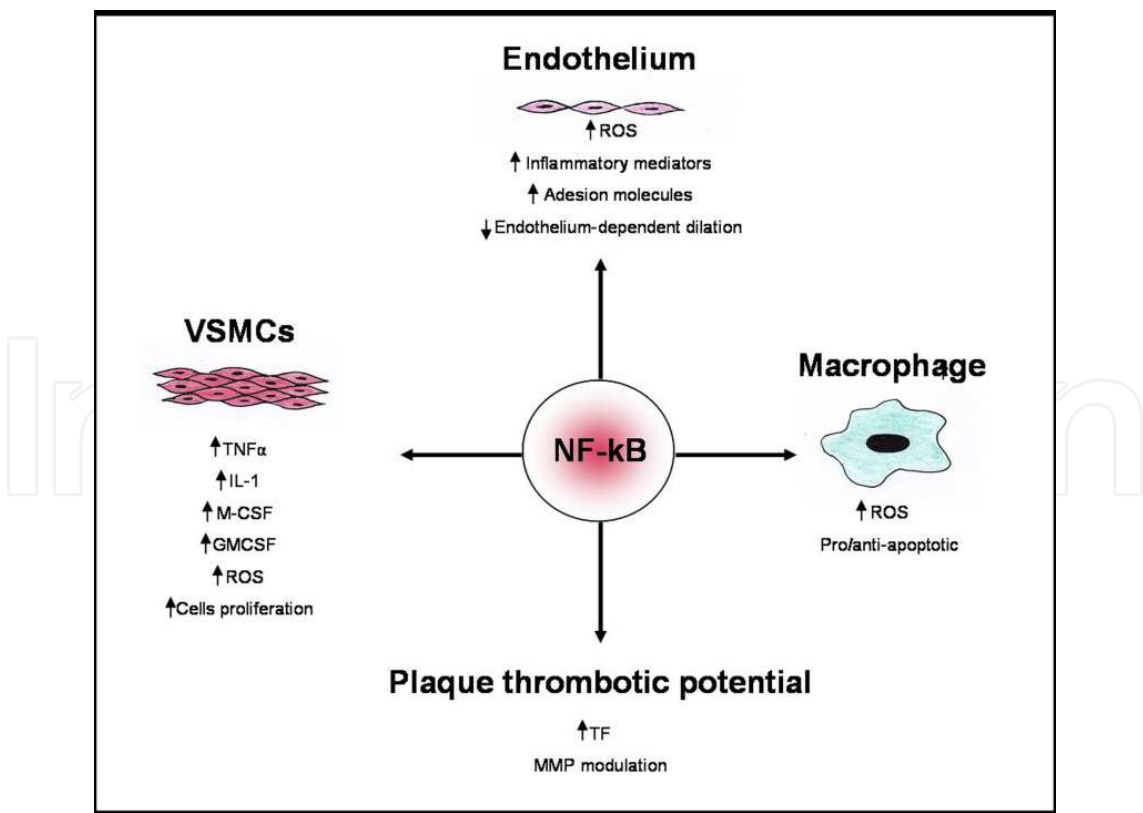

Figure 1. Representative image of the role of NF-κB in atherosclerosis

Nevertheless, the possibilities offered by a deeper understanding of the regulation of inflammatory signaling, including not just NF-κB but also other pathways, open up the promise of specific inhibition of disregulated inflammatory mechanisms causing disease.

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References

[1] Ross R. Atherosclerosis is an inflammatory disease. Am Heart J 1999;138:419–20.

[2] Husain K, Hernandez W, Ansari RA, Ferder L. Inflammation, oxidative stress and renin angiotensin system in atherosclerosis. World J Biol Chem 2015;6:209–17.

[3] Monaco C, Paleolog E. Nuclear factor kappaB: a potential therapeutic target in atherosclerosis and thrombosis. Cardiovasc Res 2004;61:671–82.

[4] Stary HC, Chandler AB, Glagov S, Guyton JR, Insull W Jr, Rosenfeld ME, Schaffer SA, Schwartz CJ, Wagner WD, Wissler RW. A definition of initial, fatty streak, and intermediate lesions of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. Circulation 1994;89:2462–78.

