



Neuregulin-1, a potential protective for Cardiovascular repair (Review)

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Abstract

Neuregulin-1, or NRG 1, is a powerful cardiomyocyte proliferator that impacts the circulatory system. Endothelial cells in the bloodstream secrete and releases it. It is essential for the development, proliferation, differentiation, apoptosis, and other cardiovascular functions of the heart. In the pathophysiology of several cardiovascular disorders, NRG 1 may repair the heart, including cardiomyopathy, and atherosclerosis, demonstrated by numerous experiments. Through the NRG 1 /ErbB pathway, NRG 1 can associate related signaling pathways, creating signal cascades to progress the microenvironment of myocardial by controlling necrotic apoptosis, oxidative stress, and cardiac inflammation. In this article, we provide an overview of recent developments in the molecular processes of NRG 1, clarifying the role that targets NRG 1 in cardiovascular disease, and identifying areas that require more investigation.

Keyword: Neuregulin-1, ErbB pathway, cardiovascular disease.

نيوريجولين-1، وسيلة وقائية محتملة لإصلاح القلب والأوعية الدموية (مراجعة)

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الخلاصة



نيوريجولين-1، أو NRG1 ، هو منشور قوي للخلايا العصبية القلبية يؤثر على الدورة الدموية. يتم إفرازه وإطلاقه بواسطة الخلايا الوعائية البطانية. يعتبر ضروري للتطور والانتشار والتميز وموت الخلايا المبرمج وغيرها من وظائف القلب والأوعية الدموية للقلب. يمكن لـ NRG1 إصلاح القلب في الفيزيولوجيا المرضية لمختلف أمراض القلب والأوعية الدموية، بما في ذلك اعتلال عضلة القلب، وتصلب الشرايين، وهو ما أثبتته العديد من التجارب. من خلال مسار NRG1 /ErbB ، يمكن لـ NRG1 ربط مسارات إشارات مماثلة، وتشكيل شلالات إشارة لتحسين البيئة الدقيقة لعضلة القلب عن طريق التحكم في موت الخلايا المبرمج النخري، والإجهاد التأكسدي، والتهاب القلب. في هذه المقالة، نقدم نظرة عامة على التطورات الأخيرة في العمليات الجزيئية لـ NRG1 ، ونوضح الدور الذي يستهدف NRG1 في أمراض القلب والأوعية الدموية، ونحدد المجالات التي تتطلب المزيد من البحث.

الكلمات المفتاحية: نيوريجولين-1، مسار ErbB، أمراض القلب والأوعية الدموية.

Introduction

NRG1 (Neuregulin-1) is a protein that is important for cell signaling in the heart, central nervous system, and mammary gland [1,2]. It is a member of the family of growth factors known as neuregulin is in charge of the development and stress-resistant mechanisms of the heart [3].

Neuregulins were discovered independently of the cardiovascular system, in the context of cancer and brain studies [4-8]. Nonetheless in the late 1990 s, a number of teams showing investigation to interfere with NRG/ErbB signaling observed that it was vital of the heart development [9-11.]

There are indications that NRG 1 affects angiogenesis, remodeling of the extracellular matrix, cardiomyocyte proliferation, and recruitment of stem cells, and other processes that enhance cardiac function in addition to stimulating cardiomyocyte proliferation [12-14]. When combined, these processes support cardiac function improvement myocardial repair, offering a novel molecular approach aimed at myocardium regeneration. According to Gassmann et al. NRG 1 is a strong stimulator of cardiovascular proliferation that is required for the expression, proliferation, and differentiation the cells of cardiac [15].

Injection of NRG 1 stimulates a number of signaling pathways that lead to cardiac regeneration and reentry and separation of the cardiomyocyte cycle in adults [14] [16]. This study illustrates the clinical applications of NRG 1 in cardiovascular repair as well as its molecular background.



Moreover, it suggested directions for future research, in addition to recent breakthroughs in cardiovascular biology.

