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Neuregulin-1, a potential therapeutic target for cardiac repair

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NRG1 (Neuregulin-1) is an effective cardiomyocyte proliferator, secreted and released by endothelial vascular cells, and affects the cardiovascular system. It plays a major role in heart growth, proliferation, differentiation, apoptosis, and other cardiovascular processes. Numerous experiments have shown that NRG1 can repair the heart in the pathophysiology of atherosclerosis, myocardial infarction, ischemia reperfusion, heart failure, cardiomyopathy and other cardiovascular diseases. NRG1 can connect related signaling pathways through the NRG1/ErbB pathway, which form signal cascades to improve the myocardial microenvironment, such as regulating cardiac inflammation, oxidative stress, necrotic apoptosis. Here, we summarize recent research advances on the molecular mechanisms of NRG1, elucidate the contribution of NRG1 to cardiovascular disease, discuss therapeutic approaches targeting NRG1 associated with cardiovascular disease, and highlight areas for future research.

KEYWORDS

cardiomyocyte proliferation, cardiac repair, cardiovascular disease, neuregulin-1 (Nrg1), therapeutic target

1 Introduction

NRG1 (Neuregulin-1) belongs to the neuregulin family of growth factors responsible for cardiac development and cardiac protection from stress (Lin et al., 2020) and is a protein that plays a central role in cell signaling in the heart, mammary gland, and central nervous system (Falls, 2003; Mei and Nave, 2014). As a cardiac regeneration growth factor, NRG1 has attracted the attention of cardiovascular medicine. NRG1 has been shown to not only stimulate cardiomyocyte proliferation (Zhao et al., 1998; Bersell et al., 2009; D'Uva et al., 2015), but also act within angiogenesis, extracellular matrix remodeling, cardiomyocyte proliferation, stem-cell recruitment, and others, that improve cardiac function (Mendes-Ferreira et al., 2016; Rebouças et al., 2016; Arora et al., 2021). Together, these mechanisms promote myocardial repair and improvement of

the cardiac function, that providing a novel molecular strategy targeting at regenerating the injured myocardium.

NRG1 is a powerful cardiovascular proliferation stimulant that is essential to the differentiation, proliferation, and expression of cardiac cells (Gassmann et al., 1995; Lee et al., 1995; Meyer and Birchmeier, 1995). NRG1 administration activates multiple signaling pathways to stimulate reentry and division of the adult cardiomyocyte cycle (D'Uva et al., 2015; Lin et al., 2015) and induce myocardial regeneration. Exogenous administration of NRG1 promotes the expression of genes related to the type of work (Zhu et al., 2010) and induces cardiomyocyte differentiation into cardiac conduction system cells (Rentschler et al., 2002), promotes stem cell differentiation into working-type cardiomyocytes (Suk Kim et al., 2003), and improves cardiac tissue function after pathological injury (Mendes-Ferreira et al., 2016; Kundumani-Sridharan et al., 2021; Sun et al., 2021), and are the most promising molecules for promoting cardiac repair under experimental conditions and clinical trials (Gao et al., 2010; Jabbour et al., 2011a; Polizzotti et al., 2015). Herein, this article summarizes the molecular mechanisms of NRG1 and its recent findings in cardiovascular biology, clinical applications in cardiovascular repair, and proposed areas of future research.

2 NRG1 and its regulation

NRG1's regulatory mechanisms are complex and include a number of signalling, molecular, and metabolic pathways. Therefore, the molecular structure of NRG1, transcription regulation modes, and the interactions of signal pathways were summarized in this part.

2.1 Basic structure of NRG1

NRG1 is the most characteristic member of the neuregulin family (Huang et al., 2015a). The NRG1 gene is found on chromosome 8 in humans and mice and on chromosome 16 in rats (Falls, 2003; Chou and Ozaki, 2010). NRG-1 encodes 21 exons (Peles et al., 1992; Steinhorsdottir et al., 2004) and generates 31 potential protein isoforms (Mei and Xiong, 2008). Depending on the structure, NRG1 isoforms are classified into six types I-VI (Meyer et al., 1997; Steinhorsdottir et al., 2004). Although different isoforms of NRG1 are expressed in cells with different efficiencies, all can complete their signaling communication with ligands (Cote et al., 2005).

NRG1 consists of NH₂-terminal ECD (extracellular structural domains), transmembrane structural domains, and highly conserved COOH-terminal ICD (intracellular structural domains) (Falls et al., 1993; Buonanno and Fischbach, 2001; Bao et al., 2004). NRG1-ECD binds to ErbB to activate ErbB signaling in target cells (Marchionni et al., 1993). It can be transferred to

the nucleus and inhibit the expression of several apoptotic regulators (Bao et al., 2004). The interaction between ErbB and ECD in cells can occur after the release of NRG1-ECD or directly after the synthesis of isoforms lacking isoforms lacking transmembrane structural domains or after protein hydrolysis in the form of transmembrane precursors (Stonecypher et al., 2006; Yin et al., 2015). NRG1-ErbB interactions can also occur in cell-cell contact (Leimeroth et al., 2002). NRG1-ICD is required for NRG1 function *in vivo* (Liu et al., 1998), interaction of CRD (cysteine-rich domain) with ErbB receptors triggers signals required for CRD-NRG1 expression cells (Bao et al., 2003), and ectopic expression of NRG1 leads to NRG1-ICD dependent apoptosis (Grimm and Leder, 1997; Grimm et al., 1998).

NRG1 is homologous to the EGF (epidermal growth factor) family (Marchionni et al., 1993; Garratt et al., 2000) and shares an EGF-like structural domain with all isoforms (Buonanno and Fischbach, 2001). The EGF-like structural domain is encoded by a common "core" exon that encodes the 5'-terminus of the EGF-like structural domain and is spliced with one of two different exons that encode the 3'-terminus of the EGF-like structural domain to produce different variants of the EGF-like structural domain (α and β) of NRG1, respectively (Buonanno and Fischbach, 2001; Falls, 2003). NRG1 α is expressed at higher levels than NRG1 β (Cote et al., 2005), while NRG1 β having a higher affinity for ErbB4 than NRG1 α (Plowman et al., 1993; Du et al., 2012). This differential may have important effects on the organism. Animal experiments have shown that NRG1 β knockout mice are embryonically lethal (Meyer and Birchmeier, 1995; Kramer et al., 1996), whereas NRG1 α knockout mice survive into adulthood with only significant defects in the alveolar development of the mammary lobe (Li et al., 2002). Even more important, NRG1 α enhances cell adhesion molecule l1 expression in human glioma cells and promotes their migration as a function of malignancy (Zhao and Schachner, 2013). These suggest that NRG1 β may play a more important role in survival than NRG1 α . And another *in vitro* experiment on cardiac muscle cells further explored the effects of both on cardiac energy metabolism. NRG1 β is a more potent activator of receptor phosphorylation and intracellular signaling than the NRG1 α , and only NRG1 β stimulated glucose uptake and protein synthesis (Cote et al., 2005). It means that only NRG1 β are biologically active on cardiac myocytes although cardiac microvascular endothelial cells express multiple NRG1 isotypes (Cote et al., 2005) (Figure 1).

2.2 Regulation of NRG1

2.2.1 Post-translational modifications

In "reverse signaling," the C-terminal fragment of pro-NRG1 (NRG1 precursor) is generated by extracellular cleavage to release mature NRG1 and is further cleaved by γ -secretase to

generate NRG1-ICD, which relocates to the nucleus to regulate gene transcription (Loeb et al., 1998; Wang et al., 2001). NRG1 expressed in the heart is a pro-NRG1 transmembrane protein that requires protease processing for activation (Cote et al., 2005). Earlier studies showed that the ADAM (a disintegrin and metalloproteinase) family of MMP (matrix metalloproteinases), specifically ADAM17 and ADAM19, play a role in the release of pro-NRG1 from the endothelial membrane (Montero et al., 2000; Shirakabe et al., 2001; Shi et al., 2003; Kurohara et al., 2004). Follow-up studies have shown that ADAM17 is the main protease involved in pro-NRG1 release, while ADAM19 does not play a role (Horiuchi et al., 2005). This indicates that other proteins that can activate pro-NRG1 may be involved, as the ADAM17-deficient mouse was expressed differently from the NRG1-deficient mouse in terms of heart defects in the embryo (Horiuchi et al., 2005). NRG1 mRNA expression and protein synthesis are mediated by neurohormones (such as angiotensin II, phenylephrine, endothelin 1) and the mechanical pressure (Lemmens et al., 2006). These factors stimulate the expression of mRNA of NRG1 by inhibiting the expression level of NRG1 (Lemmens et al., 2006). ENOS (endothelial nitric oxide synthesis) also regulates the expression of NRG1 expression, and recent studies have found that endothelial cell increases its expression of NRG1 when NO production is eliminated (Shakeri et al., 2021), and the two complement each other through the paracrine pathway.

