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REVIEW

Nuclear Transcription Factor Kappa B (NF-κB) and Molecular Damage Mechanisms in Acute Cardiovascular Diseases. A Review

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ABSTRACT

Worldwide, cardiovascular diseases (CVDs) represent one of the main causes of morbidity and mortality, and acute coronary syndromes are responsible for a large number of sudden cardiac deaths. One of the main challenges that still exist in this area is represented by the early detection and targeted monitoring of the pathophysiology involved in CVDs. During the last couple of years, researchers have highlighted the importance of molecular and epigenetic mechanisms involved in the initiation and augmentation of CVDs, culminating in their most severe form represented by acute myocardial infarction. One of the most studied molecular factors involved in this type of pathology is represented by nuclear transcription factor kappa B (NF-κB), as well as the involvement of microRNAs (miRNAs). It has been suggested that miRNAs can also be involved in the complex process of atheromatous plaque vulnerabilization that leads to an acute cardiac event. In this review paper, we describe the most important molecular mechanisms involved in the pathogenesis of CVDs and atheromatous plaque progression and vulnerabilization, which include molecular mechanisms dependent on NF-κB. For this paper, we used international databases (PubMed and Scopus). The keywords used for the search were "miRNAs biomarkers", "miRNAs in cardiovascular disease", "NF-κB in cardiovascular disease", "molecular mechanism in cardiovascular disease", and "myocardial NF-κB mechanisms". Numerous molecular reactions that have NF-κB as a trigger are involved in the pathogenesis of CVDs. Moreover, miRNAs play an important role in initiating and aggravating certain segments of CVDs. Therefore, miRNAs can be used as biomarkers for early evaluation of CVDs. Furthermore, in the future, miRNAs could be used as a targeted molecular therapy in order to block certain mechanisms responsible for inducing CVDs and leading to acute cardiovascular events.

Keywords: miRNAs, cardiovascular diseases, atheromatous plaque, plaque vulnerability

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BACKGROUND

In the last years, worldwide, according to published studies and statistics, a high percentage of patients suffer from cardiovascular diseases (CVDs). According to the World Health Organization, starting with 2005, the number of deaths caused by CVDs has reached 17.5 million, compared to only 14.4 million registered in 1991. Furthermore, the WHO has estimated a number of 20 million deaths caused by CVDs for the year 2015. CVDs include a wide range of pathologies, such as ischemic heart disease, stroke, congestive heart failure, coronary heart disease, and rheumatic heart disease, most of them manifesting as various types of cardiovascular emergencies.[1–4]

If we were to talk about the most common pathology involved in the development and augmentation of CVDs, the pro-inflammatory component stands in the first line.[5] It is well known that in certain situations, inflammation can be beneficial for defense and tissue-remodeling mechanisms. However, when the inflammation becomes overexpressed or chronic, it is responsible of inducing certain pathological phenomena at myocardial level. Among these phenomena, the most commonly mentioned are ischemia-reperfusion syndrome (IR), myocardial infarction, atherosclerosis, aortic valve disorder, and heart failure.[6–9] Therefore, the role of inflammation in triggering an acute cardiac condition is currently well established.

One of the main pathologies developed at cardiovascular level is represented by atherosclerosis, which eventually can be defined as a molecular and cellular inflammation complex.[10–13] Of course, if we were to look at a molecular and cellular level, the vascular endothelium is the main involved cofactor. From a molecular viewpoint, the key player is represented by nuclear transcription factor kappa B (NF-κB), which, according to recent studies, is responsible for the modulation of molecular and epigenetic signals at this level.[14,15]

In this paper, we aim to present the most complex molecular mechanisms involved in the development and augmentation of CVDs and especially their most severe forms of manifestation, represented by acute cardiovascular events. Moreover, we wish to highlight a series of biomarkers that could be used in the early diagnosis and monitoring of CVDs.

THE MOST COMMON MOLECULAR MECHANISMS INVOLVED IN CVDS

Mitochondrial dysfunctions are relevant factors involved in the augmentation of cardiovascular diseases and progression to an acute or critical stage. Numerous species of microRNAs are involved in the pathogenesis of mitochondrial damage, these being responsible for the excess production of oxygen free radicals (OFRs), as well as for endothelial and vascular dysfunctions.[16–23] Magenta *et al*. have investigated the effects and implications of OFRs on the epigenetic mechanisms of miRNAs.[24] Oxidative stress (OS), as well as increased production of OFRs have important implications in the pathogenesis of CVDs through the ischemia and ischemia-reperfusion (IR) syndrome injury they can cause.[18,21,22] Furthermore, from a molecular point of view, another important factor is represented by hydrogen peroxide (H_2O_2) and superoxide anion, both responsible for inhibiting cell growth and inducing cell death and senescence.[23] Following their study, they have shown that aberrant expressions of miRNA-200c induce growth arrest, apoptosis, and senescence in human umbilical vein endothelial cells.[24]

