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Review

Nrf2 in aging – Focus on the cardiovascular system

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ABSTRACT

Aging is the most critical risk factor for the development of cardiovascular diseases and their complications. Therefore, the fine-tuning of cellular response to getting older is an essential target for prospective therapies in cardiovascular medicine. One of the most promising targets might be the transcription factor Nrf2, which drives the expression of cytoprotective and antioxidative genes. Importantly, Nrf2 expression correlates with potential lifespan in rodents. However, the effect of Nrf2 activity in vascular diseases might be ambiguous and strongly depend on the cell type. On the one hand, the Nrf2 activity may protect cells from oxidative stress and senescence, on the other hand, total lack of Nrf2 is protective against atherosclerosis development. Therefore, this review aims to discuss the current knowledge on the role played by the transcription factor Nrf2 in cardiovascular diseases and its potential effects on aging.

1. Introduction

Epidemiological studies reveal that the primary risk factor for cardiovascular dysfunction is aging [1]. It is a time-dependent complex process ending up in general functional impairment and decline in health. A universal characteristic of aging at the molecular level is the accumulation of damage inside the cells. Although the molecular basis of aging seems to be largely known, including genomic instability, telomere exhaustion, epigenetic changes, impaired protein homeostasis, mitochondrial dysfunction and cellular senescence [2], detailed research on aging-related modulators may have important therapeutic implications limiting pathologies in humans. Studies of recent years have indicated a group of proteins which function may affect the process of aging. It comprises such longevity targets as mTOR [3], Foxo3A [4,5], Parp1 [6,7], and Sirt1 [8,9]. Also, a potential role for Nrf2 (nuclear factor (erythroid-derived 2)-like 2) in aging and age-related diseases has been raised [10–12]. Interestingly, the expression of Nrf2 at mRNA level is 6-fold times higher in a long-lived naked mole-rat in comparison to wild-derived mouse [13], and increase in SKN-1 (Nrf2 homologue in worms) signaling or loss of CncC (Nrf2 homologue in flies) inhibition prolongs lifespan of *C. elegans* [14] and *Drosophila* [15], respectively. Moreover, there is a positive correlation between Nrf2 activity and maximum lifespan potential in rodents [16].

Nrf2, encoded by *NFE2L2* gene, is a stress-responsive transcription factor, which has emerged as a guardian of cellular homeostasis. It belongs to cap'n'collar (CNC) subfamily of basic-leucine-zipper (bZIP) transcription factors and drives the expression of cytoprotective, antioxidant and detoxification genes through the antioxidant response element (ARE) [17].

2. CNC-bZip transcription factors family

CNC proteins are a highly conserved subfamily of bZIP transcription factors comprising four homologues: NFE2 (known as p45), Nrf1, Nrf2 and Nrf3, and two distinct members: Bach1 and Bach2, characterized by the presence of an additional BTB (Broad-complex, Tramtrack, Bric-a-brac) domain [18–22]. In all members of the NFE2 family, Nrf2-ECH homology (Neh) domains can be distinguished (Fig. 1) [12].

The Neh1 domain consists of CNC and bZIP regions and is necessary for binding to DNA, dimerization, and thanks to the presence of NLS (nuclear localization signal) and NES (nuclear export signal) sequences, it participates in shuttling of a transcription factor in the cell [23]. The redox-sensitive Neh2 domain of Nrf2 contains ETGE and DLG motifs responsible for interaction with KELCH domain of Nrf2 negative regulator Keap1 (Kelch-like ECH-associated protein 1) [24,25]. In contrast to Nrf2, Nrf1 is not inhibited by Keap1, what can be related to differences in amino acids around ETGE motif in Neh2-like (Neh2L) domain of Nrf1. Thus, Keap1 binds Neh2L with low affinity [26]. The C-terminus Neh3 domain is necessary for Nrf2 transcriptional activity through interaction with chromodomain helicase DNA binding protein

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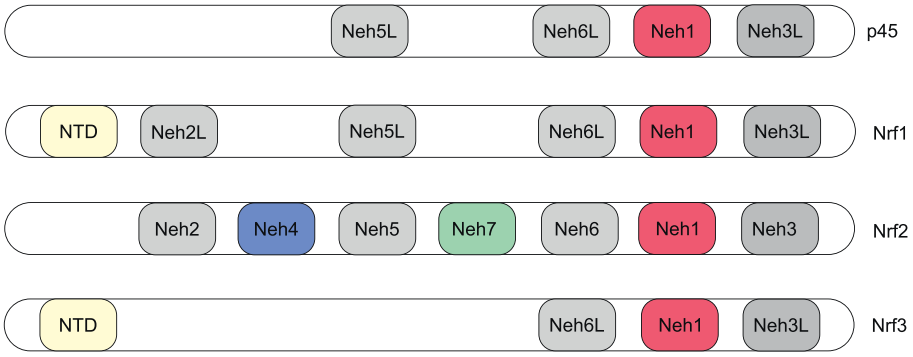

Fig. 1. NFE2 transcription factors family. p45, Nrf1, Nrf2 and Nrf3 are the members of NFE2 family, which belongs to CNC-bZIP transcription factors. All NFE2 proteins comprise structural domains Neh (Nrf2-ECH homology). Neh2L, Neh3L, Neh5L, Neh6L: Neh-like domains. NTD – N terminal domain.