[5] Wöbke TK, Sorg BL, Steinhilber D. Vitamin D in inflammatory diseases. Front Physiol 2014;5:244.

[6] Toutouzas K, Synetos A, Nikolaou C, Tsiamis E, Tousoulis D, Stefanadis C. Matrix metalloproteinases and vulnerable atheromatous plaque. Curr Top Med Chem 2012;12:1166–80.

[7] Favero G, Rodella LF, Reiter RJ, Rezzani R. Melatonin and its atheroprotective effects: a review. Mol Cell Endocrinol 2014 Feb 15;382(2):926–37.

[8] Libby P, Lichtman AH, Hansson GK. Immune effector mechanisms implicated in atherosclerosis: from mice to humans. Immunity 2013;38:1092–104.

[9] Libby P. Mechanisms of acute coronary syndromes and their implication for therapy. N Engl J Med 2013;368:2004–13.

[10] Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of plaque formation and rupture. Circ Res 2014;114:1852–66.

[11] Yamashita T, Sasaki N, Kasahara K, Hirata KI. Anti-inflammatory and immune-modulatory therapies for preventing atherosclerotic cardiovascular disease. J Cardiol 2015;5087(15):36–42.

[12] Ghosh S, May MJ, Kopp EB. NF-kappa B and Rel proteins: evolutionarily conserved mediators of immune responses. Annu Rev Immunol 1998;16:225–60.

[13] Pahl HL. Activators and target genes of Rel/NF-kappaB transcription factors. Oncogene 1999;18:6853–66.

[14] Kumar A, Takada Y, Boriek AM, Aggarwal BB. Nuclear factor-kappaB: its role in health and disease. J Mol Med (Berl) 2004;82(7):434–48.

[15] Li Q, Verma IM. NF-kappaB regulation in the immune system. Nat Rev Immunol 2002;2:725–34.

[16] Senftleben U, Karin M. The IKK/NF-kappaB pathway. Crit Care Med 2002;30:18–26.

[17] Silverman N, Maniatis T. NF-kappaB signaling pathways in mammalian and insect innate immunity. Genes Dev 2001;15:2321–42.

[18] Karin M, Delhase M. The I kappa B kinase (IKK) and NF-kappa B: key elements of proinflammatory signaling. Semin Immunol 2000;12:85–98.

[19] Karin M, Lin A. NF-kappaB at the crossroads of life and death. Nat Immunol 2002;3:221–7.

[20] Kumar A, Lnu S, Malya R, Barron D, Moore J, Corry DB, Boriek AM. Mechanical stretch activates nuclear factor-kappaB, activator protein-1, and mitogen-activated protein kinases in lung parenchyma: implications in asthma. FASEB J 2003;17:1800–11.

[21] Kumar A, Boriek AM. Mechanical stress activates the nuclear factor-kappaB pathway in skeletal muscle fibers: a possible role in Duchenne muscular dystrophy. FASEB J 2003;17:386–96.

[22] Karin M, Ben-Neriah Y. Regulatory functions of ubiquitination in the immune system. Nat Immunol 2002;3:20–6.

[23] Wilkinson KD. Signal transduction: aspirin, ubiquitin and cancer. Nature 2003;424:738–9.

[24] Collins T, Cybulsky MI. NF-kappaB: pivotal mediator or innocent bystander in atherogenesis? J Clin Invest 2001;107:255–64.

[25] Brand K, Page S, Walli AK, Neumeier D, Baeuerle PA. Role of nuclear factor-kappa B in atherogenesis. Exp Physiol 1997;82:297–304.

[26] Boring L, Gosling J, Cleary M, Charo IF. Decreased lesion formation in CCR2-/- mice reveals a role for chemokines in the initiation of atherosclerosis. Nature 1998;394:894–7.

[27] Cybulsky MI, Gimbrone MAJ. Endothelial expression of a mononuclear leukocyte adhesion molecule during atherogenesis. Science 1991;251:788–91.

[28] Iiyama K, Hajra L, Iiyama M, Li H, DiChiara M, Medoff BD, Cybulsky MI. Patterns of vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 expression in rabbit and mouse atherosclerotic lesions and at sites predisposed to lesion formation. Circ Res 1999;85:199–207.