Although there are plenty of studies regarding the molecular mechanisms responsible for cell death, the epigenetic implications still remain obscure. Recently, it was reported that the $p66^{ShcA}$ protein is involved by modifying certain mechanisms responsible for ischemia-induced cell death. From a biochemical point of view, the $p66^{ShcA}$ protein represents an N-terminal domain, being phosphorylated to threonine as a response to the attack of H_2O_2. Zaccagnini *et al*. have studied the changes involved in the ischemia/reperfusion-induced cell death by suppressing $p66^{ShcA}$ during the redox attack. They have shown that $p66^{ShcA}$ plays an important role in cell death pathways by blocking and decreasing cell death. Moreover, in this study they called into question using $p66^{ShcA}$ as a future therapeutic target for the prevention of ischemic tissue damage.[25]

Lin *et al*. have investigated the molecular mechanisms and the relations with miRNAs in the case of H_2O_2 redox attacks on vascular smooth muscle cells (VSMCs). They have shown that miRNA-21 is responsible for augmented cell death in the case of specific molecular mechanisms through redox activation.[26]

Another study shows the significant implications of vascular adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) in the pathogenesis of atherosclerosis. They have proven that VCAM-1 plays an important role in initiating atherosclerosis.[27] It is also well known that such intercellular adhesion molecules play a significant role in the complex process of coronary plaque vulnerabilization and the development of sudden coronary artery occlusion, thus leading to acute myocardial infarction. Recent studies have shown important implica-

tions of the receptor-activator of nuclear factor kappa B ligand – receptor-activator of nuclear factor kappa B – osteoprotegerin (RANKL-RANK-OPG) in the development of myocardial muscle in the embryonic phase, in muscle remodeling during a myocardial infarction, and in modulating cytokine activity in the immune-inflammatory segment of cardiac pathogenesis. Following this study, Lu *et al*. have concluded that by activating the RANKL-RANK-OPG system, the balance of pro- and anti-inflammatory cytokines is significantly affected, leading to alterations in the cardiovascular function.[28]

Another important factor in the pathogenesis of atherosclerosis is represented by peroxisome proliferator-activator receptors (PPARs). Bendaya *et al*. have shown a series of mechanisms involved in the pathogenesis of atherosclerosis through the modulation of fatty acid translocase CD36 activity in peripheral blood mononuclear cells.[29]

EPIGENETIC EXPRESSION IN CVDS

Recent studies have shown that noncoding (nc) RNA is responsible for most of the genetic regulation mechanisms.[30,31] Regarding its mechanism of action, ncRNAs are associated with chromatin and transcriptional activation responsible for the post-transcriptional control of the involved genes. Together with the identification of aberrant expressions of genes responsible for the control of a certain pathogenic mechanism, certain answers have been given regarding the genetic links and genetic mechanisms involved in altering cardiovascular functions. ncRNAs form a large family, comprising of ribosomal RNAs (rRNAs), small nucleolar RNAs (snoRNAs), transfer RNAs (tRNAs), and small nuclear RNAs (snRNAs).[32,33] Moreover, ncRNAs can be divided depending on their main mechanisms of action.[34–39] Among these, we mention the transcriptional regulation, especially represented by the modulation of GAS5, MALAT1, and NEAT1 genes; through post-transcriptional regulation or epigenetic regulation ncRNAs are involved in the chromatin-remodeling for XIST and HOTAIR genes.

miRNAs have a higher specificity when it comes to molecular mechanisms responsible for cardiovascular changes. A recent study published by Zhang *et al*. reported 65 miRNAs involved in pathological modifications at cardiovascular level.[40]

From a biochemical point of view, miRNAs are noncoding, single-stranded RNA species comprising of approximately 17–24 nucleotides.[33] The synthesis processes of miRNAs take place in the nucleus, through the action of RNA polymerase II on specific genes.[41,42] Following this nuclear reaction, the first epigenetic miRNA species are obtained, called pri-miRNAs. In the next step, RNA polymerase III, also called Drosha complex, will attack the pri-miRNAs, leading to the formation of pre-miRNAs. This reaction takes place only if it is catalyzed by the DiGeorge Syndrome Critical Region 8 (DGCR8).[43–46] The transporting protein, Exportin 5, will then act on the pre-miRNAs, which will transfer the epigenetic complex from the nucleus to the cell cytoplasm.[47–49] Once the signal that the complex has reached the cytoplasm is received, RNA polymerase III (Dicer) and trans-activator RNA binding protein (TRBP) attack it and lead to the formation of mature miRNAs.[5,50] This molecular species is then introduced in the RNA-induced silencing complex (RISC) and released in the cell under various forms. The most common forms are microvesicles, apoptotic bodies, exosomes, and high-density lipoproteins.[22]