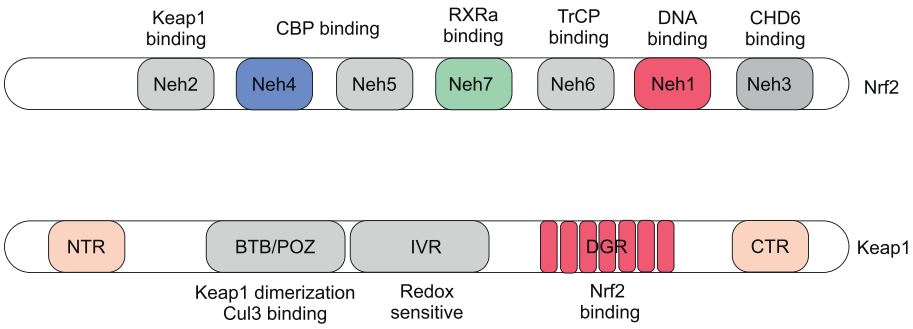

Fig. 2. The function of Nrf2 and Keap1 domains. Neh1 is a DNA binding domain. Neh2 interacts with Keap1. Neh3 binds chromodomain helicase DNA binding protein 6 (CHD6), which is necessary for gene transactivation. Neh4 and Neh5 domains recruit CBP coactivator and are responsible for transcriptional activity of Nrf2. Neh6 binds β-TrCP, which controls the stability of Nrf2. Neh7 domain interacts with RXRa, what inhibits transcriptional activity of Nrf2. Neh - Nrf2-ECH homology. CBP – CREB binding protein. RXRa - retinoid X receptor alpha. TrCP - β-transducing repeat-containing protein. CHD6 - chromodomain helicase DNA binding protein 6. NTR – N terminal region. BTB - Broad-Complex, Tramtrack and Bric a brac. POZ - POxvirus and Zinc finger. Cul3 – cullin 3. IVR - intervening region. DGR - double-glycine repeat region. CTR – C terminal region.

6 (CHD6) [27]. However, so far it is not known whether the role of a Neh3-like domain (Neh3L) in Nrf1 and Nrf3 is similar to the one in Nrf2 [28]. The Neh4 domain is present only in Nrf2 and together with Neh5 facilitates recruitment of coactivator CREB binding protein (CBP), thus increasing target gene transcription [29,30]. Likewise, the Neh5-like (Neh5L) domain of p45 and Nrf1 is responsible for transactivation. However, it is not conserved in Nrf3 [31]. β-transducing repeat-containing protein (β-TrCP) binds two motifs: DSGIS and DSAPGS found in the Neh6 domain, what enables recognition and turnover of Nrf2 protein by the ubiquitin-proteasome system (UPS) [32]. Despite possessing Neh6-like (Neh6L) domain, Nrf1 and Nrf3 turnover is regulated by the ER-associated protein degradation (ERAD) complex [26,33]. Withal, the N-terminal domain (NTD) incorporating two highly conserved subdomains like NHB1 (N-terminal homology box 1) and NHB2 enables anchorage of Nrf1 and Nrf3 in the ER [26,33]. Neh7 domain, present in Nrf2, can be bound by RXRα what represses Nrf2 transcriptional activity (Fig. 2) [34].

Despite structural homology, Nrfs are encoded by different genes and mapped at different chromosomes (Table 1). Importantly, the expression profile is regulated in a tissue-specific manner only for p45, whereas Nrf1, Nrf2, Nrf3 are widely expressed (Table 1) [12]. To determine the biological role of the CNC transcription factors, mutant mice were generated by disrupting the targeted region of the gene of interest. In case of p45 knockout animals, DNA binding and bZIP coding exon were removed [35]. In Nrf3$^{-/-}$ mice two exons responsible for DNA-binding, bZIP dimerization and CNC homology of the *NFE2L3* gene were disrupted [36]. Nrf1 null mice were developed by removing terminal exon of *NFE2L1* gene comprising the sequences coding DNA-binding and bZIP domains [37]. All those mice show a null phenotype. However, in case of Nrf2, bZIP region coding exon of *NFE2L2* gene was replaced by NLS-*LacZ* gene, leading to the formation of fusion protein Nrf2-β-galactosidase, thus creating transcriptional-knockout (tKO) animals (Table 1) [38]. Gene knock-out animal models reveal that NFE2 family members have distinct phenotypes. Knock out of p45 gene leads to the abnormalities in platelet production and death due to hemorrhages [35,39]. Mice deficient in Nrf1 are anemic and die during embryonic development [37]. Inhibition of Nrf2 transcriptional activity leads to increased susceptibility to oxidative stress and inflammation

Table 1
Comparison of NFE2 family transcription factors.

