

Advances in NF- κ B-Regulated Autophagy in Cardiovascular Disease

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Abstract:

As people's quality of life improves, the prevalence of cardiovascular disease (CVD) is increasing. The outer region of tissues or cells affected by cardiovascular disease frequently results in the presence of a pro-inflammatory protein called NF- κ B. NF- κ B plays a role in maintaining the ecological balance of NF- κ B and regulating the body's defence mechanisms. Thus, NF- κ B is frequently recognised as a promising focus of study for CVD. Studies have revealed that modified NF- κ B activity is accompanied by alterations in other crucial biological processes, such as autophagy. Autophagy, a process in which cells recycle their own components, is associated with apoptosis, proliferation, and changes in antioxidants in tissues and cells. As a result, autophagy is becoming recognised as a crucial factor in the damage-related changes that occur in CVD. Nevertheless, the impact of NF- κ B-regulated autophagy on the progression of CVD is contradictory. This review presents the primary discoveries about NF- κ B-controlled autophagy in CVD.

Keywords:

CVD, NF- κ B, Autophagy

1. Introduction

Autophagy plays a pivotal role in the pathogenesis of cardiovascular disease (CVD), with irreversible cardiovascular lesions being its primary cause. Consequently, comprehending the impact of autophagy on CVD is crucial for effectively addressing this condition. NF- κ B, an inflammatory factor, has been demonstrated to stimulate autophagy production. In pulmonary arterial hypertension (PAH), diseased lung tissue exhibits altered levels of autophagy proteins, and modulating autophagy can alleviate PAH [1]. Atherosclerosis is characterized by heightened NF- κ B-regulated autophagy activity [2]. Furthermore, NF- κ B-induced autophagy in vascular cells can lead to vascular injury [3]. However, research on the molecular mechanisms underlying NF- κ B regulation of autophagy in CVD is limited. Therefore, this study aims to elucidate the role of NF- κ B-regulated autophagy in CVD (Figure 1).

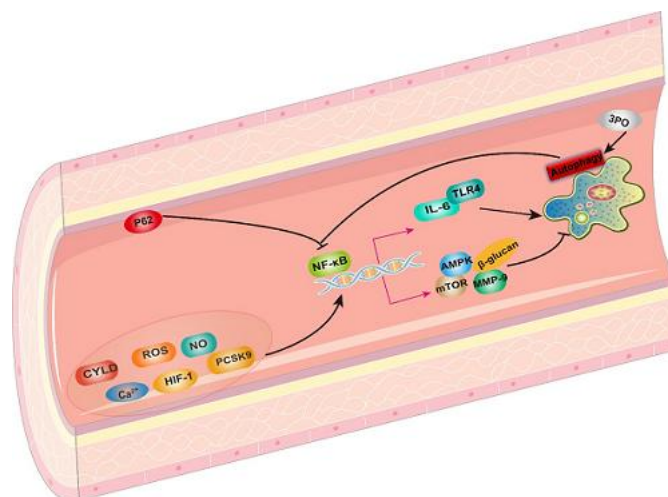


Figure 1. *NF-κB in the cardiovascular regulates the signaling pathway of autophagy.*

2. NF-κB as An Upstream Signaling Molecule

NF-κB, an inflammatory mediator, plays a pivotal role in cardiovascular disease. Within a pool of five monomers, namely NF-κB1 (p50), NF-κB2 (p52), RelA (p65), RelB, and c-Rel, which form homodimers or heterodimers comprising a related protein complex, there exist 15 NF-κB-associated complexes [4]. In the cytoplasm, NF-κB binds to the inhibitor of κB (IκB) [5] when IκB is specifically phosphorylated by IκB through the classical IκB kinase (IKK) pathway, facilitated by a specific ubiquitylated ligase from the SCF family [6], or through the non-classical IKK holoenzyme pathway (which includes the NF-κB essential modifier, NEMO). The absence of NEMO ubiquitin in the two IκB kinase subunits (IKKα & IKKβ) transmits upstream signals to IKKα & IKKβ [7], leading to the activation of IκB, which subsequently dissociates from the complex to activate NF-κB. Activated NF-κB translocates to the nucleus and binds to specific DNA sequences, exerting effects on immunity, inflammation, cancer, autophagy, cell death, and more [8,9]. NF-κB exhibits profound pro-inflammatory effects. In the autoimmune disease of rheumatoid arthritis, NF-κB activation contributes to joint damage through bone erosion [10]. Consequently, inhibition of IKK/NF-κB signaling has been found to impede tumor progression in colorectal and hepatocellular carcinomas [11]. Clearly, NF-κB contributes to the pathophysiological progression of various diseases. Given the growing interest in the relationship between NF-κB and autophagy, it is crucial to elucidate the interplay between autophagy and NF-κB signaling to advance research in this field.