Regulatory of NRG 1

The intricate regulation mechanisms of NRG 1 encompass several signaling molecular, and metabolic pathways. Thus, section included a summary of the signal pathways contacts, transcription control modalities, and the molecular structure of NRG 1

NRG 1's Fundamental Structure

According to Huang et al., NRG1 is the neuregulin family that is the most distinctive [17]. In humans and mice, the NRG1 gene is located on chromosome 8, whereas in rats, it is located on chromosome 6 [18,19]. NRG1 encodes 21 exons and results in 31 potential protein isoforms, according to Steinthorsdottir et al [20,21]. NRG1 isoforms are divided into six categories I-IV based on their structural differences [22]. Despite varying in their efficiency of expression in cells, distinct isoforms of NRG1 are all capable of concluding their signaling conversation with ligands [23]. is composed of transmembrane structural domains, highly conserved 1-NRG terminal ECD –terminal ICD)intracellular structural domains(, and NH₂ -COOH (extracellular structural domains) [24,25]. In order to initiate ErbB signaling in target cells, NRG- 1 – ECD interacts to ErbB [26]. It has the ability to enter the nucleus and prevent the production of many apoptotic regulators [25].

In cells, ErbB and ECD can interact following the release of NRG- 1 – ECD, immediately following the synthesis of isoforms devoid of transmembrane structural domains, or following protein hydrolysis resulting in the formation of transmembrane precursors [27]. Cell-cell contact can also result in NRG1-ErbB interactions [28]. NRG 1- ICD is necessary for NRG 1 role in vivo [29], ectopic NRG 1 expression causes NRG 1- ICD dependent apoptosis [30]. In addition, CRD (cysteine-rich domain) interaction with ErbB receptors activates signals necessary for CRD-NRG1 expression cells [31]. NRG 1 shares an EFG-like structural domain with all isoforms and is homologous to the EGF (epidermal growth factor) family [32]. By splicing one of two exons that encode the 3'-terminus of the EGF-like structural domain with the common "core" exon that encodes the 5'-terminus of the EGF-like structural domain,

rendering falls produces the EGF-like structural domain [1]. As a result, the EGF-like structural domain (α and β) takes on different variations.

Comparing NRG1 β and NRG1 α , NRG1 β has a greater affinity for ErbB4 and NRG1 α is expressed at higher levels [23]. The organism may be significantly impacted by this disparity [33]. NRG1 β knockout mice are embryonically deadly, according to animal investigations [34], but NRG1 α knockout mice live to adulthood with only notable abnormalities in the mammary lob's alveolar development [35]. More significantly, NRG1 α increases the expression of the cell adhesion protein 11 in human glioma cells and facilitates their migration in response to malignancy [36].

These imply that NRG 1 β might be more crucial to survival than NRG 1 α . The influence of both on the metabolism of cardiac energy were subsequently investigated in an additional in vitro study using cardiac muscle cells. Only NRG 1 β enhanced glucose uptake and protein synthesis, and NRG1 β is a more powerful activator of intracellular signaling and receptor phosphorylation than NRG 1 α [23]. Cote et al. explain that, many NRG 1 isotypes are expressed by cardiac microvascular endothelial cells; however, only NRG 1 β is physiologically active in cardiac myocytes (figure 1) [23].