	p45	Nrf1	Nrf2	Nrf3
Encoding gene	*NFE2*	*NFE2L1*	*NFE2L2*	*NFE2L3*
Chromosome	Human 12	Human 17	Human 2	Human 7
Tissue profile	Expressed in hematopoietic cells and also in colon and testis	Widely expressed	Widely expressed	Widely expressed (highest expression in human placenta)
Cellular localization	Nuclear in PML body, can be translocated to the cytoplasm (inactive)	Endoplasmic reticulum membrane, can translocate to the nucleus	Cytoplasmic, upon stress translocated to the nucleus	Endoplasmic reticulum membrane and nuclear envelope
Mice model	Total knockout (removed exon encoding DNA binding and bZIP fragment)	Total knockout (removed exon encoding DNA binding and bZIP region)	Transcriptional knockout (exon encoding bZIP region replaced by NLS-*LacZ*)	Total knockout (removed two exons encoding: DNA binding, bZIP dimerization and CNC homology)

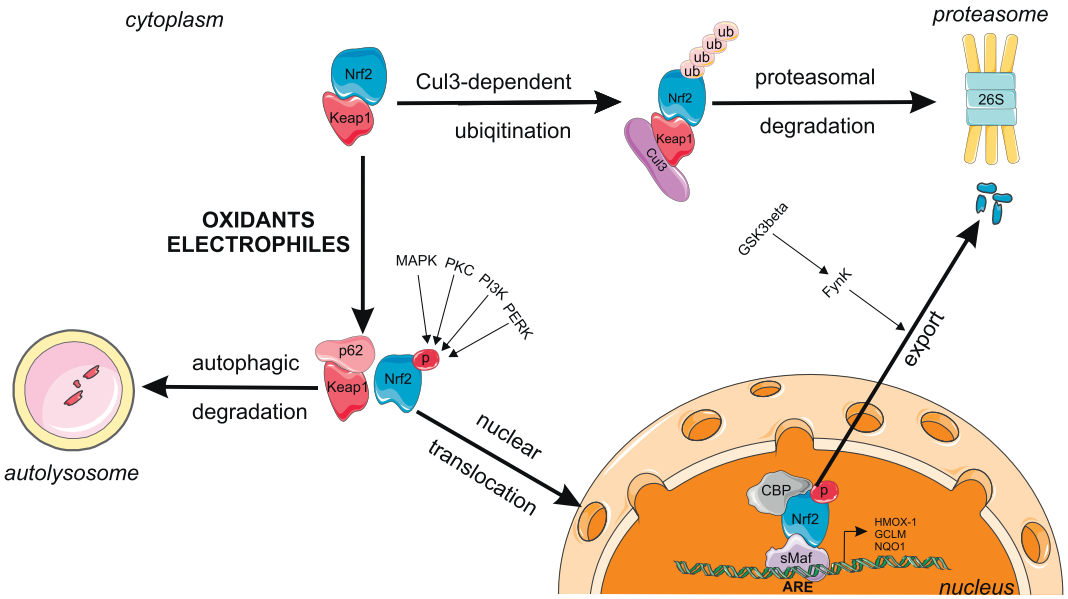

Fig. 3. Nrf2 cytoplasm-nuclear shuttle. In basal conditions Nrf2 is bound in the cytoplasm by Keap1 and is degraded by ubiquitin-proteasome system *via* cullin3-E3 dependent mechanism. In stress conditions, Nrf2 is liberated from Keap1 repression, undergoes phosphorylation and translocates into the nucleus. After association with sMaf and CBP it activates transcription of target genes. Export of Nrf2 from the nucleus depends on phosphorylation by glycogen synthase kinase 3 beta (GSK3β) and Fyn kinase (FynK). Keap1 undergoes p62-dependent autophagic degradation. Cul3 – cullin3. Ub – ubiquitin. ARE – antioxidant responsive element. CBP - CREB binding protein. sMaf – small musculoaponeurotic fibrosarcoma protein. *HMOX1* – heme oxygenase 1. *GCLM* - glutamate-cysteine ligase modifier subunit. *NQO1* - NAD(P)H:quinone acceptor oxidoreductase 1. 26S proteasome – ATP-dependent protease complex. MAPK - mitogen-activated protein kinase. PKC – protein kinase C. PI3K - phosphoinositide 3-kinase. PERK - protein kinase localized in the endoplasmic reticulum.

[40,41], whereas Nrf3-null mice do not show apparent abnormalities [36].