3. The Process of Autophagy Formation in Organisms

In recent years, with the extensive investigation of NF-κB, it has been increasingly recognized that NF-κB is intricately associated with autophagy in cardiovascular diseases. Autophagy is a relatively conserved cellular self-regulation mechanism in eukaryotes. Its purpose [12] is to degrade foreign substances, defective macromolecules, and organelles, while generating nutrients to sustain cellular growth, facilitated by intracellular lysosomes or vesicles. Autophagy can be classified into three categories: macroautophagy, microautophagy, and chaperone-mediated autophagy. The process of autophagy is primarily governed by macroautophagy (hereafter referred to as autophagy). At the site of phagocytic vesicle assembly in

yeast cells, also known as the pre-autophagosome structure or omegasome, which is a phosphatidylinositol 3-phosphate-enriched subdomain of the mammalian endoplasmic reticulum, autophagy initiates by extending and forming autophagic vesicles to sequester the contents. The size of autophagic vesicles is determined based on the size of the cargo, leading to the closure and formation of autophagosomes with a double membrane structure. These autophagosomes ultimately fuse with lysosomes to form autophagolysosomes, delivering the contents for self-digestion and decomposition [13]. In the context of ischemic stroke, reduced NF- κ B expression and impaired autophagy have been observed following lumbar kinase treatment, leading to attenuated cerebral infarct volume and neuroinflammation [14]. Conversely, promoting titin expression inhibits NF- κ B while significantly enhancing autophagy expression and promoting P62 degradation, thereby improving coronary patients [15]. Therefore, when NF- κ B influences inflammation in disease, and activated autophagy can exert both protective and detrimental effects, it becomes imperative to specifically elucidate the signaling pathway of NF- κ B-activated autophagy.

4. Autophagy Regulated by the NF- κ B Signaling Pathway

NF- κ B-mediated autophagy exhibits bidirectionality. NF- κ B has been demonstrated to stimulate autophagy by binding to three binding sites within the first intron of Beclin1 [16]. In human lung cancer cells, the NF- κ B binding sites A5S49, spanning from 731 to 722, bind to the promoter of human GD3 synthase, amplifying the sequence and inducing LC3B conversion to enhance autophagy [17]. Conversely, NF- κ B activation also inhibits autophagy. In LPS-induced intestinal epithelial cells, the inflammatory factor NF- κ B is abundantly expressed, while autophagic flux is impaired [18]. Inhibition of NF- κ B expression has been observed to increase the ratio of autophagy-related proteins ATG5 and LC3B in cardiomyocytes [19]. Similarly, promoting autophagy has been found to reduce the expression of inflammatory factors. In macrophages treated with autophagy inhibitors, a high expression of inflammatory factors such as NF- κ B and IL-1 β is observed. Subsequent treatment with melatonin reverses the increase in inflammation and promotes autophagy occurrence [20]. The interplay between NF- κ B and autophagy is mutually regulated, and its specific association with cardiovascular disease requires further exploration.

5. NF- κ B-regulated Autophagy in Cardiovascular Disease

Autophagy plays an indispensable role in cardiovascular diseases, and dysregulation of autophagy has been shown to be relevant in diseases such as PAH, atherosclerosis (AS), and myocardial ischemia/reperfusion (I/R). An important factor in the development of cardiovascular diseases is the influence of inflammatory mediators. Inflammatory signaling in the vasculature leads to alterations in autophagy in cardiovascular cells, which in turn affects the pathophysiological process of the disease.

5.1. Autophagy regulated by NF- κ B in PAH

Vascular remodeling is recognized as one of the most crucial etiological factors in pulmonary hypertension. In a murine model of pulmonary hypertension induced by wild larkin, the administration of NF- κ B inhibitors significantly mitigated medial wall thickness and alleviated right ventricular hypertrophy. This effect was achieved by impeding NF- κ B nuclear translocation, thereby inhibiting autophagy occurrence [21].