2.2.2 NRG1-ErbB signal pathway

NRG1 is produced mainly by endocardial vascular endothelial cells (Russell et al., 2014) and is an endogenous ligand of the ErbB family (Bouyain et al., 2005). NRG1 functioned through the receptor ErbB that all the biological effects of NRG1 were significantly reversed by the co-administration of NRG1 and ErbB inhibitor (Ding et al., 2021). The ErbB family consists of (ErbB1/EGFR), ErbB2 (HER2), ErbB3 (HER3) and ErbB4 (HER4) (Olayioye et al., 2000). All ErbB receptors are expressed on cardiac endothelial cells, fibroblasts and highly proliferative cells (Yarden and Sliwkowski, 2001), with ErbB3 and ErbB4 highly expressed on monocytes and cardiac macrophages (Carraway and Cantley, 1994; Campreciós et al., 2011), and ErbB2, ErbB4 on adult cardiomyocytes (Ma et al., 2016). The NRG1 gene encodes multiple isoforms of ErbB ligands (Pinkas-Kramarski et al., 1998; Buonanno and Fischbach, 2001). Although NRG-encoded protein isoforms by NRG differ greatly in their overall structure, the structural domain similar to EGF is sufficient to binding to receptors and trigger signals (Holmes et al., 1992).

NRG “forward” signaling, i.e., signaling from NRG-producing cells to NRG-responsive cells, leads to cellular responses, including stimulation or inhibition of proliferation, apoptosis, migration, differentiation, and adhesion (Yarden and

Sliwkowski, 2001). In typical positive signaling, NRG1 binds to ErbB3 and ErbB4 ECD in differentiated cardiomyocytes and induces conformational changes (Jones et al., 1998), gaining higher affinity for other ErbB receptors (Kataria et al., 2019). NRG1 ligand binding triggers homodimerization of ErbB4 and heterodimerization of ErbB2/3, ErbB2/4, ErbB3/4 (Carraway and Cantley, 1994; Sweeney et al., 2001; Yarden and Sliwkowski, 2001), followed by downstream signaling through the central pathway (Xu et al., 2010; Fernandez-Cuesta et al., 2014). In some studies, the NRG1-ErbB pathway is believed to be a compensatory protective mechanism for cardiac injury (Bersell et al., 2009; Odiete et al., 2012; Dugaucquier et al., 2020). The NRG1-ErbB signaling axis is a critical mediator of cardiac development, and growing evidence supports a role for this system in the intricate cross-talk between the microvascular endothelium and myocytes in the adult heart.

2.2.3 Signaling cascades

1) NRG1-Hippo-YAP pathway

NRG1-ErbB4 has been shown to strongly regulate the Hippo-YAP (Yes-associated protein) pathway (Haskins et al., 2014). Haskins et al. identified the transcriptional program induced by NRG1-ErbB4 signaling as the true molecular signature of the Hippo-YAP pathway by analyzing the expression of YAP-regulated genes in several functional readouts of the NRG1 activation pathway (Haskins et al., 2014). NRG1 administration stimulates re-entry and division of the adult cardiomyocyte cycle by triggering ErbB2/ErbB4-dependent inhibition of the Hippo-YAP signaling pathway (Bersell et al., 2009; D’Uva et al., 2015; Lin et al., 2015), increasing cardiomyocyte numbers rather than hypertrophic growth (D’Uva et al., 2015; Lin et al., 2015).

The components of the Hippo pathway are divided into two main categories: core kinase modules and transcriptional modules, of which the kinase modules include MSTs (mammalian sterile 20-like kinases), LATSs (large tumor suppressor kinases), SAV1 (salvador homolog 1), MOB1s (mops one binder kinase activator proteins), and RASSFs (ras associated domain family), which are responsible for the repression of the transcriptional coactivator YAP and its homologue TAZ (transcriptional coactivator with PDZ binding motif). When the Hippo signaling pathway is activated, MST1/2 forms a complex with SAV1 that phosphorylates and activates the LATS1/2-MOB1 complex, which phosphorylates YAP and TAZ, and the phosphorylated YAP and TAZ pathway complexes are moved out of the nucleus, where they remain in the cytoplasm and are degraded by the protease system to lose transcriptional activity (Zhang and Re, 2017). This prevents their nuclear localization and thus inhibits cardiomyocyte proliferation (Heallen et al., 2011a; Dey et al., 2020). When the Hippo-YAP signaling pathway is inhibited, YAP dephosphorylates and translocates to the nucleus to bind to

transcription factors such as TEAD (transcriptional coactivator with PDZ binding motif) to initiate the transcriptional process to promote mitosis (Lin and Pu, 2014). Therefore, outside the regeneration window, this suggests that modulation of the NRG1-Hippo-YAP pathways could unlock adult mammals' ability to regenerate their hearts.

There is increasing evidence that YAP signaling interacts with PI3K (phosphatidylinositol-3-kinase)-AKT (a serine/threonine kinase) signaling to positively regulate cardiomyocyte cycle progression (Sudol, 2014; Lin et al., 2015). ErbB4 activates PI3K signaling in response to IGF (insulin-like growth factor) which plays a role in promoting cardiomyocyte growth and inhibiting fibrosis (MeiKim et al., 2013). YAP activates the IGF-PI3K signaling pathway in cardiomyocytes, leading to inactivation of GSK3 β (glycogen synthase kinase 3 β) and an increase in its downstream β -catenin content (Xin et al., 2011a). Furthermore, YAP can directly target the expression of Pik3cb (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta), the catalytic subunit of PI3K, to activate the PI3K-AKT pathway (Lin et al., 2015) to indirectly promote β -catenin activity.

2) NRG1-PI3K-AKT pathway

NRG1-ErbB4 can inhibit through PI3K-AKT pathway macrophages to reduce myocardial inflammation and fibrosis (Vermeulen et al., 2017), while inhibiting cardiac endoplasmic reticulum stress to reduce reperfusion injury (Fang et al., 2017). NRG1 maintains cardiac troponins by the ErbB2-PI3K pathway, which may lessen doxorubicin-induced cardiac dysfunction (Bian et al., 2009). Together, these studies confirmed that the activation of the NRG1-ErbB pathway plays a protective role in myocardial injury and may be involved in cell apoptosis and differentiation, as found in studies that NRG1/ErbB2 regulates cell differentiation and apoptosis through the PI3K/Akt pathway (Hong et al., 2021; Lu et al., 2021; Mahiny-Shahmohammady et al., 2022). *In vitro*, NRG1 treatment up-regulated ErbB3 phosphorylation, and increased the expression of PI3K and phosphorylation-AKT (Meng et al., 2021) to modulate the activation of PI3K-AKT pathway. In conclusion, NRG1 can act on ErbB2, ERBB3 and ERBB4, respectively activates PI3K-AKT pathway.

EGF induces YAP nuclear accumulation through PI3K-dependent blockade of YAP phosphorylation. EGF triggers the rapid translocation of YAP into the nucleus along with YAP dephosphorylation, both of which depend on LATS. EGF receptor inhibits the Hippo pathway through activation of PI3K and PDK1, but independent of AKT activity. The entire Hippo core complex dissociates in response to EGF signaling in a PI3K-PDK1-dependent manner, leading to inactivation of LATS, dephosphorylation of YAP, and YAP nuclear accumulation and transcriptional activation of its target gene. In turn, activated YAP induces transcription of amphiregulin (Zhang et al., 2009)

and promotes positive feedback regulation of Hippo signaling by activation of EGF receptor.