2.1. The Keap1-Nrf2-ARE system: molecular basis of action and regulation

In normal, non-stressful conditions Nrf2 resides in the cytoplasm, where it binds to cytoskeleton-associated protein Keap1, known as an inhibitor of Nrf2 (INrf2) (Fig. 3) [42]. Structurally, 5 domains can be discerned in Keap1: Kelch domain, known as a double-glycine repeat (DGR) region, N-terminal region (NTR), BTB (also known as POZ, POxvirus and Zinc finger) domain, cysteine-rich intervening (IVR) region and C-terminal (CTR) domain (Fig. 2) [25]. The Keap1-Nrf2 interaction occurs through binding of the Neh2 domain within Nrf2 and DGR domain of dimerized Keap1 (Fig. 2) [25]. Subsequently, Nrf2 is degraded by the ubiquitin-proteasome system *via* cullin3-E3 dependent mechanism. Cullin 3 (Cul3), which is an E3 ubiquitin ligase complex subunit, binds directly to Keap1 at the IVR fragment. In the next step, Nrf2 is degraded *via* 26S proteasome (Fig. 3) [43]. Under physiological conditions, the half-life of Nrf2 in the cytoplasm is no longer than 15-20 min [42]. Upon oxidative stress or electrophiles stimulation, highly reactive cysteine residues (Cys273 and Cys288) at IVR and (Cys151) at BTB fragments of Keap1 are oxidized, what results in its conformation changes and leads to the release of Nrf2 from the inhibitory complex [25,42]. At the same time, p62 binds to the DGR region of Keap1, what redirects it to autophagy-dependent degradation [44]. Besides, p21 protein can directly attach to the Neh2 domain of Nrf2, thus increasing its dissociation from inhibitory complex and preventing re-binding to Keap1 [45]. Numerous endogenous (e.g., reactive oxygen species, 15-deoxy-Δ12,14-prostaglandin J_2) or exogenous (e.g., triterpenoids, isothiocyanates, dithiolethiones) molecules can oxidize Cys residues of Keap1 [42]. Additionally, a Keap1 conformational change-mediated Nrf2 release may occur *via* S-nitrosylation of thiol residues in nitric oxide-dependent cytoprotective mechanism [46]. The liberated Nrf2 translocates to the nucleus, where it binds to its consensus sequence. Besides the conformation changes in Keap1, the cytoplasm-nucleus shuttle of Nrf2 is regulated by its phosphorylation by kinases involved in signal transduction in the cell, such as mitogen-activated protein kinases (MAPK), protein kinases C (PKC), phosphatidylinositol 3-kinase (PI3K) or protein kinase localized in the endoplasmic reticulum (PERK) [47,48]. Phosphorylation of serine/threonine residues (Ser40 and Tyr568) in Nrf2 was shown to increase its nuclear localization and activity [48]. In the nucleus, Nrf2 heterodimerizes with the small Maf proteins (MafF, MafG, and MafK) and in such complex binds to the cis-regulatory element ARE of consensus sequence 5'-RTGABnnnGCR-3' at target genes [48,49]. Furthermore, Nrf2 may also heterodimerize with proteins belonging to the Jun family (c-Jun, Jun-B, Jun-D), what also enhances its binding to the consensus sequence [48,50]. p300/CBP additionally regulates activation of ARE-binding *via* acetylation of lysine residues (Lys588 and Lys591) present in the Neh1 domain of Nrf2 [51]. Upon binding to ARE, Nrf2 activates expression of variety of target genes including detoxifying enzymes (glutathione S-transferase (*GST*), NAD(P)H:quinone oxidoreductase (*NQO1*)), stress-responsive proteins (heme oxygenase-1 (*HMOX1*)) and reactive oxygen species scavenging enzymes (glutathione peroxidase (*GPX*), superoxide dismutases (*SOD*)) [48]. Notwithstanding, prolonged retention of Nrf2 in the nucleus and thus its hyperactivation may evoke detrimental effects. Keap1 null mice with constant nuclear accumulation and activation of Nrf2 died postnatally due to malformations of the esophagus and forestomach [52]. Therefore, the amount of nuclear Nrf2 must be strictly regulated. GSK3β–dependent Fyn kinase phosphorylation of Tyr568 in the Neh3 domain of Nrf2 causes its export from the nucleus and subsequent degradation (Fig. 3) [32,53].

2.2. Nrf2 and age – implications for cardiovascular disease

More than 80% of cardiovascular deaths in the United States occur in people aged 65 and older [54]. It shows that aging is associated with adverse effects in the cardiovascular system. One of the most recognized theories explaining the mechanisms of aging is the free radical theory of aging developed by Harman in the 1950s [55], which states that aging is a result of the accumulation of damage caused by excessive oxidative stress. However, there are also data contradicting this theory