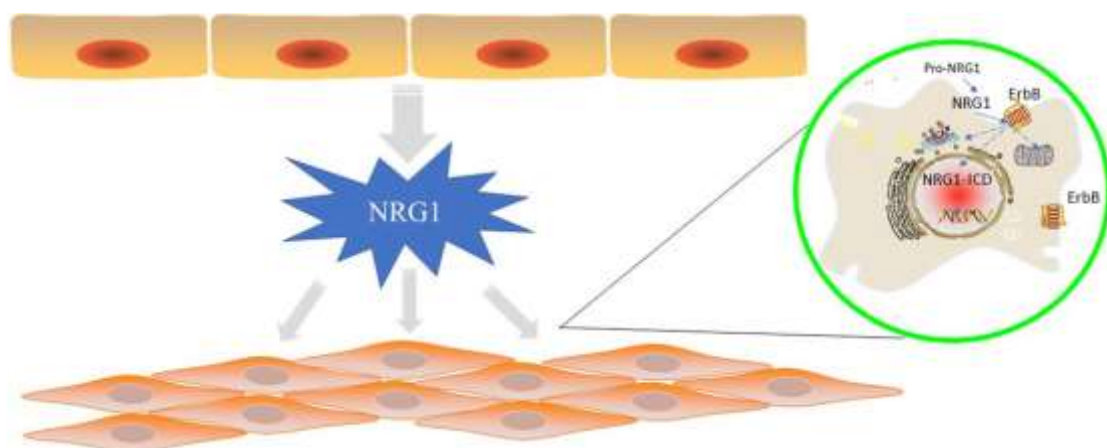


Figure 1: Endothelial cells in cardiovascular vessels secrete NRG1, which is regulated by ErbB proteins in endothelial cells or cardiomyocytes [23].

NRG 1 and Cardiovascular Diseases

The ventricular wall, cardiac valves and conduction system, and microvasculature are the primary sites of action for NRG 1's downstream signaling [37]. To completely highlight the significance of NRG 1 in the onset of cardiovascular illnesses, we have compiled a summary of its physiological and pathological functions in cellular and cardiovascular tissues in this section. Recent studies have demonstrated the significance of NRG 1 in the genesis and progression of cardiovascular disorders, including cardiotoxicity, arrhythmia, MI/IR, HF, and atherosclerosis. The paper provides an overview of NRG 1's function in cardiovascular disorder (Figure 2) along with the relevant pathways

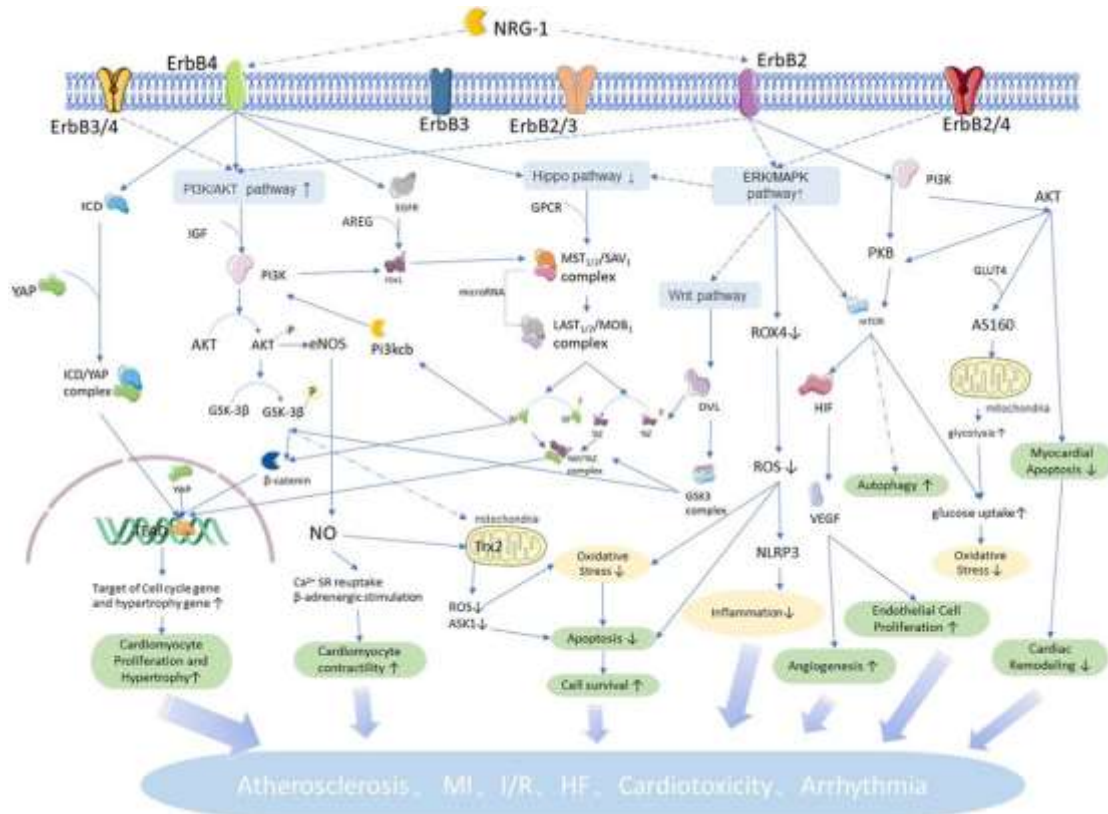


Figure 2: NRG1 related pathways and roles in cardiovascular [38].