3) other related pathways

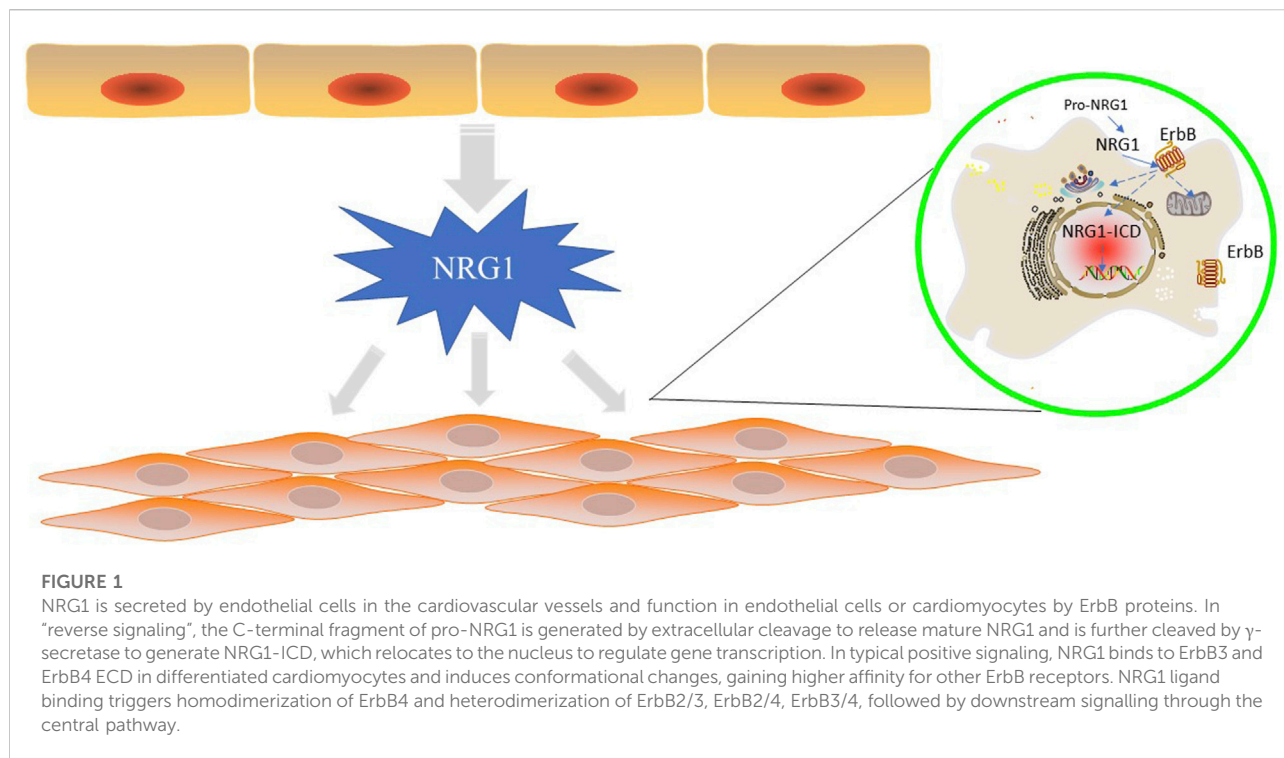
Based on the available literature, it is known that NRG1 can regulate cardiac physiopathological processes through the interaction between Hippo pathway, Wnt pathway, ERK (extracellular signal-regulated kinase) pathway, RISK pathway and mTOR (rapamycin) pathway.

NRG1-ErbB2 is involved in the negative regulation of cardiomyocyte autophagy by activating the PI3K/PKB/mTOR and MAPK (monophosphate-activated protein kinase)/ERK/mTOR pathways (An et al., 2013; Surviladze et al., 2013). Interestingly, recent studies have found that ErbB2 signaling can lead to YAP to promote cell proliferation in an ERK-dependent manner rather than Hippo (Aharonov et al., 2020), and can also indirectly promote the onset of cardiac regeneration through interactions of the AKT and GSK3 β / β -catenin pathway (D'Uva et al., 2015). For example, inactivation of cardiac SAV not only inhibits the Hippo pathway, releasing YAP into the nucleus for direct interaction with β -catenin (Heallen et al., 2013) to enhance its transcriptional activity, but also upregulates the classical Wnt pathway (Heallen et al., 2011b) to act on target genes to promote cell mitosis process.

It has been demonstrated that NRG1 induces upregulation of ligand protein expression to promote the differentiation of embryonic stem cells into working cardiomyocytes via MEK (mitogen-extracellular activated protein kinase)-ERK (Zhu et al., 2010; Wang and Huang, 2014). In cardiac transplantation, rhNRG1 (recombinant human NRG1) attenuates left ventricular remodeling and myonodal disorders by up-regulation of the RISK pathway (Liu et al., 2006; Gao et al., 2010) to create conditions to maintain donor heart function. Due to the interaction between signaling pathways and other signal crosstalk between cells, the signaling cascades of NRG1 is still unclear, and further research is still needed.

3 NRG1 with cardiovascular diseases

The downstream signaling of NRG1 acts mainly in the ventricular wall, heart valves and conduction system, and microvasculature (Rupert and Coulombe, 2015). In this section, we summarize the physiological and pathological roles of NRG1 in cellular and cardiovascular tissues to fully illustrate the important role of NRG1 in the development of cardiovascular diseases. Novel research shows that NRG1 plays an important role in the occurrence and development of cardiovascular diseases, such as atherosclerosis, MI/IR, HF, cardiotoxicity, and arrhythmia. We summarize the role of NRG1 in cardiovascular diseases (Figure 2) in conjunction with the related pathways. In addition, animal experiments and clinical



studies related to the treatment of cardiovascular diseases by NRG1 are summarized in Table 1.

3.1 NRG1 and atherosclerosis

3.1.1 NRG1 and cell aging

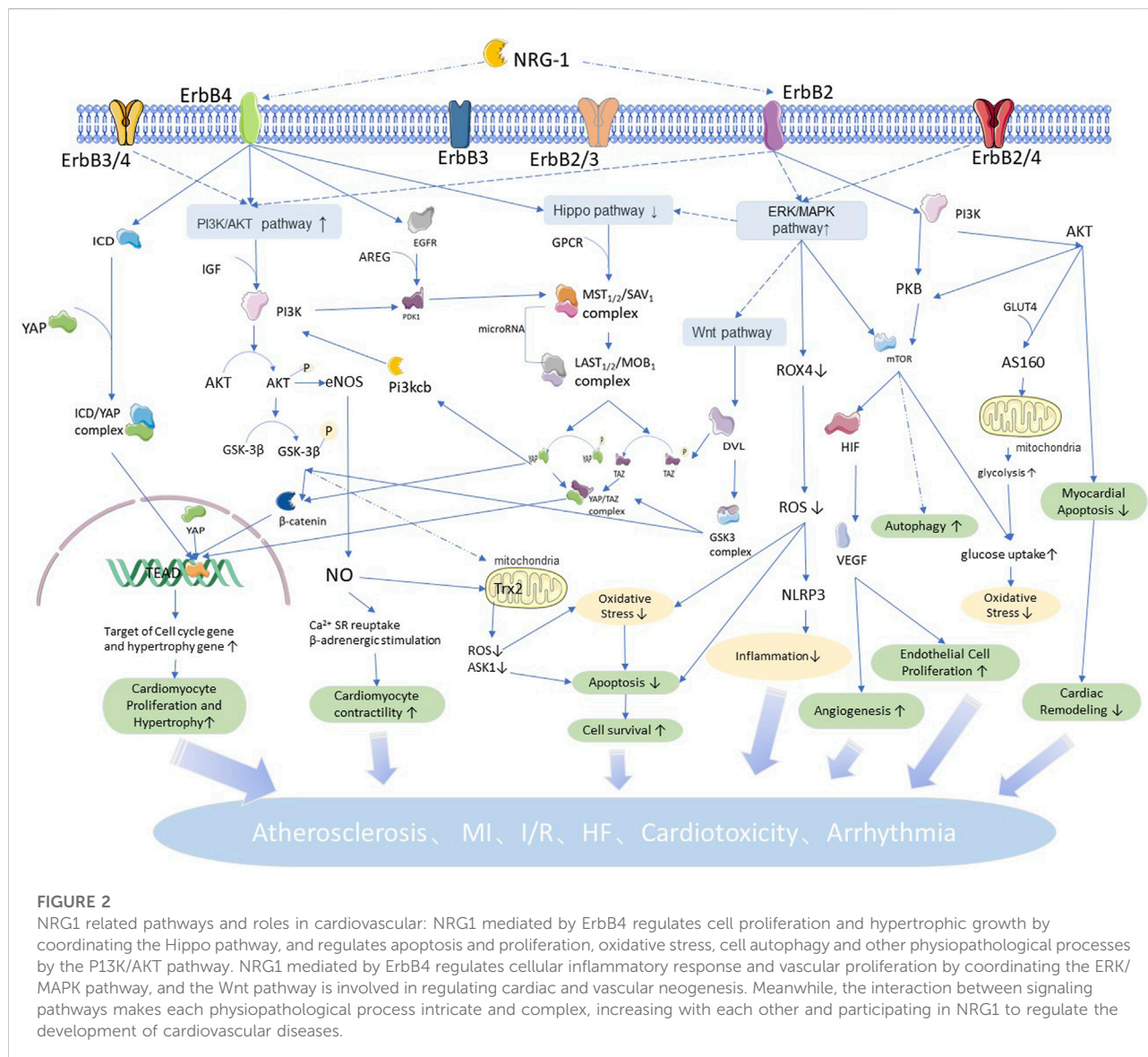
Cellular senescence is driven by chronic inflammation and oxidative stress. The senescence of EC (endothelial cell) and VSMC (vascular smooth muscle cell) can cause atherosclerosis (Minamino and Komuro, 2008; Nakano-Kurimoto et al., 2009; Wang and Bennett, 2012), and cellular senescence and SASP (senescence-associated secretory phenotype) play an important role in cardiovascular aging and disease (Gorenne et al., 2006; Minamino and Komuro, 2007; Sikora et al., 2011). Cells can enter a state of senescence caused by DNA damage due to intrinsic and extrinsic stressors, called “stress-induced premature senescence” (SIPS) (Correia-Melo et al., 2014). Oxidative stress and hyperglycemia are the two main factors that contribute to SIPS (Gorenne et al., 2006; Minamino and Komuro, 2007; Sikora et al., 2011).