[29] Brand K, Page S, Rogler G, Bartsch A, Brandl R, Knuechel R, Page M, Kaltschmidt C, Baeuerle PA, Neumeier D. Activated transcription factor nuclear factor-kappa B is present in the atherosclerotic lesion. J Clin Invest 1996;97:1715–22.

[30] Wilson SH, Caplice NM, Simari RD, Holmes DRJ, Carlson PJ, Lerman A. Activated nuclear factor-kappaB is present in the coronary vasculature in experimental hypercholesterolemia. Atherosclerosis 2000;148:23–30.

[31] Hernandez-Presa MA, Ortego M, Tunon J, Martin-Ventura JL, Mas S, Blanco-Colio LM, Aparicio C, Ortega L, Gomez-Gerique J, Vivanco F, Egido J. Simvastatin reduces NF-kappaB activity in peripheral mononuclear and in plaque cells of rabbit atheroma more markedly than lipid lowering diet. Cardiovasc Res 2003;57:168–77.

[32] Gradinaru D, Borsa C, Ionescu C, Prada GI. Oxidized LDL and NO synthesis: biomarkers of endothelial dysfunction and ageing. Mech Ageing Dev 2015;6374(15):28–37.

[33] Simionescu M, Antohe F. Functional ultrastructure of the vascular endothelium: changes in various pathologies. Handb Exp Pharmacol 2006;176:41–69.

[34] Mehta D, Malik AB. Signaling mechanisms regulating endothelial permeability. Physiol Rev 2006;86(1):279–367.

[35] Sima AV, Stancu CS, Simionescu M. Vascular endothelium in atherosclerosis. Cell Tissue Res 2009;335(1):191–203.

[36] Donato AJ, Morgan RG, Walker AE, Lesniewski LA. Cellular and molecular biology of aging endothelial cells. J Mol Cell Cardiol 2015;2828(15):34–6.

[37] Lesniewski LA, Durrant JR, Connell ML, Folian BJ, Donato AJ, Seals DR. Salicylate treatment improves age-associated vascular endothelial dysfunction: potential role of nuclear factor kappaB and forkhead Box O phosphorylation. J Gerontol A Biol Sci Med Sci 2011;66(4):409–18.

[38] Walker AE, Kaplon RE, Pierce GL, Nowlan MJ, Seals DR. Prevention of age-related endothelial dysfunction by habitual aerobic exercise in healthy humans: possible role of nuclear factor κB. Clin Sci (Lond) 2014;127(11):645–54.

[39] Pierce GL, Lesniewski LA, Lawson BR, Beske SD, Seals DR. Nuclear factor-{kappa}B activation contributes to vascular endothelial dysfunction via oxidative stress in overweight/obese middle-aged and older humans. Circulation 2009;119(9):1284–92.

[40] Csiszar A, Smith K, Labinskyy N, Orosz Z, Rivera A, Ungvari Z. Resveratrol attenuates TNF-alpha-induced activation of coronary arterial endothelial cells: role of NF-kappaB inhibition. Am J Physiol Heart Circ Physiol 2006;291(4):1694–9.

[41] Xiao J, Song J, Hodara V, Ford A, Wang XL, Shi Q, Chen L, Vandeberg JL. Protective effects of Resveratrol on TNF-α-induced endothelial cytotoxicity in baboon femoral Arterial endothelial cells. J Diabetes Res 2013;2013:185172–80.

[42] Donato AJ, Henson GD, Morgan RG, Enz RA, Walker AE, Lesniewski LA. TNF-α impairs endothelial function in adipose tissue resistance arteries of mice with diet-induced obesity. Am J Physiol Heart Circ Physiol 2012;303(6):672–9.

[43] Gareus R, Kotsaki E, Xanthoulea S, Van der Made I, Gijbels MJ, Kardakaris R, Polykratis A, Kollias G, de Winther MP, Pasparakis M. Endothelial cell-specific NF-kappaB inhibition protects mice from atherosclerosis. Cell Metab 2008;8(5):372–83.

[44] Bjorkbacka H, Kunjathoor VV, Moore KJ, Koehn S, Ordija CM, Lee MA, Means T, Halmen K, Luster AD, Golenbock DT, Freeman MW. Reduced atherosclerosis in MyD88-null mice links elevated serum cholesterol levels to activation of innate immunity signaling pathways. Nat Med 2004;10:416–21.