(summarized in [56]), which evidence that overexpression of anti-oxidative enzymes does not extend the lifespan of mice [57], *Drosophila* [58] and *C. elegans* [59]. Hence, the cause of aging could be broadened to 'biological imperfectness', which leads to the accumulation of cellular damage [56]. Even so, the oxidative damage may contribute to aging as one of the several mechanisms [56,60]. Indeed, vascular aging is accompanied by chronic oxidative stress resulting from increased ROS production and failure to activate ARE-driven gene expression [61], and imbalance in antioxidative capacity is similar between aged mice and Nrf2 transcriptionally defective animals [62]. Irrespective of the role of Nrf2 as a master regulator of oxidative protection, which represents its predominant function, this transcription factor also mediates the general adaptive response of the cell, regulating inflammation, proteostasis and metabolism [63–65]. Therefore, this may explain its pathophysiological implications in aging reaching beyond orchestration of redox homeostasis. Considering the frequency of cardiovascular complications and deaths in aged people, the vascular system seems to be the primary target for Nrf2-mediated protection in aging. All the more that Nrf2 is known to preserve healthy endothelial phenotype [66–71]. The endothelium is a tissue located at the border between blood and tissues, and its key role is a regulation of vascular tone, thromboresistance, inflammation of the vascular wall and cellular adhesion [72]. It is also the one, which is the most exposed to detrimental signals in a vessel wall. Although endothelium is composed of a monolayer, it can respond to several physical and chemical stimuli to exert its crucial role in the cardiovascular system. Aged or senescent endothelial cells become dysfunctional, lose reendothelialization and angiogenesis capacity and get pro-atherogenic and pro-thrombotic phenotype [73]. Peering at the anatomical changes within the aorta, age leads to an increase in its size, diameter [74,75], thickness [76] and length [74,77]. Among endothelial cells, one can distinguish irregularly shaped cells and vascular smooth muscle cells (VSMC) which in response to injury migrate towards the intima [78]. The age-related changes are connected to the decrease in the elastic properties of the aortic wall [79]. Rupture of elastin fibers together with their decreased regenerative potential [80–82] is accompanied by overproduction of collagen [83] and its crosslinking by non-enzymatic glycation by advanced glycation end products (AGE) (Fig. 4) [84,85]. The appearance of glycated collagen is said to be responsible for increased inflammation and ROS level in the aging aorta [86]. Elastin degradation is resulting from the upregulation of matrix metalloproteinases (MMPs), and inhibition of MMPs helps to preserve intact elastin fibers, abrogates collagen deposition and inhibits the increase in blood pressure [87]. Altogether, it results in increased arterial stiffness, impaired vasodilatation, and angiogenesis and is directly linked to the occurrence of cardiovascular disorders [88]. Of note, senescent endothelial cells were noticed in the aorta of Zucker diabetic rats [89], neointima of rabbit carotid arteries subjected to balloon denudations [90], and atherosclerotic lesions of human coronary arteries [91]. Thus, prevention of endothelial cell dysfunction by Nrf2 might be of particular significance in aging.

Importantly, aging impairs the ability to mount an effective Nrf2-dependent defense in various cell types [92–98], including vascular cells [61,99] and cardiac cells [100]. The reason for a declined Nrf2 signaling remains unidentified, though [63]. The other way around, also inhibition of Nrf2 leads to the premature cellular senescence [101–106]. However, the influence of Nrf2 deficiency on senescence of vascular cells has not been studied yet.

Interestingly, Nrf2 associations with aging seem to be universal throughout species, starting from human [98,107], rat [62,95] and mouse [100], finishing with *Drosophila* [108] and *C. elegans* [109]. Age-related decrease in Nrf2 activity displays a tissue-specific pattern. The studies comparing old and young *Drosophila* show that ARE-driven transcription was increased in the head and abdomen [110], while it was diminished in intestinal stem cells [111]. Studies in rats showed that age does not affect Nrf2 nuclear level in the proximal renal tubule [112]. However, in case of the cardiovascular system, there is a decreasing tendency, which was shown in rat aortas [61] and carotid artery and VSMC from Rhesus monkey [99].

Reciprocal associations between aging, cardiovascular diseases, and Nrf2 can be reflected by numerous studies evidencing the significance of Nrf2 signaling in the protection of the cardiovascular system.

2.3. Nrf2 in vascular homeostasis

Prominent protective mechanisms in the cardiovascular system are dependent on NO, CO, H_2S, endothelins and proper response of endothelial layer to blood mechanical forces [113–116]. However, with age the endothelium becomes dysfunctional, and there is decreased production along with the impaired response to above factors (summarized in [117–120]).

Mechanical forces have a high impact on endothelial cells, and subsequently, these cells have a powerful mechanism to counteract shear stress and regulate the vascular function. However, mechanical forces can also have an impact on smooth muscle and adventitial cells through paracrine stimulation [121]. The ability of the endothelium to influence vasodilatation of smooth muscle cells was first described in 1980 as an endothelial-derived relaxing factor – EDRF [122], which later turned out to be nitric oxide (NO). NO is produced from L-arginine by endothelial nitric oxide synthase (eNOS, NOS3), diffuses to smooth muscle cells and exerts its role through the increase in cGMP level produced by guanyl cyclase [123]. Shear stress affects eNOS activity and increases transcription of *NOS3* gene [124,125]. Furthermore, laminar shear stress increases the number of S-nitrosylated proteins