NRG1 is known to have improved glucose metabolism (Pentassuglia et al., 2016) and antioxidant (Wang et al., 2021) effects, so it may have anti-SIPS potential. Data suggests that NRG1 significantly inhibits stress-induced premature senescence in vascular cells *in vitro* and in the aorta of diabetic mice *in vivo* (Shakeri et al., 2018), and application of rhNRG-1 for 9 weeks to type 1 diabetic mice attenuates diabetes-induced vascular

senescence (Shakeri et al., 2018). Consistently, deficiency of the NRG1 receptor ErbB4 induced cellular senescence both *in vitro* and *in vivo* (Shakeri et al., 2018), and diabetes induced significantly more vascular senescence in mice lacking the ErbB4 receptor in SMC compared to wild-type littermates (Shakeri et al., 2018), suggesting the efficacy of NRG1 in anti-cellular senescence. The effects of NRG1 on cell proliferation and apoptosis have been well described (Yarden and Sliwkowski, 2001; Xu et al., 2014), but the effects of NRG1/ErbB signaling on cellular senescence remain to be elucidated.

3.1.2 NRG1 and endothelial cell damage

Previous experiments have demonstrated that NRG1 prevents foam cell formation in primary cultured human monocyte-derived macrophages (Xu et al., 2009). Also, chronic infusion of NRG1 β into ApoE^{-/-} mice inhibited macrophage infiltration in the arterial wall (Xu et al., 2009), it reduced endocytosis of acetylated LDL (low density lipoprotein) and cholesterol ACAT-1 (acyltransferase-1) activity, and it increased cholesterol efflux from human macrophages to apolipoprotein A1 (Xu et al., 2009). This again confirms the inhibitory effect of NRG1 β on atherosclerotic lesions. Co-incubation of VSMCs with norepinephrine and oxidized LDL inhibited NRG1 expression and induced proliferation and phenotypic transformation of VSMCs (Jiao et al., 2008). NRG1 reduces proliferation and migration of neointima formation after vascular injury in rats by reducing VSMCs (Clement et al., 2007). These findings suggest a negative



correlation between NRG1 expression and proliferation in VSMCs. Stimulation of ErbB3 by NRG1 β has been reported to inhibit EC proliferation (Amin et al., 2006), and ErbB3 may be a potential therapeutic target of the NRG1-ErbB pathway against atherosclerosis.

3.1.3 NRG1 and vascular stress

In addition, the NRG1/ErbB signaling system is essential for the response to vascular stress (Parodi and Kuhn, 2014). NRG1 has anti-adrenergic effects on the cardiovascular system (Lemmens et al., 2004) leading to vasodilation. It was shown that microinjection of NRG into the ventral lateral aspect of the medulla oblongata, a major vasodilatory center, reduced blood pressure in rats (Matsukawa et al., 2013). NRG1 β is an activator of nicotinic acetylcholine receptors, which may improve the

atherosclerotic vascular load for cardioprotective effects by balancing the autonomic nervous system (Okoshi et al., 2004).

3.2 NRG1 and myocardial infarction

3.2.1 NRG1 and oxidative stress

Myocardial infarction is characterized by a peak in cardiomyocyte death on the first day (Whelan et al., 2010; Del Re et al., 2019). The latest research shows that no association with other variables, NRG-1 plasma levels decreased significantly following PCI/RIC and remained decreased up to 1 month following AMI (Haller et al., 2022). ROS (Reactive oxygen species) generated in cardiac ischemia-reperfusion induce NRG1 β /ErbB4 activation (Kuramochi et al., 2004a), implying

TABLE 1 The role of NRG1 in cardiovascular disease.

Disease	NRG1 expression	Human studies	Examples of <i>in vivo</i> studies
Heart failure	rhNRG1	Both phase 1 and 2 trials have been completed finding sustained improvement in LVEF in systolic heart failure patients at 90-days follow-up. A phase 3 trial is currently on going. (Gao et al., 2010; Jabbour et al., 2011b)	rhNRG1 produced global improvements in cardiac function in a canine model of pacing-induced heart failure. (Liu et al., 2006) rhNRG1 can significantly improve left ventricular remodeling and cardiac function in the failing heart, this beneficial effect is related to reducing mitochondrial dysfunction, myocyte apoptosis and oxidative stress. (Guo et al., 2012) rhNRG1 treatment attenuates pulmonary arterial and right ventricular remodelling and dysfunction in a rat model of monocrotaline-induced pulmonary arterial hypertension, and has direct anti-remodelling effects on the pressure-overloaded right ventricular. (Mendes-Ferreira et al., 2016) #FF0000 NRG1 induces cardiac hypertrophy and impairs cardiac performance in post-myocardial infarction rats. (Zurek et al., 2020)
Atherosclerosis	rhNRG1	The effect of job strain on early atherosclerosis is dependent on NRG1 genotype in men. (Hintsanen et al., 2007)	rhNRG1 treatment induced systemic activation of ErbB2 and ErbB4 receptors in both heart and kidneys and prevented left ventricular dilatation, improved left ventricular contractile function, and reduced atherosclerotic plaque size. (Vandekerckhove et al., 2016) #FF0000 rhNRG1 improved cardiac performance, with the survival benefits in the ischemic model being additive to those of angiotensin-converting enzyme inhibitor therapy. (Liu et al., 2006) cMLCK is a downstream effector of rhNRG-1 involved in rhNRG1-induced cardiac function improvement. (Gu et al., 2010)
Myocardial infarction	rhNRG1	A single sample determination of NRG1 β at emergency departments presentation is not predictive of a final diagnosis of MI or acute coronary syndrome. (Yiadom et al., 2016)	#FF0000 Overexpression of ErbB4 rejuvenates aged mesenchymal stem cells and enhances angiogenesis via PI3K/AKT and MAPK/ERK pathways. (Liang et al., 2019) The concentration of NRG1 was rapidly upregulated after myocardial IR. NRG1 preconditioning with an optimal concentration of 4 μ g/kg has cardioprotective effects against IR injury through a PI3K/Akt-dependent mechanism <i>in vivo</i> . (Fang et al., 2010)
Ischemia reperfusion	NRG1	None	#FF0000 Remote ischemic preconditioning play an anti-remodeling and anti-inflammatory role by acting of the NRG1/ErbB3 signal. (Pilz et al., 2019)
Cardiotoxicity	Engineered bivalent NRG1 β	None	Engineered bivalent NRG1 β promotes cardiomyocyte survival and improves cardiac function. Given the reduced proneoplastic potential of Engineered bivalent NRG1 β versus NRG, engineered bivalent NRG1 β has translational potential for cardioprotection in patients with cancer receiving anthracyclines. (Jay et al., 2013)

cMLCK, cardiac myosin light chain kinase; IR, ischemia reperfusion; rhNRG1, human recombinant NRG1.

that NRG1 β /ErbB4 signaling regulates myocardial injury in an environment of oxidative stress. NADPH oxidase 4 (NOX4) is the major ROS synthesizing enzyme in cardiac tissue (Matsushima et al., 2014). Previous experiments have demonstrated that NRG1 can inhibit NOX4 activity by activating the ERK1/2 (Wang et al., 2018) pathway in

myocardial reperfusion injury, thereby downregulating ROS production (Caja et al., 2009). Specific overexpression of ErbB2 in young rat hearts induces the expression of antioxidant genes such as mitochondrial GPx1 (glutathione peroxidase 1) and catalase (Belmonte et al., 2015). NRG1 can inhibit hydrogen peroxide by acting ErbB4-Akt signaling or by

direct activation of paracrine signaling by ErbB4 independent of NRG in adult rat ventricular myocytes (Kuramochi et al., 2004a), thus inhibiting hydrogen peroxide stimulated adult rat ventricular myocytes apoptosis (Kuramochi et al., 2004a) to achieve self-protection. Thus, NRG1 exerts an anti-apoptotic effect on myocardium by coordinating the oxidative stress process.