Similarly, in rats with hypoxia-induced hypoxic pulmonary hypertension, remodeling of small pulmonary arteries was linked to NF- κ B activation, which promoted autophagy expression in lung tissue [3]. The release of Ca^{2+} and cylindroma protein in pulmonary artery smooth muscle cells (PASMCs) can stimulate the expression of NF- κ B [22,23]. Moreover, under hypoxic conditions, NF- κ B is further upregulated in PASMCs through the stimulation of HIF-1 and ROS [24,25]. Consequently, PASMCs exhibit robust autophagy and proliferation, which can be significantly altered by employing the autophagy inhibitor 3-MA, leading to the arrest of PASMCs in the G1 phase [3]. Activation of NF- κ B in endothelial cells triggers downstream interleukin-6-induced autophagy expression, further exacerbating inflammation [26]. The role of autophagy in the signaling pathway of NF- κ B, which can be activated through various mechanisms, has the potential to regulate the disease progression of PAH.

5.2. Autophagy regulated by NF- κ B in AS

The primary factor underlying atherosclerosis is the development of arterial plaque, with inflammation playing a crucial role in plaque formation, progression, and rupture. Low-density lipoprotein (LDL) is highly expressed in AS serum, and PCSK9 can activate NF- κ B expression to suppress autophagy [27], thus exerting a protective effect. The incorporation of artemisinin and procyanidin into the biomimetic membrane for AS treatment reduces the expression of ROS and NO in the vasculature. Consequently, the inhibition of NF- κ B expression promotes AMPK/mTOR-dependent autophagy, facilitating cholesterol efflux [28]. The generation of oxidized zithromax from LDL oxidation at low doses stimulates the production of phosphorylated NF- κ B, inducing autophagy to alleviate endoplasmic reticulum stress. However, at high doses, the inhibition of autophagy by oxidized zithromax exacerbates endoplasmic reticulum stress, impairing endothelial cell function and accelerating endothelial cell apoptosis [29]. While abundant LDL obstructs autophagic flux, P62 knockdown activates NF- κ B, suppressing matrix metalloproteinase-9 expression, and promoting autophagy to protect macrophages, thereby enhancing plaque vulnerability [30]. Macrophage polarization toward the pro-M1 phenotype is crucial in AS pathogenesis, with the M1 phenotype promoting NF- κ B-dependent β -glucan expression and inhibiting autophagy [31]. On the other hand, the anti-inflammatory M2 macrophage phenotype plays a protective role. The utilization of the small molecule 3PO in AS inhibits glycolysis and promotes M2 polarization. This inhibits vascular proliferation and facilitates autophagy, leading to the degradation of activated NF- κ B, effectively preventing AS [32]. It is evident that autophagy exerts a protective role in AS, and targeting NF- κ B to reactivate autophagy may present a novel approach for alleviating AS.

5.3. The modulation of autophagy by NF- κ B in I/R

I/R injury arises from the pathological alterations in tissues and organs during ischemia, a state characterized by insufficient oxygen and nutrient supply. In I/R-injured cardiomyocytes, ROS were observed to stimulate the activation of NF- κ B and the autophagy protein Beclin1. The administration of NF- κ B reversed this phenomenon [33]. In contrast, in lung tissues, a substantial upregulation of MicroRNA-145 was observed following I/R injury. This led to an elevation in NF- κ B acetylation levels and transcriptional activity, along with the accumulation of numerous autophagosomes. Interestingly, autophagy exhibits a distinct pattern in the context of I/R injury in the liver. Treatment of a liver model of I/R injury with berberine demonstrated its ability to protect against I/R injury by suppressing NF- κ B

expression while enhancing autophagy [34]. Conversely, pre-treatment with geranylgeranyl prior to I/R liver injury alleviated the injury by reducing the expression of both NF- κ B and autophagy [35]. The differential regulation of autophagy by NF- κ B may be attributed to the distinct methods of drug administration, as berberine administration was combined with nanobiotechnology to facilitate drug delivery.

6. Conclusions

Mounting evidence suggests that NF- κ B serves as a pivotal inflammatory factor in CVD. Both in vivo and in vitro CVD models have demonstrated varying levels of NF- κ B expression, which impact autophagy. Autophagy plays a crucial role in the cell cycle, apoptosis, cell proliferation, and macrophage phenotype transformation. Its primary function is to mount a stress defense response against injury. Nevertheless, the precise control exerted by NF- κ B on autophagy in CVD remains elusive. Further investigation is warranted to explore whether NF- κ B inhibits or upregulates autophagy to confer a protective effect. This investigation should encompass the upstream and downstream signaling pathways of NF- κ B and autophagy, aiming to identify targeted therapeutic strategies. The comprehensive exploration of NF- κ B-mediated autophagy holds promise as a novel therapeutic approach in CVD, offering valuable clinical insights.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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