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Chapter 2

# NF-κB — A Key Factor in Atherogenesis and Atheroprogression

Francesca Bonomini, Gaia Favero and Rita Rezzani

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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.

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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 proinflammatory 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].

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## 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 exogeneous 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

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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-$\alpha$ (TNF-$\alpha$), 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-$\alpha$ 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 atherogenesis 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 percentage 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 IκB$\alpha$ 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

http://dx.doi.org/10.5772/61894

feedback regulation with TNF$\alpha$, 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 IκB$\alpha$ 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.

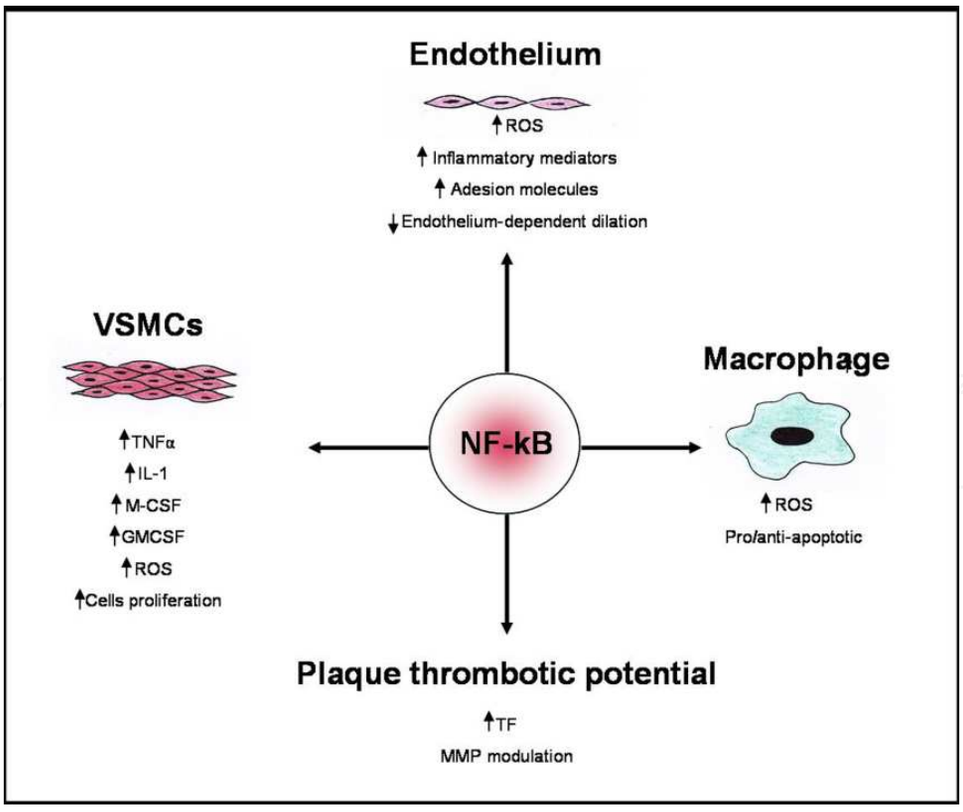


**Figure 1.** Representative image of the role of NF-κB in atherosclerosis

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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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