3.2.2 NRG1 and myocardial inflammatory injury

AMI (acute myocardial infarction) induces blood leukocytosis, which is negatively correlated with patient survival (Jiang et al., 2022). Excessive inflammation in endangered myocardial regions induced by MI can lead to increased cardiomyocyte death through pro-apoptotic signaling pathways and further cardiac remodeling (Nahrendorf et al., 2010; Griffiths et al., 2017). NRG1 receptor epidermal growth factor receptors ErbB2 and ErbB4 were expressed on cardiac fibroblasts in the infarct area. Systemic blockade of ErbB function in MI model mice enhanced senescence and apoptosis of cardiac fibroblasts and exacerbated inflammation (Shiraishi et al., 2022).

It has been shown that NRG1 can reduce ROS production through ERK1/2 inhibition of NOX4 and inhibit the NLRP3/caspase-1 pathway, thereby attenuating myocardial oxidative damage and inflammatory responses in MI (Wang et al., 2021). NRG1-mediated NOX4 inhibition is dependent on ERK1/2 activation (Wang et al., 2021). NOX4-mediated ROS production promotes activation of NLRP3 inflammatory vesicles (Abais et al., 2015; Moon et al., 2016), stimulates upregulation of NLRP3 inflammatory vesicles (Kawaguchi et al., 2011; Sandanger et al., 2013), and promotes activation of the inflammatory response by the organism. In a model of septic cardiomyopathy, NRG1 can inhibit NLRP3 inflammatory vesicles (Abais et al., 2015). NRG1 β has also been reported to reduce the pro-inflammatory response by attenuating COX-2 (cyclooxygenase 2) expression in monocyte U937 cells (INVALID CITATION) and can also exert anti-inflammatory antioxidant effects in myocardial tissues and cells by activating AKT/eNOS pathways (Kuramochi et al., 2004a; Timolati et al., 2006; Brero et al., 2010). The role of NRG1 in reducing inflammatory damage in cerebral IR has been previously reported (Wu et al., 2015). However, studies on the anti-inflammatory effects of NRG1 in myocardial tissue are limited.

3.2.3 NRG1 and energy metabolism

Under stress conditions such as insufficiency and stress overload, lipid metabolism not only cannot meet the heart's energy needs, but also exacerbates oxidative stress (Opie, 1976), with the heart increasing glucose uptake and decreasing the consumption of fatty acids to maintain the high energy demands required for sustained contraction (Shao and Tian, 2015; Riehle and Abel, 2016; Szablewski, 2017). Under such stressful conditions, myocardial endothelial cells also release

NRG1 as a cardioprotective factor (Kuramochi et al., 2004a; Hedhli et al., 2011). NRG1-ErbB2 signaling has been found to induce cardiomyocytes in the border region of the injured heart to dedifferentiate and shift their metabolism from oxidative phosphorylation to glycolysis in zebrafish, as evidenced by the decrease in mitochondrial genes and the increase in glycolytic genes (Honkoop et al., 2019). NRG1 improves the pharmacokinetic properties and produces metabolic benefits by reducing the double inhibition of hepatic gluconeogenesis and cholesterol intake in obese mice (Zhang et al., 2018). These results indicate that NRG1 promotes energy metabolism in zebra fish, which maintain regeneration, and in mammals, which significantly reduce regeneration after birth. The activation of the NRG1-ErbB2 signal helps to reduce glucose consumption after heart damage and promote the use of glucose energy. RhNRG1 increases glucose uptake by neonatal rat ventricular myocytes through ErbB2/ErbB4 and PI3K (Liu et al., 2006). In the adult heart, glucose uptake by cardiac myocytes is believed to be primarily achieved by the glucose transporter protein GLUT4 (glomerular glucose transporter 4) (Shao and Tian, 2015; Riehle and Abel, 2016). In a neonatal rat ventricular myocyte model, similar to insulin, rhNRG1 can induce glucose uptake by activating the PI3K-Akt-AS160 (Akt substrate of 160 kDa) pathway and GLUT4 translocation, and unlike insulin, the rhNRG1-induced effects are not mediated by insulin receptorsubstrate proteins (Liu et al., 2006). RhNRG-1 has been shown to enhance glucose uptake by neonatal rat ventricular myocyte through a mechanism associated with the ErbB2/ErbB4, PI3K-Akt (Pentassuglia et al., 2016).

The mammalian target of mTOR regulates human cardiac protein synthesis and energy metabolism (Laplane and Sabatini, 2012; Saxton and Sabatini, 2017). MTORC1 activity, a complex of mTOR, is associated with protein synthesis and physiological hypertrophy, and mTORC2, another complex, regulates glucose uptake (Kumar et al., 2008; Liu et al., 2014; Sato et al., 2014). NRG1 β has a direct and specific stimulatory effect mediated by mTOR in the cardiac myocyte signaling cascade with direct and specific stimulatory effects (Pentassuglia et al., 2016). ErbB receptor activity is associated with mTOR signaling, and mTOR inhibitors improve the outcome of ErbB2-positive breast cancer (Vicier et al., 2014). Although mTOR inhibition appears to have therapeutic value in cancer, cardiomyocyte mTORC1 deficiency leads to cardiac dysfunction in mice (Zhang et al., 2010; Shende et al., 2011). In a rat neonatal cardiomyocyte model, NRG1/ErbB signaling enhances glucose uptake and protein synthesis, but NRG1 β -induced mTORC1 plays a minor role in protein synthesis, while mTORC2 appears to be independent of glucose uptake (Pentassuglia et al., 2016).

3.2.4 NRG1 and cell multiplication

Hypertrophic growth, multinucleation, and polyploids are characteristics of cardiovascular cells in mammals, and are the underlying cause of changes in cardiac cell growth before and

after birth (Ikenishi et al., 2012; Tane et al., 2015). Cardiomyocytes undergo this process rapidly in infarcted and failing hearts in response to growth stimuli, leading to an increase in the number of multinucleated and polyploid cells in damaged myocardial tissue (Herget et al., 1997; Tevzadze et al., 2005; Stephen et al., 2009; Lázár et al., 2017; Kajstura et al., 2010), and cardiomyocytes grow hypertrophically without being able to achieve a quantitative increase. Furthermore, as the heart ages and the myocardium is released from the cell cycle, Hippo activity increases significantly, while YAP activity decreases considerably (Heallen et al., 2013; von Gise et al., 2012) and cell proliferation is endogenously inhibited. In recent years, clinical trials of the new approach to stem cell transplantation have shown limited success, but long-term effectiveness remains unknown (Wei et al., 2019; Hotham and Henson, 2020; Schwach et al., 2020). NRG1 was found to promote mitosis through ErbB (D'Uva et al., 2015) for efficient cell proliferation.

In mice, NRG1 administration has been shown to induce proliferation and cardiac regeneration in adult cardiomyocytes (Bersell et al., 2009). In fact, transient induction of ErbB2 signaling in juvenile and adult mice cardiomyocytes was sufficient to strongly induce cardiomyocyte dedifferentiation and proliferation and to trigger cardiac regeneration after myocardial infarction (D'Uva et al., 2015). In zebrafish, NRG1 is dramatically induced in perivascular cells after cardiac injury, and inhibition of its co-receptor ErbB2 disrupts the proliferative response of cardiomyocytes to injury (Gemberling et al., 2015). Following ischemic heart injury in adolescents or adults, transient expression of ErbB2 similarly triggers cardiomyocyte dedifferentiation, proliferation, neointima formation, and cardiomyocyte redifferentiation, which together lead to anatomical and functional regeneration (Lee et al., 1995; Lai et al., 2010; Liu et al., 2010; Staudt et al., 2014). This provides a definitive clinical experimental basis for the ability of NRG1-ErbB2 to effectively promote cell proliferation. Furthermore, NRG1-ErbB4 has been shown to induce mononuclear cardiomyocyte proliferation without affecting the level of apoptotic cell death (Zhu et al., 2010). These evidences suggest the feasibility of NRG1-ErbB pathway expression for myocardial regeneration as well as a clear value for clinical studies. However, as the organism matures, the cardiac level of ErbB2 decreases and its mitogenic promoting effect is significantly weaker in late postnatal development and adulthood than in the neonatal period (D'Uva et al., 2015; Polizzotti et al., 2015; Aharonov et al., 2020). Therefore, the strategy of combining NRG1 with ErbB2 overexpression or ErbB2-inducible factors should be further explored.