[45] Mullick AE, Soldau K, Kiosses WB, Bell TA, III Tobias PS, Curtiss LK. Increased endothelial expression of Toll-like receptor 2 at sites of disturbed blood flow exacerbates early atherogenic events. J Exp Med 2008;205:373–83.

[46] Miller YI, Viriyakosol S, Binder CJ, Feramisco JR, Kirkland TN, Witztum JL. Minimally modified LDL binds to CD14, induces macrophage spreading via TLR4/MD-2, and inhibits phagocytosis of apoptotic cells. J Biol Chem 2003;278:1561–8.

[47] Miller YI, Viriyakosol S, Worrall DS, Boullier A, Butler S, Witztum JL. Toll-like receptor 4-dependent and -independent cytokine secretion induced by minimally oxidized low-density lipoprotein in macrophages. Arterioscler Thromb Vasc Biol 20055;25:1213–9.

[48] Michelsen KS, Wong MH, Shah PK, Zhang W, Yano J, Doherty TM, Akira S, Rajavashisth TB, Arditi M. Lack of Toll-like receptor 4 or myeloid differentiation factor 88 reduces atherosclerosis and alters plaque phenotype in mice deficient in apolipoprotein E. Proc Natl Acad Sci USA 2004;101:10679–84.

[49] Hajra L, Evans AI, Chen M, Hyduk SJ, Collins T, Cybulsky MI. The NF-kappa B signal transduction pathway in aortic endothelial cells is primed for activation in regions predisposed to atherosclerotic lesion formation. Proc Natl Acad Sci USA 2000;97:9052–7.

[50] Orr AW, Sanders JM, Bevard M, Coleman E, Sarembock IJ, Schwartz MA. The subendothelial extracellular matrix modulates NF-kappaB activation by flow: a potential role in atherosclerosis. J Cell Biol 2005;169:191–202.

[51] Manea A, Manea SA, Gafencu AV, Raicu M. Regulation of NADPH oxidase subunit p22(phox) by NF-κB in human aortic smooth muscle cells. Arch Physiol Biochem 2007;113:163–72.

[52] Kuwano Y, Kawahara T, Yamamoto H, Teshima-Kondo S, Tominaga K, Masuda K, et al. Interferon-gamma activates transcription of NADPH oxidase 1 gene and upregulates production of superoxide anion by human large intestinal epithelial cells. Am J Physiol Cell Physiol 2006;290:433–43.

[53] Anrather J, Racchumi G, Iadecola C. NF-kappaB regulates phagocytic NADPH oxidase by inducing the expression of gp91phox. J Biol Chem 2006;281:5657–67.

[54] Osterud B, Bjorklid E. Role of monocytes in atherogenesis. Physiol Rev 2003;83(4):1069–112.

[55] Brand K, Eisele T, Kreusel U, Page M, Page S, Haas M, Gerling A, Kaltschmidt C, Neumann FJ, Mackman N, Baeurele PA, Walli AK, Neumeier D. Dysregulation of monocytic nuclear factor-kappa B by oxidized low-density lipoprotein. Arterioscler Thromb Vasc Biol 1997;17:1901–9.

[56] Khan BV, Parthasarathy SS, Alexander RW, Medford RM. Modified low-density lipoprotein and its constituents augment cytokineactivated vascular cell adhesion molecule-1 gene expression in human vascular endothelial cells. J Clin Invest 1995;95:1262–70.

[57] Palmetshofer A, Robson SC, Nehls V. Lysophosphatidic acid activates nuclear factor kappa B and induces proinflammatory gene expression in endothelial cells. Thromb Haemost 1999;82:1532–7.

[58] Calara F, Dimayuga P, Niemann A, Thyberg J, Diczfalusy U, Witztum JL, Palinski W, Shah PK, Cercek B, Nilsson J, Regnström J. An animal model to study local oxidation of LDL and its biological effects in the arterial wall. Arterioscler Thromb Vasc Biol 1998;18:884–93.