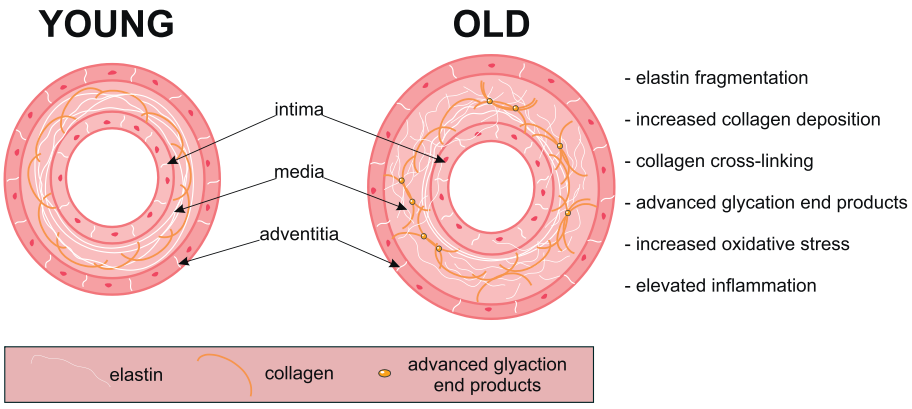

Fig. 4. Structural differences between young and old aortas. Aging leads to elastin fragmentation, increased collagen deposition, collagen cross-linking, the presence of advanced glycation end products, increased oxidative stress and elevated inflammation.

[126], which play a crucial role in signaling in endothelial cells [127].

Nitric oxide leads to Nrf2 nuclear translocation through the oxidative stress-dependent mechanism [128]. It is probably achieved due to the S-nitrosylation of Keap1. Such modification decreases Keap1 ability to repress Nrf2 [46,129]. Nitric oxide may, therefore, prevent the VSMC death through activation of ARE and induction of HO-1 [130]. The decrease in the NO availability is considered to be due to its scavenging by ROS and formation of peroxynitrite or uncoupling of eNOS, which then produces superoxide anion. Of note, Nrf2 was shown to counteract the eNOS uncoupling [131].

Another signaling molecule regulating vascular tone is hydrogen sulfide (H_2S). The concentration of H_2S in the aorta is 20-200 times higher comparing to other tissues, what suggests its crucial role in the cardiovascular system [132]. In fact, H_2S promotes endothelial cell proliferation and migration, fights inflammation and favors vasodilatation [133]. Additionally, it has been reported that the protective effects of H_2S are mediated through Nrf2 induction [134]. H_2S inhibits calciprotein-induced VSMC calcification through induction of *NQO1* in a Nrf2-dependent manner [135]. Induction of Nrf2 may be the result of Keap1 inhibition by its sulfhydrylation induced by H_2S [136].

The third crucial vascular gasotransmitter is carbon monoxide (CO), a product of heme degradation by HO-1, one of the Nrf2 target genes. CO, through the activation of p38, inhibits apoptosis of both endothelial and VSMCs [137,138]. Additionally, it suppresses SMC proliferation [139] and intimal hyperplasia upon balloon injury [140]. CO plays a crucial role in suppression of inflammation through several mechanisms: modulation of TLR-dependent macrophage response to LPS [141,142], decreased expression of proinflammatory genes [141] and diminished leukocyte infiltration in the aorta [140]. CO also induces Nrf2, and the latter plays a crucial role in the anti-inflammatory action of CO [143]. The crosstalk of NO and CO plays a pivotal role in the maintenance of vascular tone. CO, similarly to NO, can affect the level of cGMP through the activation of guanyl cyclase [144]. Levels of these two gasotransmitters are reciprocally regulated, increase in one results in a decrease of the other [145,146].

Endothelial cells contribute to the regulation of vascular tone also through secretion of endothelins [147]. The most studied is endothelin-1 (ET-1). Cellular effects of ET-1 result from interactions with one of 2 homological G-protein coupled receptors: endothelin receptor type A (ET-A) and endothelin receptor type B (ET-B). Although both receptors bind ET-1 with subnanomolar affinities, they act on different signaling pathways *via* multiple G proteins and β-arrestin. In that way, they exert opposite effects on the vascular homeostasis [148]. ET-A irreversibly binds ET-1 and induces long-term vasoconstriction, whereas ET-B causes vasodilatation through the increased secretion of NO. In the vasculature, ET-A is present predominantly in smooth muscle cells, whereas the ET-B receptor is located on endothelial cells [147]. Additionally, ET-B serves as a 'clearance receptor' and helps to remove ET-1 from the circulation *via* lysosomal degradation [149,150]. In response to nitro fatty acids, Nrf2 directly regulates *ETB* expression through antioxidant response element located in the *ETB* gene enhancer. Elevation in ET-B level leads to the scavenging of endothelin 1 from blood and to increase in vasodilatory action [151].

When considering the role of Nrf2 in the maintenance of vascular tone, it is essential to mention reactive oxygen species. ROS play a crucial role in signaling, stimulate various kinases, activate physiological angiogenesis. Primary sources of ROS in vascular cells are NADPH oxidases and uncoupled eNOS. However, with age, the ability of cells to mount the antioxidative response diminishes, what results in oxidative stress. The latter results in increased inflammation, endothelial dysfunction, decreased NO bioavailability, enhanced neointima formation and vascular wall remodeling (summarized in [152–155]). Nrf2, as a central regulator of the response to oxidative stress, helps to preserve physiological level of ROS, disabling disruption of vascular homeostasis.

All the above factors contribute to the maintenance of a vascular tone, which is a crucial determinant of blood pressure [156]. Abnormalities of blood pressure regulation are leading to the onset of hypertension, atherosclerosis and other cardiovascular disorders.