In the NRG1-Hippo-YAP signaling axis, deletion of YAP in the embryonic heart prevents cardiomyocyte proliferation and leads to myocardial dysplasia (von Gise et al., 2012; Xin et al., 2011b). In contrast, deletion of Sav1 or LST1/2, upstream negative regulators of YAP, and cardiomyocyte-specific hyperactivation of YAP increases embryonic cardiomyocyte

proliferation (Heallen et al., 2011a; Heallen et al., 2013; von Gise et al., 2012; Xin et al., 2013). However, these experiments induce adult cardiac regeneration by inducing early cardiomyocytes with strong regenerative capacity, with limited clinical operability and application. Also, in this pathway, its downstream effector YAP/TAZ complex is overactivated in human cancers and is a hallmark of cancer. Therapeutic YAP/TAZ activation may contribute to the development of cancer (Harvey et al., 2013; Janse van Rensburg et al., 2018). The ability to harness the regenerative power of YAP/TAZ in a safe manner is critical for clinical application.

3.2.5 NRG1 and angiogenesis

NRG1 is also a proangiogenic factor that plays an important role in angiogenesis and arteriogenesis after ischemic injury (Hedhli et al., 2012). Myocardial ECs upregulate NRG1 release during ischemic injury (Fukazawa et al., 2003; Hedhli et al., 2011). The receptor for NRG1, ErbB2, was found to be expressed only in ECs, but not in cardiomyocytes from adult mouse hearts (Kundumani-Sridharan et al., 2021). NRG1-ErbB2 can regulate angiogenesis not only through the activation of HIF-1 α (hypoxia-inducible factor-1 α) via the PI3K/AKT/mTOR pathway (Karar and Maity, 2011), but also through paracrine up-regulation of VEGF to induce angiogenesis (Xu et al., 2010). In a study by Kundumani Sridharan (Kundumani-Sridharan et al., 2021) et al., it was shown that NRG1 β -ErbB2 signaling also protects ECs through the ErbB2/4-cSrc-NO axis and the ErbB2/4-ATG5-Trx2 (thioredoxin-2) axis. Although it is difficult to perform pro-angiogenic therapy after AMI (Grines et al., 2002; Hedman et al., 2003; Henry et al., 2003; Wu et al., 2021), proangiogenic therapy still has the potential to benefit patients in the acute phase of IR (Wu et al., 2021).

NRG1 regulates endothelial progenitor cell biology by affecting their survival and differentiation capacity (Safa et al., 2011; Hedhli et al., 2012). EPDCs (epicardial-derived cells) are transformed from epicardial progenitor cells and develop into cardiac fibroblasts and VSMCs (Acharya et al., 2012; Katz et al., 2012), which are essential for myocardial and coronary vascular development (Smits et al., 2018). Consecutive genetic and pharmacological studies have also shown that the arrest of fibroblast differentiation is mediated by YAP, which controls both the composition of ECM (extracellular matrix) and vascular remodeling during cardiac development (Xiao et al., 2018). Although the role of the NRG1-Hippo-YAP pathway in noncardiomyocytes remains less clear, these findings suggest that the NRG1-Hippo-YAP pathway is required for cardiac fibroblast differentiation and coronary vascular development.

3.3 NRG1 and ischemia reperfusion

The ischemic and hypoxic myocardial microenvironment leads to myocardial injury, induces an inflammatory response (Li

et al., 2021), and initiates self-repair processes such as apoptosis and autophagy (Steffens et al., 2020). In the endothelium, IR injury leads to activation of EC (i.e., expression of pro-inflammatory molecules), increased permeability and edema, and impaired vasodilation (Wan and Rodrigues, 2016; Colliva et al., 2020; Wagner and Dimmeler, 2020). In turn, endothelial injury and dysfunction promote vasoconstriction, thrombosis, and coronary occlusion, leading to cardiac inflammation and injury, adverse cardiac remodeling, and hypertrophy (Prabhu and Frangogiannis, 2016; Gibb et al., 2020; Erkens et al., 2021).

NRG1 preconditioning protects the heart against ischemia/reperfusion injury through a PI3K/Akt-dependent mechanism (Fang et al., 2010). In Langendorff analyzes, the ErbB4 inhibitor suppressed the phosphorylation of ErbB4 and the RISK pathway and aggravated myocardial edema and fiber fracture, thereby inhibited the cardioprotective effects of NRG1 (Wang et al., 2018). For assessment of downstream signals, the PI3K inhibitor and the MEK inhibitor suppressed the phosphorylation of AKT and ERK1/2 respectively and abolished the cardioprotective effects induced by NRG1 (Wang et al., 2018). Another experiment further confirmed this idea, and proposed that NRG1 might protect the heart from IR damage by inhibiting endoplasmic reticulum stress through the PI3K-Akt pathway (Fang et al., 2017). Endothelial colony-forming cells were capable of actively releasing NRG1, which, in turn, reduced apoptosis and increased the proliferation of human pluripotent stem cell-derived cardiomyocytes via the PI3K/Akt signaling pathway (Hong et al., 2021), while transcriptional silencing of NRG1 abrogated these cardioprotective effects. Moreover, endothelial colony-forming cells are uniquely suited to support human pluripotent stem cell-derived cardiomyocytes, making these progenitor cells ideal for cardiovascular regenerative medicine (Hong et al., 2021).

RIPC (remote ischemic preconditioning) is an interventional procedure in which multiple short-cycle IR cycles applied in a remote vascular bed can prevent IR injury. The endothelial NRG1 β -ErbB2 signaling pathway has been shown to have a good protective effect in RIPC-induced cardiac injury (Hedhli et al., 2011; Lemmens et al., 2011; Parodi and Kuhn, 2014; Kundumani-Sridharan et al., 2021). RIPC rescues the loss of mitochondrial Trx2 mediated by IR through NRG1 β -dependent protection against endothelial ErbB2 loss in mice is an important previously unrecognized mechanism of RIPC-mediated protection against MI (Kundumani-Sridharan et al., 2021). Trx2 has been shown to inhibit mitochondrial ROS generation and ASK1 (apoptosis signal-regulated kinase 1) to maintain cardiac function (Huang et al., 2015b). NO is known to alter autophagy and endothelial cell NO production may inhibit cardiomyocyte autophagy leading to loss of Trx2 (Sarkar et al., 2011). Loss of Trx2 in cardiomyocytes leads to activation of ASK1 and promotes apoptosis in cardiomyocytes (Huang et al., 2015b). Endothelial ErbB2 reduces ASK1-mediated apoptosis in cardiac tissue by mediating the phosphorylative inactivation of ATG5 (autophagy related 5), thus

inhibiting Trx2 degradation in mitochondria (Kundumani-Sridharan et al., 2021). Up-regulation of the ErbB2/4-ATG5-Trx2 pathway protects against cardiomyocyte apoptosis (Nonn et al., 2003; Huang et al., 2015b), providing a new therapeutic idea against myocardial apoptosis. Although NRG1 has been shown to have a beneficial role in cardiac function, circulating NRG1 levels correlate with the severity of HF (Ky et al., 2009), which is not related to the ability to repair damaged myocardium.

In the NRG1-Hippo-YAP signaling axis, inhibition of Hippo pathway expression can somewhat reduce the level of apoptosis in peri-infarct cardiomyocytes and reduce the expansion of infarct size. YamamotoYang et al. (2003) demonstrated in myocardial infarction model mice experiments that MST1 was significantly activated upon apoptosis and that cardiac-specific overexpression of MST1 transgenes activated mouse apoptosis-associated proteins caspase3 and caspase9 in cardiac tissues, resulting in increased apoptosis in cardiomyocytes (Odashima et al., 2007). On the contrary, specific knockdown of MST1 in their cardiac tissues significantly improved apoptosis in mice (Odashima et al., 2007). Cardiac-specific overexpression of MST1 in mice leads to progressive deterioration of cardiac function (Yamamoto et al., 2003), which may be the result of increased myocardial oxygen consumption and apoptosis due to elevated wall pressure.

3.4 NRG1 and heart failure

3.4.1 NRG1 with myocardial hypertrophy and myocardial fibrosis

During the healing process of heart, damaged myocardial tissue undergoes myocardial hypertrophy, myocardial fibrosis, and ventricular remodeling, ultimately leading to myocardial hyposystolic function and heart failure (Wang et al., 2017a; Lindsey et al., 2018). In cases of heart failure, NRG1/ErbB signaling is significantly impaired (Galindo et al., 2014; Gupte et al., 2017), and administration of NRG1 attenuates the progression of HF, inhibits myocardial fibrosis and apoptosis, and reduces oxidant-producing enzymes (Gupte et al., 2017). Conditional knockout of ErbB2 in mice with accelerated heart failure after stress overload or adriamycin injury (Crone et al., 2002; Ozcelik et al., 2002) showed that the NRG/ErbB pathway acts as a stress response signal between microvascular endothelial cell and myocytes to maintain cell survival and cardiac function.