Furthermore, regarding the action mechanisms, researchers came to the conclusion that miRNAs are involved in inflammation, in the redox response, nutrient sensing, and silent mating-type information regulation 2 homolog (SIRT1)-regulated events.[44,51]

They have also proven that by stimulating miRNA-21, certain proteins that augment the cellular injury are stimulated, among which the most significant is programmed cell death 4 (PDCD4). Olivieri *et al*. have studied a series of microRNA expressions in the case of vascular cell senescence.[52] Following their study, they have reported an overexpression for miRNA-146a, miRNA-9, miRNA-204, and miRNA-367 in vascular cell injury.[52]

Ucar *et al*. have also shown significant implications of the overexpression of the miRNA-212/132 family in cardiovascular diseases. The molecular mechanisms they studied were related to the activity of the FoxO3 transcription factor; they have also shown that the overexpression of miRNA-212/132 leads to an overstimulation of pro-hypertrophic NFAT signaling. Last but not least, it was proven that by inhibiting the activity of miRNA-132 with antagonizing injections, one can considerably reduce cardiac hypertrophy in animal experiments.[53]

miRNAS AND ACUTE MYOCARDIAL INFARCTION

In a similar study, Long *et al*. have proven significant links between aberrant expressions of miRNA-1 and miRNA-126 and acute myocardial infarction.[54]

Another study has shown significant implications for miRNA-30a, miRNA-195, and let-7b in acute myocardial infarction. Numerous other studies have also reported ab-

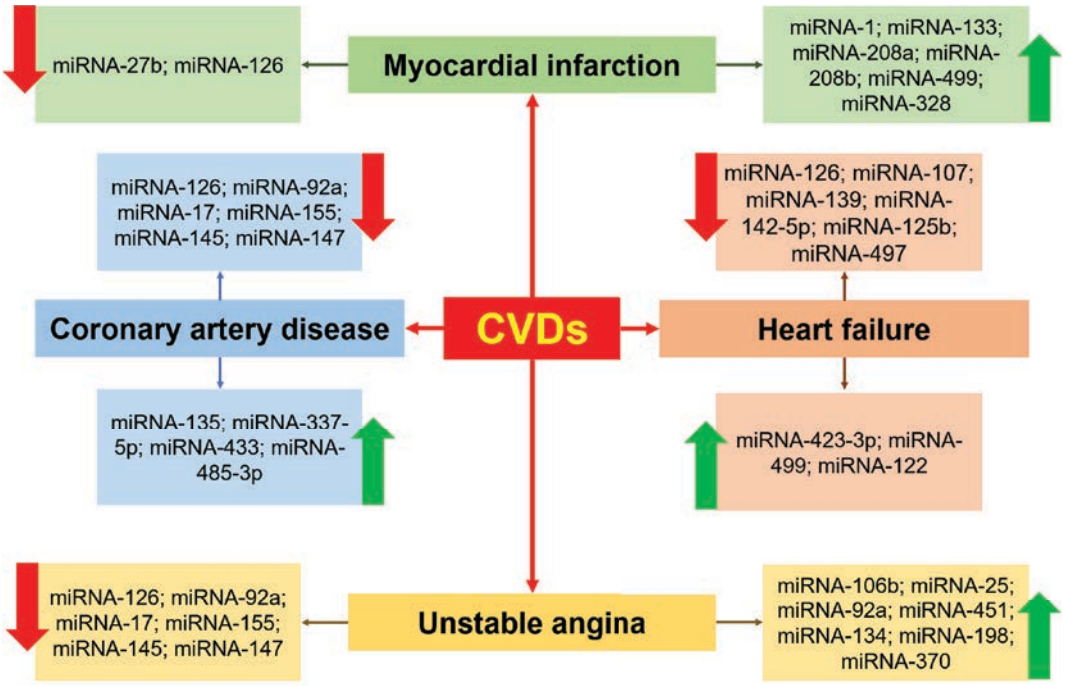

FIGURE 1. miRNA expression in the most common cardiovascular diseases (CVDs).[56,58-66]

errant changes in the expression of miRNA-1, miRNA-133, miRNA-208a/b, miRNA-499, miRNA-318, and miRNA-126 in the case of acute myocardial infarction.[55]