2.4. Nrf2 and hypertension

Gaseous transmitters play a crucial role in the maintenance of vascular homeostasis and prevention of hypertension (reviewed in [157–159]). However, an important role is attributed to angiotensin II (AngII)-triggered redox signaling [153]. Not only is there an increase in blood pressure upon treatment with AngII, but it also affects vascular inflammation and endothelial function (reviewed in [160]). Moreover, there is an increased activity of AngII with age [161,162]. Inhibition of AngII signaling is considered protective, leading to an increase of the lifespan [163–165]. Of note, AngII induces Nrf2 translocation [166]. What is more, depletion of Nrf2 exacerbates AngII-induced ROS and cardiac hypertrophy through a mechanism involving p27 (Kip) [167].

Nrf2 is considered as a mechanosensitive transcription factor [168], no wonder then that it is activated in several models: DOCA salt-induced hypertension [169], chronic pressure overload [170] and aortic constriction [171]. Similarly, treatment with verapamil, an FDA-approved drug for hypertension, leads to Nrf2 activation due to Keap1 degradation [172]. Nrf2 activator, tBHQ, was shown to prevent microvascular endothelial dysfunction, remodeling, contractility, and hypertension during 14-day infusion of AngII to male mice [173]. Nrf2 downregulation and decrease of a nuclear shuttle were reported in stroke-prone hypertensive rats [166]. Chronic pressure overload led to Nrf2 activation through NOX4 dependent mechanisms, and Nrf2 KO mice had attenuated response to NOX4 overexpression-dependent protective mechanisms [170].

Additionally, the sympathetic vasomotor tone and arterial blood pressure are regulated by neurons that reside in the rostral ventrolateral medulla (RVLM) and are called cardiovascular center [174]. Furthermore, when BP is suddenly elevated, the activities of the arterial baroreceptors and vagal afferent nerves, and the neuronal activity of the caudal VLM (CVLM) are increased *via* the nucleus *tractus solitarius*. As a consequence, more inhibitory amino acid GABA is released between the synaptic transmission from CVLM neurons to RVLM neurons leading to the suppression of RVLM and decrease in BP [174]. Neurons in RVLM are susceptible to increased ROS, and the development of hypertension in rodents is attributed to the sympathoexcitation caused by oxidative stress in RVLM [175,176]. It was shown that *Nfe2l2* deletion in the RVLM increases ROS production and reduces GABA release, thus elevating blood pressure, increasing sympathetic outflow, and impairing baroreflex function [175]. Importantly, *Nfe2l2* knockout in RVLM was concomitant with lower expression of *Nqo1*, *Hmox1*, *Sod2*, and *Cat* [175]. Given that mice have a limited reserve to increase cardiac output, vasoconstriction-induced increase in peripheral resistance is likely the predominant contributor to hypertension seen in these RVLM Nrf2 knockout mice [175,177]. Furthermore, tBHQ decreases mean arterial pressure and plasma norepinephrine in rats [178,179]. The effect was reversed by knockout of *Nfe2l2* by adeno-associated virus-mediated small interfering RNA in the hypothalamic paraventricular nucleus (PVN), a brain region that influences the sympathetic outflow in the central nervous system [178].

Although we start to understand the role of Nrf2 in blood pressure regulation in rodents, its significance in humans is still unclear. Few populational studies presented that single nucleotide polymorphism in *NFE2L2* (rs6721961 CA + AA) and *KEAP1* (rs110857735 the AA or CA) may be associated with altered blood pressure and higher hazard rate of fatal and nonfatal cardiovascular outcomes [180,181]. However, those studies were limited to selected populations of Japanese and Italians, respectively.

2.5. Nrf2 in cardiac I/R injury

Cardiovascular diseases can lead to myocardial infarction due to extreme reduction in coronary blood perfusion. Reperfusion, which occurs after prolonged ischemia during MI, facilitates ROS production and increased local inflammation, thus widening the infarction zone [182]. $Nrf2^{-/-}$ mice are more susceptible to I/R injury, whereas enhanced Nrf2 translation protects wild type animals *via* binding of La protein to its 5'UTR [183]. Accordingly, Nrf2 KO mice are more prone to develop heart failure and have a higher mortality rate in 10 days post-MI [184]. Endo- or exogenous Nrf2 activation is beneficial for the ischemic/reperfused heart. Glucocorticoid-dependent induction of endogenous prostaglandin D_2 leads to the cardioprotection *via* activation of the Nrf2 pathway [185]. Many reports have demonstrated that the induction of Nrf2 by its endogenous activators protects against the side effects of myocardial I/R injury [186–188]. Moreover, preconditioning by Nrf2 activation *via* administration of α-lipoic acid was shown to be beneficial during myocardial injury [188].