M2-like macrophage-mediated regulation of NRG1/ErbB signaling has a substantial effect on fibrotic tissue formation in the infarcted adult mouse heart and is critical for suppressing the progression of senescence and apoptosis of cardiac fibroblasts (Shiraishi et al., 2022). A recent study showed that the NRG1 β -ErbB4 pathway also inhibits macrophage activation and reduces myocardial hypertrophy and fibrosis (Vermeulen et al., 2017). The molecular mechanism underlying the regulation of fibrotic tissue formation in the infarcted myocardium was shown in part to be attenuation of apoptosis and senescence of cardiac

fibroblasts by the activation of NRG1/ErbB/PI3K/Akt signaling (Shiraishi et al., 2022).

However, NRG1 has also been proposed to induce cardiomyocyte hypertrophy (De Keulenaer et al., 2019). In a cardiac magnetic resonance study, it was shown that rhNRG1-treated rats had significantly increased left ventricular wall thickness after MI and increased plasma N-terminal B-type natriuretic peptide precursor levels in a rhNRG1 dose-dependent manner (Zurek et al., 2020), confirming the detrimental effects of rhNRG1-induced hypertrophy and worsened cardiac function.

3.4.2 NRG1 with left ventricular function

The NRG1/ErbB system is essential for cardiac development, is activated in the early stages of compensated HF, under conditions of myocardial stress, and decreases with disease progression and decompensation (Lemmens et al., 2007; Mendes-Ferreira et al., 2013). NRG1 administration improves cardiac dysfunction and reduces mortality in several models of LV (left ventricular) failure (Liu et al., 2006), and clinical trials have demonstrated the efficacy and safety of NRG1 in improving LV function in patients with HF (Gao et al., 2010; Jabbour et al., 2011a).

Abnormal Ca^{2+} handling in cardiac myocytes has been shown to affect excitation-contraction coupling and cellular function, leading to systolic dysfunction and arrhythmias (Johnson and Antoons, 2018). A recent study found that NRG1 β increased Ca^{2+} current density in LV cardiomyocytes and promoted Ca^{2+} handling protein expression levels, which improved LV cardiac function in volume-overloaded HF rats (Wang et al., 2019). However, this experiment lacks direct evidence of an effect on calcium-handling function.

RhNRG1 is currently being tested in clinical trials as a new treatment for HF (Gao et al., 2010; Jabbour et al., 2011a). Early studies found that recombinant NRG1 β improved myocardial contractility and diastolic capacity in rat models of chronic HF induced by ischemic, dilated, and viral cardiomyopathies (Liu et al., 2006). Similar improvements in cardiac function have been observed in dogs (Liu et al., 2006) and primates (Li et al., 2007). NRG1 attenuates the development of HF in several animal models, including diabetic cardiomyopathy (Liu et al., 2006; Odiete et al., 2013; Vandekerckhove et al., 2016). Advanced cardiomyopathy is an important cause of HF (Seidman and Seidman, 2001). Evidence suggests that weakening ErbB2 activity in the heart can directly contribute to cardiomyopathy and HF (Ozcelik et al., 2002). Therefore, ErbB2 holds promise as a potential target for clinical intervention in HF by NRG1. However, despite proposed explanations for the improvement in cardiomyocyte structure, contractility and proliferation of NRG1 (De Keulenaer et al., 2019), few studies have reported its effects on cardiac output and overall longitudinal strain, as well as LVEF and LV volume (Zurek et al., 2020), making it difficult to fully explain the benefits of NRG1 on left heart function.

3.5 NRG1 and cardiotoxicity

NRG1 β is expressed in the cardiac microvascular endothelium, and promotes the growth and survival of cardiac myocytes in culture through the activation of ErbB2 and ErbB4 receptor tyrosine kinases (Fukazawa et al., 2003). On the one hand, NRG1 β could reduce circulating levels of proinflammatory cytokines in rats with sepsis, adjust diaphragmatic proinflammatory cytokine level, mitigate diaphragmatic oxidative injury, and lessen diaphragm cell apoptosis, improving the function of the diaphragm and playing a role in the protection of the diaphragm by activating the signalling of PI3K/Akt (Liu et al., 2020). On the other hand, expression of NRG1 and recombinant NRG1 β protects myocytes from anthracycline and β -adrenergic receptor-induced cell injury and death (Zhao et al., 1998; Sawyer et al., 2002; Fukazawa et al., 2003; Kuramochi et al., 2004b).

The pro-survival effect of NRG1 occurs through activation of ErbB2/4 in myocytes and downstream signaling in the PI3K/Akt pathway. Direct evidence for the cardiotoxic effects of NRG1 against anthracyclines is the protective activity of NRG1 against adriamycin-mediated myofibrillar disorders and prevention of troponin toxic degradation in cultured cardiomyocytes (Sawyer et al., 2002; Bian et al., 2009). NRG1 cardioprotective activity was also inferred *in vivo* by adriamycin-aggravated systolic dysfunction in heterozygous NRG1 mutant mice and exacerbated chamber dilation in ErbB4 knockout mice specific to the ventricles (Liu et al., 2005; Vasti et al., 2012). Therefore, expression of NRG1/ErbB not only promotes the proliferation of cardiomyocytes and reduces myocardial damage, but also reduces anthraquinone cardiotoxicity, which is undoubtedly beneficial for populations that require anthraquinone applications.

3.6 NRG1 and arrhythmia

NRG1 regulates myocardial function and sympathetic vagal homeostasis and is dynamically involved in the hemodynamic homeostasis of the cardiovascular system. NRG1 desensitizes the myocardium to the positive inotropic effects of isoprenaline through activation of eNOS, providing regulatory feedback on the autonomic imbalance present in acute cardiac stress and chronic HF (Zhao et al., 1999; Lemmens et al., 2004). Cardiomyocytes lacking NRG1 signaling are unable to adequately balance β -adrenergic activation by inhibiting parasympathetic activity (Okoshi et al., 2004; Brero et al., 2010).

Conditional ErbB2 mutant mice also exhibit prolonged ventricular repolarization time (increased QTc) and tachycardia (Ozcelik et al., 2002), which are not normally associated with dilated cardiomyopathy in humans. NRG1 has been reported to affect ventricular contractility and heart rate in perfused rat hearts as well as currents in K^+ -isolated sinus

node myocytes (Wu et al., 2000). Changes in K⁺ or Na⁺ channel activity in humans and mice result in increased QTc and tip twisting arrhythmias (Keating and Sanguinetti, 2001). ErbB receptors classically activate various signaling cascades and affect K⁺ channels, non-selective cation channels and G protein-coupled receptors, all of which affect cardiac function (Wischmeyer et al., 1998; Prenzel et al., 1999; Schaefer et al., 2000).

4 NRG1 as a potential therapeutic target for cardiac repair

NRG1 treatment improves volume overload (Wang et al., 2012), adriamycin-induced LV dysfunction (Bian et al., 2009), as well as ischemia (Cohen et al., 2014) and diabetic cardiomyopathy (Li et al., 2011). Studies using NRG1 for cardiovascular regeneration and repair have focused on exogenous administration, and *in vivo* and *in vitro* experiments have confirmed its clinical effectiveness, respectively, and its greater potential and clinical value in the treatment of cardiovascular disease.

4.1 RhNRG1 and engineered bivalent NRG1 β

The previously research shown that treatment with rhNRG1 improves pulmonary arterial hypertension by decreasing pulmonary arterial remodeling and endothelial dysfunction, as well as by restoring right ventricular function (Mendes-Ferreira et al., 2016). And recent study demonstrated that rhNRG1 treatment can decrease right ventricular intrinsic diastolic stiffness, through the improvement of calcium handling and cardiac remodeling signalling (Adão et al., 2019). The conclusion in Australia trial showed that short-term administration of rhNRG-1 results in acute and sustained improvement in cardiac function but it is an open-label study without a placebo group. In phase II clinical trials of rhNRG1 in the treatment of patients with chronic HF (Gao et al., 2010; Jabbour et al., 2011a) of China, Short-term administration of rhNRG-1 (0.6 μ g/kg) in chronic HF patients could result in sustained improvement of cardiac pumping and inhibition or reversal of ventricular remodeling even 3 months after treatment, which is safe and well tolerated. RhNRG1 is emerging as a promising therapeutic option for cardiovascular disease and cardiac dysfunction.