Regarding the expression of miRNAs in CVDs, Fichtlscherer *et al.* have shown significant changes in the endothelium for miRNA-126, miRNA-17, miRNA-20a, miRNA-92a, miRNA-221, miRNA-21, miRNA-199a-5p, miRNA-27a, miRNA-130a, and let-7d.[56] A number of studies speak about the implications of miRNAs in different molecular and pathogenic mechanisms such as cholesterol metabolism, where changes in the expressions of miRNA-103, miRNA-26, miRNA-30c, miRNA-27a, miRNA-27b, miRNA-106b, and miRNA-144 have been reported. Recent research in smooth muscle differentiation demonstrated changes in the expressions of miRNA-1, miRNA-21, miRNA-26a, miRNA-29b, miRNA-125b, miRNA-126, miRNA-132, miRNA-133a, miRNA-133, miRNA-143, miRNA-145, miRNA-208, miRNA-638, miRNA-663, and let-7d.[57]

Figure 1 shows the most important changes in miRNA expression in the most common cardiovascular diseases.[56,58-66]

NF-κB, INFLAMMATION, AND ATHEROSCLEROSIS

Another important factor involved in the molecular mechanisms that lay at the basis of cardiovascular diseases is represented by nuclear factor kappa B (NF-κB).[15] Regarding its mechanism of action, NF-κB is responsible of the regulation of pro-inflammatory cytokines and their modulation inside the cardiac tissue, especially during IR injury. From a structural viewpoint, NF-κBs are proteins containing approximately 300 amino acids, also called RELSIH (Rel). These comprise of heterodimers and homodimers, and their subunits include NF-κB1 (p50), NF-κB2 (p52, p49 and p50B), p65 (RelA), and cRel. A series of inhibitors are involved in the inhibition reactions of NF-κB, among which the most important ones are represented by IκBα, IκBβ, IκBε, bcl-3, p105-p50, p100-p52, and the IκBγ-p105 gene.[15,67-70] From a pathological point of view, NF-κB is involved in the modulation of certain genes responsible for the further modulation of the pro-inflammatory activity and of the immune response. The most common activation reactions of NF-κB are represented by phosphorylation and activation of IκB kinase complex.

In a study on NF-κB involvement in the development of atherosclerosis, Hajra *et al.* have shown that the components of NF-κB/IκB are most likely responsible for the pathogenesis of CVDs by initiating and augmenting the atherosclerotic process.[71] Kanters *et al.* have also shown a significant decrease in the expression of interleukin 10 (IL-10) pro-inflammatory cytokine after the inhibition of NF-κB. Following their study, they have reported that inactivating NF-κB will affect the balance between pro-inflammatory and anti-inflammatory mechanisms.[72]

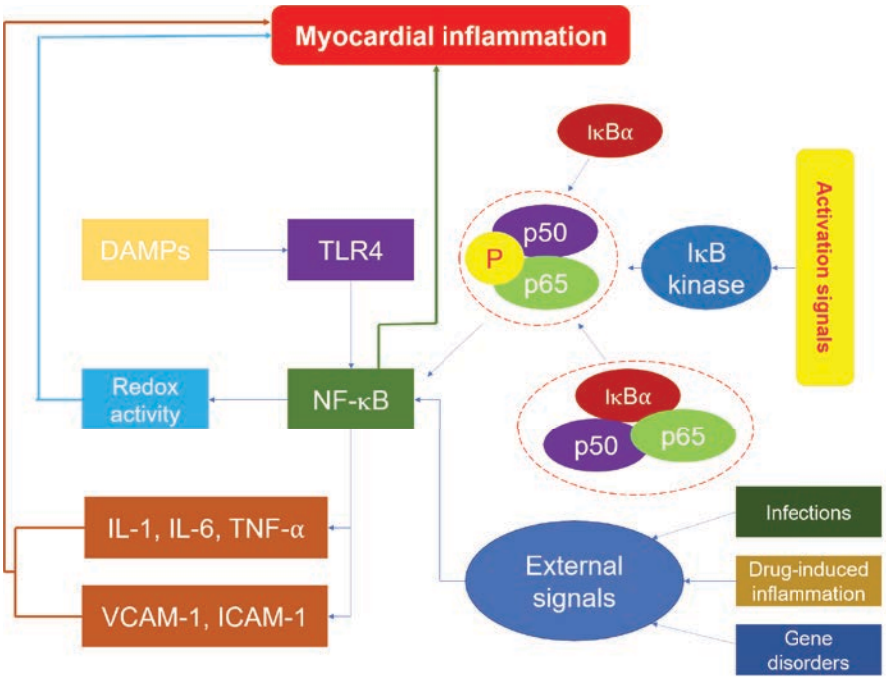

FIGURE 2. NF-κB implications in myocardial inflammation, induced by TLR4. For details please see text.