Atherosclerosis and NRG 1

1. Cell aging and NRG 1

Oxidative stress and persistent inflammation are the major causes of cellular senescence. Senescence-associated secretory phenotype (SASP) and cellular senescence play a significant



role in aging of cardiovascular and [39] the senescence of EC (endothelial cell) and VSMC (vascular smooth muscle cell) can cause atherosclerosis [40]. Stress-induced premature senescence (SIPS) is a condition in which cells undergo senescence as a result of DNA damage brought on by both intrinsic and extrinsic stressors [41]. The two primary causes of SIPS are oxidative stress and hyperglycemia [39].

NRG1 may have anti-SIPS potential because it is recognized to have enhanced metabolism of glucose [42] and antioxidant properties [43]. According to data, NRG 1 significantly reduce the premature senescence caused by stress in vascular cells in vitro and in the aorta of diabetic mice in vivo [44]. Additionally, feeding type 1 diabetic mice rhNRG 1 for nine weeks reduces the senescence caused by diabetes in the vascular system.

The effectiveness of NRG 1 in preventing cellular senescence has been demonstrated by the consistent induction of cellular senescence both in vitro and in vivo [44] and the significantly greater induction of vascular senescence in ErbB 4 receptor-deficient mice in SMC when associated to wild-type littermates [44]. NRG 1/ErbB signaling's effects on cellular senescence are still unclear, however, its effects on apoptosis and cell proliferation are well-established [45].

2. Endothelial Cell Damage and NRG 1

Preceding studies have shown that in primary human macrophages generated from monocyte cells, NRG 1 inhibits the production of foam cells [46]. Moreover, they found that long-term NRG 1 β infusion into ApoE^{-/-} mice prevented macrophage infiltration in the arterial wall, Reduced ACAT- 1 (acyltransferase-1) activity and acetylated low density lipoprotein endocytosis, and enhanced cholesterol efflux from human macrophages to apolipoprotein A 1 [46].

This further supports NRG 1 β 's inhibitory action on atherosclerotic lesions. When oxidized LDL and norepinephrine were co-incubated with VSMCs, NRG 1 expression was suppressed, and VSMC proliferation and phenotypic transition were stimulated [47]. By reducing VSMCs, NRG1 inhibits the migration and proliferation of neointima growth following vascular damage in rats [48].



These results point to a negative relationship between VSMC growth and NRG 1 expression. Referring to Amin et al., ErbB3 stimulation by NRG 1 β has been shown to suppress EC proliferation, suggesting that ErbB3 could be a possible healing target of the NRG 1- ErbB pathway to prevent atherosclerosis [49].

3. Vascular Stress and NRG 1

Furthermore, the response to vascular stress depends on the NRG 1/ErbB signaling pathway [50]. Vasodilation results from NRG 1's anti-adrenergic actions on the cardiovascular system [51]. Rats' blood pressure was demonstrated to drop when NRG was microinjected into the ventral lateral side of the medulla oblongata, a significant vasodilator area [52]. By regulating the autonomic nervous system. NRG 1 β , an activator of nicotinic acetylcholine receptors, may enhance the vascular burden of atherosclerotic for cardio protective benefits [53].

Myocardial infarction and NRG 1

Subsequently a myocardial infarction, the first day has the highest rate of cardiomyocyte mortality [54]. Referring to the most recent research, the levels of NRG 1 plasma declined dramatically after PCI/RIC and continued to decline for up to one month after AMI, with no correlation with other factors [55].

Reactive oxygen species, or ROS, are produced during cardiac ischemia-reperfusion and cause NRG 1 β / ErbB4 activation [56]. This suggests that NRG 1 β / ErbB 4 signaling controls myocardial damage in an oxidative stress environment. The primary ROS-synthesizing enzyme in cardiac tissue is NADPH oxidase 4 (NOX 4) [57].