[59] Dichtl W, Nilsson L, Goncalves I, Ares MP, Banfi C, Calara F, Hamsten A, Eriksson P, Nilsson J. Very low-density lipoprotein activates nuclear factor-kappaB in endothelial cells. Circ Res 1999;84:1085–94.

[60] Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. Nature (Lond) 1993;362:801–9.

[61] Amento EP, Ehsani N, Palmer H, Libby P. Cytokines and growth factors positively and negatively regulate interstitial collagen gene expression in human vascular smooth muscle cells. Arterioscler Thromb 1991;11:1223–30.

[62] Baeuerle PA, Henkel T. Function and activation of NF-κB in the immune system. Annu Rev Immunol 1994;12:141–79.

[63] Barath P, Fishbein MC, Lao J, Bernson J, Helfaut RH, Forrester JS. Tumor necrosis factor gene expression in human vascular smooth muscle cells detected by in vitro hybridization. Am J Pathol 1990;137:503–9.

[64] Hiscott J, Marois J, Garoufalis J, D'Addarion M, Roulston A, Kwan I, Pepin N, Lacoste J, Nguyen H, Bensi G, Fenton M. Characterization of a functional NF-kappa B site in the human interleukin-1b promoter: evidence for a positive autoregulatory loop. Mol Cell Biol 1993;13:6231–40.

[65] Rosenfeld ME, Ylä-Herttuala S, Lipton BA, Ord VA, Witztum JL, Steinberg D. Macrophage colony-stimulating factor mRNA and protein in atherosclerotic lesions of rabbits and humans. Am J Pathol 1992;140:291–300.

[66] Clinton SK, Underwood R, Haynes L, Sherman ML, Kufe DW, Libby P. Macrophage colony-stimulating factor gene expression in vascular cells and in experimental and human atherosclerosis. Am J Pathol 1992;140:301–16.

[67] Müller JM, Ziegler-Heitbrock HWL, Baeuerle PA. Nuclear factor kappa B, a mediator of lipopolysaccharide effects. Immunobiology 1993;187:233–56.

[68] Witztum JL, Steinberg D. Role of oxidized low density lipoprotein in atherogenesis. J Clin Invest 1991;88:1785–92.

[69] Berliner JA, Territo M, Andalibi A, Navab M, Liao F, Cushing S, Imes S, Kim J, Van Lenten B, Lusis AJ, Fogelman AM. Modified lipoproteins and atherogenesis. In: Gotto JAM. (Ed.) Cellular and Molecular Biology of Atherosclerosis. Springer-Verlag London Ltd., London. 1992. Pp. 77–80.

[70] Qwarnström EE, Ostberg CO, Turk GL, Richardson CA, Bomsztyk K. Fibronectin attachment activates the NF-κB p50/p65 heterodimer in fibroblasts and smooth muscle cells. J Biol Chem 1994;269:30765–8.

[71] Nakajima T, Kitajima I, Shin H, Takasaki I, Shigeta K, Abeyama K, Yamashita Y, Tokioka T, Soejima Y, Maruyama I. Involvement of NF-κB activation in thrombin-induced human vascular smooth muscle cell proliferation. Biochem Biophys Res Commun 1994;204:950–5.

[72] Yoshimura S, Morishita R, Hayashi K, Yamamoto K, Nakagami H, Kaneda Y, Sakai N, Ogihara T. Inhibition of intimal hyperplasia after balloon injury in rat carotid artery model using cis-element "decoy" of nuclear factor-κB binding site as a novel molecular strategy. Gene Ther 2001;8:1635–42.

[73] Yamasaki K, Asai T, Shimizu M, Aoki M, Hashiya N, Sakonjo H, Makino H, Kaneda Y, Ogihara T, Morishita R. Inhibition of NFjB activation using ciselement "decoy" of NFjB binding site reduces neointimal formation in porcine balloon-injured coronary artery model. Gene Ther 2003;10:356–64.

[74] Ohtani K, Egashira K, Nakano K, Zhao G, Funakoshi K, Ihara Y, Kimura S, Tominaga R, Morishita R, Sunagawa K. Stent-based local delivery of nuclear factor-jB decoy attenuates in-stent restenosis in hypercholesterolemic rabbits. Circulation 2006;114:2773–9.