Moreover, numerous studies demonstrated that the activity of NF-κB has important implications on the hemodynamic status, cytokine activity, matrix signaling, angiotensin II activity, advanced glycation mechanisms, and adhesion molecules such as VCAM-1 and ICAM-1. Recent studies have reported a series of implications of NF-κB in the formation of the atherosclerotic plaque through mechanisms that include the expression of a dominant-negative IκBα suppressor (DNIκBα). Gareus *et al.* have studied the mechanisms of NF-κB involved in the genesis of atherosclerosis.[14] Following this study, they have shown that NF-κB is involved in the endothelial pro-inflammatory response and activates the pathogenesis of atherosclerosis.[14]

Recently, it was reported that oxidized LDL (oxLDL) presents a series of implications in the development of CVDs by activating endothelial receptors. Changes at the level of vascular endothelium are possible because of the activation of NF-κB, which further modulates the pro-inflammatory molecular activity through the activation of E-selectin, VCAM-1, and ICAM-1. Following their study, Yurdagul *et al.* proved that oxLDL are responsible for the activation of IκB kinase β (IKKβ) and NF-κB, which then lead to an overexpression in pro-inflammatory genes.[73]

Another important role in the pathogenesis of CVDs is played by dendritic cells (DCs), which represent the pathological liaison between the innate and adaptive immune systems. The maturation of CDs includes a number of different steps, among which the most important ones are the high cell surface expression of CD-stimulatory cytokines (CD40, CD86, and CD-80) responsible for the augmentation of certain processes such as tumor necrosis factor alpha (TNF-α), interleukin 10 (IL-10), interleukin 12 (IL-12), and type I interferon (IFN-γ). Obviously, NF-κB is involved in all these biochemical and epigenetic reactions by triggering the activation and transcription of the genes involved.[74]

Meng *et al.* have studied the implications of NF-κB in these mechanisms, reporting that angiotensin II is involved in the activation of DCs through the p65/NF-κB system.[74]

Regarding the molecular mechanisms responsible for myocardial inflammation, the most widely discussed are pattern recognition receptors (PPRs) through the recognition and activation of damage-associated molecular patterns (DAMPs). Apart from PRRs, another molecular line is represented by the Toll-like receptors (TLRs), widely studied in relation with the mechanisms of myocardial inflammation. Regarding the expression of TLRs in the myocardial tissue, numerous studies have reported a significantly higher expression of TLR both in the cardiac myocytes and in the endothelial cells. Among these are the following: TLR-4, TLR-2, TLR-3, TLR-6, TLR-1, TLR-8, TLR-10, and TLR-7. Out of this large family, specialty studies have shown numerous implications of TLR4

in CVDs. From a molecular point of view, in the activation of TLR4 intervenes the myeloid differentiation factor 81 (MyD88), which is responsible of the connection between Toll/Interleukin-1 (Toll/IL-1) receptor (TIR) and TLR4. As a result, the κB (IκB) kinase α (IKKα)/IKKβ/IKKγ molecular complexes are activated, which are further responsible of IKβ phosphorylation. The NF-κB transcription factor will then result from the phosphorylated IKβ. Once the NF-κB is activated, a series of other reactions will be augmented, molecular reactions responsible for the overexpression of interleukin-6 (IL-6), interleukin-1 (IL-1), and TNF-α[6,75,76] (Figure 2).

CONCLUSIONS

A series of pathologies that are both induced and augmented by genetic and molecular mechanisms are involved in the development of CVDs and in the complex physiopathological chain of acute myocardial infarction. The most relevant factors for this process include the pro-inflammatory status and alteration of the balance between pro-inflammatory and anti-inflammatory factors. This molecular imbalance is induced by the over-expression or inhibition of NF-κB. Based on current literature, we can conclude that NF-κB is involved in most pro- and anti-inflammatory processes underlying CVDs. Moreover, by using the expression of certain specific miRNAs, we can prevent certain cardiovascular pathologies, and we can choose the most appropriate therapeutic interventions in order to block molecular damage patterns. However, further research regarding the usage of these epigenetic species in the therapy of CVDs, and especially of acute coronary syndromes, is necessary.

CONFLICT OF INTEREST

Nothing to declare.

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