Previous research has shown that NRG 1 can suppress ROS production in cardiac reperfusion injury by activating the ERK 1/ 2 pathway, which in turn inhibits NOX 4 activity [58]. Antioxidant genes including catalase and mitochondrial GPx 1 (glutathione peroxidase 1) are expressed when specific overexpression of ErbB 2 is expressed in juvenile rat hearts [59].

In adult rat ventricular myocytes, NRG 1 can inhibit hydrogen peroxide through ErbB 4-Akt signaling or by directly activating paracrine signaling by ErbB 4 independent of NRG [56]. This prevents stimulated adult rat ventricular myocytes with hydrogen peroxide from apoptosing in order to achieve self-protection. Thus, by regulating the oxidative stress mechanism, NRG1 prevents myocardial apoptosis.



1. Myocardial Inflammatory Injury and NRG 1

Blood leukocytosis caused by an acute myocardial infarction (AMI) is inversely connected with patient survival [60]. Pro-apoptotic signaling cascades and further heart remodeling can result from extreme inflammation in the areas of heart at risk from MI [61]. In the infarct region of cardiac fibroblasts, ErbB 2 and ErbB 4 epidermal growth factor receptors were expressed in the NRG 1 receptor. In MI model mice, systemic inhibition of ErbB activity increased myocardial fibroblast senescence and apoptosis and worsened inflammation [62].

NRG 1 is demonstrated that suppress the NLRP 3/caspase-1 pathway and decrease ROS generation by ERK 1/2 inhibition of NOX 4, which attenuates inflammatory responses and cardiac oxidative damage in MI [63]. Erk 1/2 activation is necessary for NRG 1- mediated NOX 4 inhibition [63]. The production of reactive oxygen species (ROS) by NOX 4 is known to activate NLRP 3 inflammatory vesicles [64], stimulate the upregulation of NLRP3 inflammatory vesicles [65], and encourage the organism to initiate an inflammatory response NRG 1 can prevent NLRP3 inflammatory vesicles in a septic cardiomyopathy model [66].

Furthermore, NRG 1 β has been shown to inhibit the expression of COX- 2 (cyclooxygenase 2) in monocyte U937 cells, which reduces the pro-inflammatory response. It has also been shown to have anti-inflammatory antioxidant effects in cardiac cell and tissues through the eNOS/AKT pathways [67].

Previous research has documented NRG 1's function in lowering inflammatory damage in cerebral IR [68]. Studies on NRG 1's anti-inflammatory effects on cardiac tissue, however, are limited.

2. Energy Metabolism and NRG 1

The heart increases its uptake of glucose and reduces its consumption of fatty acids to maintain the high energy demands necessary for sustained contraction under stress condition like insufficiency and stress overload [69]. This not only makes lipid metabolism unable to meet the heart's energy needs, but it also exacerbates oxidative stress [70].

Furthermore, as cardio protective agent, cardiac endothelial cells release NRG- 1 under such stressful circumstances [71]. According to research, NRG 1-ErbB2 signaling produces cardiomyocytes in the area next to the damaged heart in zebrafish to dedifferentiate and



switching to glycolysis from oxidative phosphorylation. This is indicated by an increase in glycolytic genes and a decrease in mitochondrial genes [72].

In obese mice, NRG 1 reduces the double suppression of hepatic gluconeogenesis and cholesterol intake, improving the pharmacokinetic characteristics and providing metabolic advantages [73]. Accordingly, NRG 1 stimulates energy metabolism in both mammals, which greatly decrease regeneration after birth, and zebra fish, which retain regeneration. The NRG 1- ErbB 2 signal is activated in a way that promotes the utilization of glucose energy and decreases the amount of glucose consumed following cardiac injury.

Conclusion

As resulte of the review studies, successful cardiac repair requies three essntial events: the regeneration of the myocardium's hematologic reconstitution, the elimination of interstitial fibrosis, and the replenishment of cardiac cells. Fewer study has been done on the cardiac microenvironment and more on the path of myocardial proliferation following a MI. current research has focused heavily on the promotion of heart healing by the intervention of cardiac growth factor NRG 1 and identify areas that require more investigation.

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