[75] Autieri MV, Yue TL, Ferstein GZ, Ohlstein E. Antisense oligonucleotides to the p65 subunit of NF-jB inhibit human vascular smooth muscle cell adherence and proliferation and prevent neointima formation in rat carotid arteries. Biochem Biophys Res Commun 1995;213:827–36.

[76] Grassia G, Maddaluno M, Musilli C, De Stefano D, Carnuccio R, Di Lauro MV, Parratt CA, Kennedy S, Di Meglio P, Ianaro A, Maffia P, Parenti A, Ialenti A. The IjB kinase inhibitor nuclear factor-jB essential modulator-binding domain peptide for inhibition of injury-induced neointimal formation. Arterioscler Thromb Vasc Biol 2010;30:2458–66.

[77] Yoshida T, Owens GK. Molecular determinants of vascular smooth muscle cell diversity. Circ Res 2005;96(3):280–91.

[78] Kanters E, Gijbels MJ, van der Made I, Vergouwe MN, Heeringa P, Kraal G, Hofker MH, de Winther MP. Hematopoietic NF-jB1 deficiency results in small atherosclerotic lesions with an inflammatory phenotype. Blood 2004;103:934–40.

[79] Yoshida T, Yamashita M, Horimai C, Hayashi M. Smooth muscle-selective inhibition of nuclear factor-κB attenuates smooth muscle phenotypic switching and neointima formation following vascular injury. J Am Heart Assoc 2013;2(3):230–3.

[80] Moore KJ, Tabas I. Macrophages in the pathogenesis of atherosclerosis. Cell 2011;29;145(3):341–55.

[81] Tabas I. Consequences and therapeutic implications of macrophage apoptosis in atherosclerosis: the importance of lesion stage and phagocytic efficiency. Arterioscler Thromb Vasc Biol 2005;25(11):2255–64.

[82] Tabas I. Macrophage death and defective inflammation resolution in atherosclerosis. Nat Rev Immunol 2010;10(1):36–46.

[83] Littlewood TD, Bennett MR. Apoptotic cell death in atherosclerosis. Curr Opin Lipidol 2003;14(5):469–75.

[84] Yao S, Tian H, Miao C, Zhang DW, Zhao L, Li Y, Yang N, Jiao P, Sang H, Guo S, Wang Y, Qin S. D4F alleviates macrophage-derived foam cell apoptosis by inhibiting endoplasmic reticulum stress-CHOP pathway. J Lipid Res 2015 [Epub ahead of print].

[85] Bubici C, Papa S, Pham CG, Zazzeroni F, Franzoso G. NF-kappaB and JNK: an intricate affair. Cell Cycle 2004;3(12):1524–9.

[86] Luo JL, Kamata H, Karin M. IKK/NF-kappaB signaling: balancing life and death-a new approach to cancer therapy. J Clin Invest 2005;115(10):2625–32.

[87] Pamukcu B, Lip GY, Shantsila E. The nuclear factor--kappa B pathway in atherosclerosis: a potential therapeutic target for atherothrombotic vascular disease. Thromb Res 2011;128(2):117–23.

[88] Papa S, Bubici C, Zazzeroni F, Pham CG, Kuntzen C, Knabb JR, Dean K, Franzoso G. The NF-kappaB-mediated control of the JNK cascade in the antagonism of programmed cell death in health and disease. Cell Death Differ 2006;13(5):712–29.

[89] Ottonello L, Bertolotto M, Montecucco F, Bianchi G, Dallegri F. Delayed apoptosis of human monocytes exposed to immune complexes is reversed by oxaprozin: role of the Akt/IkappaB kinase/nuclear factor kappaB pathway. Br J Pharmacol 2009;157(2): 294–306.

[90] Kucharczak J, Simmons MJ, Fan Y., Gelinas C. To be, or not to be: NF-κB is the answer – role of Rel/NF-κB in the regulation of apoptosis. Oncogene 2003;56:8961–82.

[91] Liu H, Pope R.M. The role of apoptosis in rheumatoid arthritis. Curr Opin Pharmacol 2003;3:317–22.