RhNRG1 stimulates the proliferation of embryonic/fetal/neonatal cardiomyocytes, hypertrophic growth, sarcoma formation, and survival in isolation (Zhao et al., 1998; Lai et al., 2010). Although ErbB2 and ErbB4 play an important role in NRG1-promoted cardiac repair, overexpression of ErbB2 receptor subunits can promote uncontrolled cancer growth (Wadugu and Kühn, 2012), which would be the greatest limitation of clinical

interventions to achieve myocardial regeneration with ErbB2. Previous studies have shown that ErbB3 play an adaptive role in overcoming the heart pressure overload (Yin et al., 2021) and the human protein database shows that the expression of ErbB3 is similar between immune cells and heart fibroblasts. Therefore, its therapeutic effect on heart disease cannot be ignored and is expected to be a potential target for overcoming rhNRG1 defects. Based on this theory, Lee et al. (Jay et al., 2013) designed engineered bivalent NRG1 β , an effect mediated by receptor biasing toward ErbB3 homotypic interactions uncommonly formed by native NRG1 β , resulting in some cases in decreased migration, inhibited proliferation, and increased apoptosis (Jay et al., 2011). Engineered bivalent NRG1 β exhibits reduced tumor potential compared to NRG1 and still retains its cardioprotective properties (Jay et al., 2011; Jay et al., 2013).

4.2 NRG1 gene transduction

Gene fusions are heterozygous genes generated by structural DNA rearrangements, including translocations and insertions, transcriptional passages or splicing (Latysheva and Babu, 2016), resulting in dysregulated activity. The mechanism involving NRG1 gene fusions that induce cancer is due to ErbB-mediated pathway activation (Laskin et al., 2020) leading to aberrant cell proliferation. NRG1 fusions are enriched in aggressive mucinous adenocarcinoma of the lung, but have a low incidence in multiple tumor types (Nakaoku et al., 2014; Jones et al., 2017; Heining et al., 2018; Trombetta et al., 2018). Gene based therapies using gene delivery systems (eg, viral and nonviral vectors) to regulate gene expression at the cellular level can treat post-infarction pathological changes (Cao et al., 2019). In an experimental study in which a lentivirus carrying the human NRG1 gene was injected into the infarcted myocardium of rats, NRG1 gene transduction of the established a stable expression system in the infarcted heart and further activated the PI3K/Akt/eNOS pathway to promote neovascularization and prevent apoptosis (Xiao et al., 2012). In general, gene-based NRG1 therapy helps to reduce post-infarction cardiomyocyte loss, promote neoangiogenesis, and improve cardiac function. Furthermore, two studies have confirmed that endogenous up-regulation of NRG1/ErbB2 signaling and the promotion of NRG1 expression can also be achieved through exercise training (Cai et al., 2016; Cai et al., 2018), suggesting that there is great room for the development of methods to up-regulate NRG1 expression.

4.3 NRG1 and other growth factors

VEGF (vascular endothelial growth factor) and angiotensin (Ang)-1 may regulate myocardial angiogenesis and survival via the NRG1/ErbB signaling pathway. VEGF or Ang-1 can significantly promote NRG1 expression and secretion in human cardiac

microvascular endothelial cells (Wu et al., 2018). In turn, NRG1 treatment also increased significantly the expression of VEGF and Ang-1 in human coronary artery smooth muscle cells (Gui et al., 2018). Qiliqiangxin could attenuate anoxia-induced injuries in cardiac microvascular endothelial cells via NRG1/ErbB signalling which involves repairing damaged myocardial endothelial cells by affecting the expression and secretion levels of NRG1 and VEGF (Wang et al., 2017b).

These findings indicated NRG1 could increase the myocardial angiogenesis, probably via the direct effects of NRG1 and via the increasing expression of VEGF and Ang1 which provide a reliable basis for NRG combined with VEGF and other growth factors for cardiac repair. Furthermore, Lemmens et al. reported that mechanical strain increases endothelial NRG1 synthesis and release, but ang-II and adrenergic agonists decrease endothelial NRG1 synthesis and release (Lemmens et al., 2006; Lemmens et al., 2007). The mechanisms of the inverse relationship of Ang-2 on NRG1 are not clear and further research is still needed.

5 Concluding remarks and future directions

Successful cardiac repair requires three key phenomena: myocardial cell replenishment, removal of interstitial fibrosis, and hematologic reconstitution of the regenerating myocardium. Current research has focused on the direction of post-infarction myocardial proliferation, with less research in the cardiac microenvironment. Promotion of cardiac repair through the intervention of cardiac growth factor NRG1 has become a hot topic of current research. NRG1 has therapeutic effects on many forms of heart disease by directly acting on cardiomyocytes, endothelial cells, macrophages, and fibroblasts to promote cell proliferation, anti-apoptosis, anti-inflammatory and antioxidant effects, and regulate myocardial energy metabolism.

Biomaterials have emerged as innovative scaffolds for the delivery of both cells and proteins in tissue engineering applications. The combination of NRG-encapsulating scaffolds with cells capable of inducing cardiac regeneration could represent an ambitious and promising therapeutic strategy for the repair of diseased or damaged myocardial tissue (Simón-Yarza et al., 2015). Because nanoscale phenomena play an important role in cell signal transduction, enzyme action and cell cycle (Li et al., 2018), and shows excellent performance in the field of targeted drug therapy and the development of biomaterials, nanotechnology will hopefully be used in conjunction with NRG1 to repair the heart. Other emerging technology, such as DNA nano-threads (Baig et al., 2020), it can achieve deliver targeted drug through circular DNA scaffolding for the potential

applications. These emerging technologies can accelerate the development of NRG1 therapy for cardiovascular diseases.

The mechanisms by which NRG/ErbB signaling is cardioprotective have been elucidated. The results of promising clinical trials of two different forms of recombinant NRG1 in systolic heart failure support further investigation of this biologic therapy. However, NRG1/ErbB still needs a lot of experiments to explore safe and feasible methods because it is hampered by the low efficiency of improving cardiac regeneration and side effects. And current experimental models are mainly limited to nonhuman animal models and to *in vitro* cellular models, it is difficult to completely replicate the real myocardial microenvironment of human. But it provides a direction for future research on cardiac repair in cardiovascular diseases.

Author contributions

YW wrote the main text. JW contributed equally to this work. PZ, XZ, YW retrieve and organize the documents. YZ and XC had great contribution in second time revision, polishing manuscript and helping in revising figures.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Glossary

ADAM a disintegrin and metalloproteinase

AREG amphiregulin

ATG5 autophagy related 5

AMI acute myocardial infarction

ACAT-1 acyltransferase-1

COX-2 cyclooxygenase 2

CRD cystein-rich domain

cMLCK cardiac myosin light chain kinase

ECD extracellular structural domain

EGF epidermal growth factor

eNOS Endothelial nitric oxide synthase

ERK extracellular signal-regulated kinase

EPDCs epicardial derived cells

ECM extracellular matrix

FGF2 fibroblast growth factor 2

GSK3 β glycogen synthase kinase 3 β

GLUT4 glomerular glucose transporter 4

GPx1 glutathione peroxidase 1

HF heart failure

HIF-1 α hypoxia-inducible factor-1 α

IR ischemia/reperfusion

ICD intracellular structural domain

IGF insulin-like growth factor

LATSs large tumor suppressor kinases

LVEF left ventricular ejection fraction

LV left ventricular

LDL low-density lipoprotein

MI myocardial infarction

MMP matrix metalloproteinases

MSTs Mammalian sterile 20-like kinases

MOBs mps one binder kinase activator proteins

mTOR rapamycin

MEK mitogen-extracellular activated protein kinase

MAPK adenosine monophosphate-activated protein kinase

NRG-1 Neuregulin-1

PI3K phosphatidylinositol-3-kinase

Pik3cb phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta

Akt-AS160 Akt substrate of 160 kDa (AS160)

RASSFs ras associated domain family

PDK1 phosphatidylinositol-dependent kinase 1

rhNRG1 recombinant human NRG1

ROS reactive oxygen species

RIPC remote ischemic preconditioning

SAV1 salvador homolog 1

SASPs senescence-associated secretory phenotypes

SIPS stress-induced premature senescence

TAZ transcriptional coactivator with PDZ-binding motif

TEAD transcriptional enhanced associate domain

Trx2 thioredoxin-2

VEGFA vascular endothelial growth factor A

VSMCs vascular smooth muscle cells

YAP yes-associated protein

VEGF vascular endothelial growth factor