[92] Shoelson SE, Lee J, Yuan M. Inflammation and the IKκB/IκB/NFκB axis in obesity- and diet-induced insulin resistance. Int J Obes Relat Metab Disord 2003;3:S49–52.

[93] Dandona P, Aljada A, Chaudhuri A, Mohanty P, Garg R. Metabolic syndrome: a comprehensive perspective based on interactions between obesity, diabetes, and inflammation. Circulation 2005;111:1448–54.

[94] Kasibhatla S, Brunner T, Genestier L, Echeverri F, Mahboubi A, Green DR. DNA damaging agents induce expression of Fas ligand and subsequent apoptosis in T lymphocytes via the activation of NF-κB and AP-1. Mol Cell 1998;1:543–51.

[95] Nemerson Y. Tissue factor: then and now. Thromb Haemost 1995;74(1):180–4.

[96] Zoldhelyi P, Chen ZQ, Shelat HS, McNatt JM, Willerson JT. Local gene transfer of tissue factor pathway inhibitor regulates intimal hyperplasia in atherosclerotic arteries. Proc Natl Acad Sci USA 2001; 98:4078–83.

[97] Mackman N, Morrissey JH, Fowler B, Edgington TS. Complete sequence of the human tissue factor gene, a highly regulated cellular receptor that initiates the coagulation protease cascade. Biochemistry 1989;28:1755–62.

[98] Mackman N. Protease inhibitors block lipopolysaccharide induction of tissue factor gene expression in human monocytic cells by preventing activation of c-Rel/p65 heterodimers. J Biol Chem 1994;269:26363–7.

[99] Orthner CL, Rodgers GM, Fitzgerald LA. Pyrrolidine dithiocarbamate abrogates tissue factor (TF) expression by endothelial cells: evidence implicating nuclear factor-kappa B in TF induction by diverse agonists. Blood 1995;86:436–43.

[100] Wrighton CJ, Hofer-Warbinek R, Moll T, Eytner R, Bach FH, de Martin R. Inhibition of endothelial cell activation by adenovirus-mediated expression of I- kappa B alpha, an inhibitor of the transcription factor NF-kappa B. J Exp Med 1996;183:1013–22.

[101] Wei H, Yin L, Feng S, Wang X, Yang K, Zhang A, Zhou H. Dual-parallel inhibition of IL-10 and TGF-β1 controls LPS-induced inflammatory response via NF-κB signaling in grass carp monocytes/macrophages. Fish Shellfish Immunol 2015;44(2):445–52.

[102] Galis ZS, Sukhova GK, Lark MW, Libby P. Increased expression of matrix metallo-proteinases and matrix degrading activity in vulnerable regions of human athero-sclerotic plaques. J Clin Invest 1994;94:2493–503.

[103] Bond M, Fabunmi RP, Baker AH, Newby AC. Synergistic upregulation of metallo-proteinase-9 by growth factors and inflammatory cytokines: an absolute requirement for transcription factor NF-kappa B. FEBS Lett 1998;435:29–34.

[104] Bond M., Chase AJ, Baker AH, Newby AC. Inhibition of transcription factor NF-kap-paB reduces matrix metalloproteinase-1, -3 and -9 production by vascular smooth muscle cells. Cardiovasc Res 2001;50:556–65.

[105] Feldmann M, Andreakos E, Smith C, Bondeson J, Yoshimura S, Kiriakidis S, Monaco C, Gasparini C, Sacre S, Lundberg A, Paleolog E, Horwood NJ, Brennan FM, Foxwell BM. Is NF-kappaB a useful therapeutic target in rheumatoid arthritis? Ann Rheum Dis 2002;61(Suppl 2):ii13–8.

[106] Chase AJ, Bond M, Crook MF, Newby AC. Role of nuclear factor-kappa B activation in metalloproteinase-1, -3, and -9 secretion by human macrophages in vitro and rab-bit foam cells produced in vivo. Arterioscler Thromb Vasc Biol 2002;22(5):765–71.

[107] Xu XP, Meisel SR, Ong JM, Kaul S, Cercek B, Rajavashisth TB, Sharifi B, Shah PK. Oxidized low-density lipoprotein regulates matrix metalloproteinase-9 and its tissue inhibitor in human monocyte-derived macrophages. Circulation 1999;99(8):993–8.