2.6. Nrf2 in restenosis

Restenosis is a post-operative narrowing of a blood vessel lumen due to excessive proliferation of vascular smooth muscle cells and incomplete endothelialization [189]. Consequently, it leads to the restricted blood flow in a large number of patients undergoing angioplasty. Upon injury, accumulating platelets release different mitogenic factors that activate VSMC. Activated VSMC change to the synthetic phenotype, which is, contrary to contractile phenotype, characterized by high proliferative and migratory activity enabling restoration of the vessel. Physiologically, change to synthetic phenotype is reversible when the damage is healed. However, in the presence of several mitogenic factors, such as aFGF, bFGF, VEGF, IGF-1, and PDGF, VSMC may fail to switch back to contractile phenotype, what further contributes to the pathogenic neointima overabundance and vascular remodeling [190].

One of the most potent mitogens for VSMC is platelet-derived growth factor (PDGF) [191], which exerts its role through the increase in H_2O_2 [192]. As the increase in ROS level plays a crucial role in the response of VSMC to injury, the significance of Nrf2 in VSMC phenotype switching was intensely studied. Several strategies which drove Nrf2 activation were used: chemical activators [193], depletion of its negative regulator-CD36 [194] or increase in NOX4-driven superoxide [195]. Importantly, all of them led to the same conclusion that Nrf2 activation helps to maintain the contractile (low-proliferating) phenotype of VSMC (Fig. 5). On the other hand, depletion of Nrf2 results in the enhanced PDGF-induced VSMC migration *in vitro*, whereas mice lacking Nrf2 develop enhanced neointimal hyperplasia [196]. Supportively, a decrease in Nrf2 level is observed in highly proliferating VSMC [197]. In accordance, Nrf2 gene overexpression was found to suppress human and rabbit aortic smooth muscle cell proliferation, diminish inflammation and oxidative injury in balloon-injured rabbit arteries [198]. The beneficial effect of Nrf2 on the maintenance of VSMC contractile phenotype may be attributed to the induction of its target genes and decrease in ROS level [196,199].

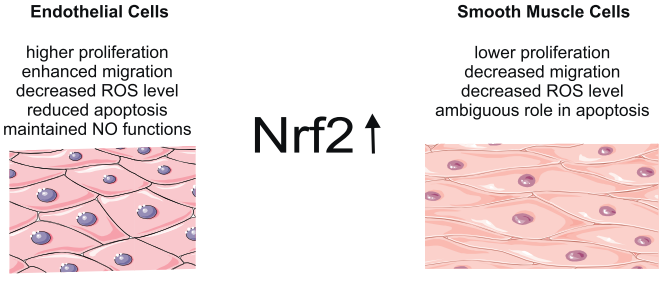

Fig. 5. Influence of Nrf2 on endothelial (ECs) and smooth muscle cells (SMCs). Increased Nrf2 activity may result in different effects in ECs and SMCs. In contrary to SMCs, ECs exhibit enhanced proliferation and migration. On the other hand, reactive oxygen species (ROS) level is decreased in both cell types. NO – nitric oxide.

The increase of HO-1 level might be critical for the regulation of restenosis [196–198], as inhibition of this enzyme leads to the highly proliferating status of SMC [198,200]. Accordingly, free heme increases proliferation of VSMC [201]. Other studies showed a beneficial role of Nrf2-driven transcription of *NQO1* [199]. On the other hand, Nrf2 activation by dimethyl fumarate was shown to inhibit VSMC proliferation through upregulation of p21 protein and cell cycle arrest but through NQO1- and HO-1-independent mechanism [193]. Additionally, depletion of Keap1 increased the number of apoptotic SMC and therefore it was proposed as another mechanism of protection from neointima formation [202].

2.7. Nrf2 and atherosclerosis

Atherosclerosis is a chronic inflammatory disease with genetic and environmental background, characterized by the deposition of lipids in the artery wall, the infiltration of inflammatory cells and the destruction of endothelial and media layers (summarized in [203]). Oxidative stress is one of leading contributors to atherosclerosis (reviewed in [155]). Knockout of several antioxidant enzymes, such as *Gpx1*, *Prdx2* and *Hmox1* worsen atherosclerotic plaque formation [204–206]. That is why the role of Nrf2 seems crucial in the process. Mounting of antioxidant response by Nrf2 should counteract formation of atherosclerotic plaques. However, the role of Nrf2 in atherosclerosis in *in vitro* and *in vivo* models is ambiguous and is heavily dependent on the experimental setting.

Global Nrf2 knockout leads to a decreased number of aortic atherosclerosis lesions [207–209]. Interestingly, the reduction is more pronounced in males (47%) than females (18.5%) in comparison to heterozygote littermates and total lack of Nrf2 reduces the formation of more advanced lesions in 54-week-old mice [207]. Transplantation of $Nrf2^{-/-}$ bone marrow to $ApoE^{-/-}$ attenuated formation of atherosclerotic plaques, what highlights the proatherogenic activity of Nrf2 [209]. On the other hand, the peritoneal macrophages isolated from $Nrf2^{-/-}$ mice have a proinflammatory, M1 phenotype [210] and transplantation of $Nrf2^{-/-}$ bone marrow to $LDLR^{-/-}$ mice aggravates formation of foam cells and atherosclerotic lesion area [210,211]. Thus, up to date the role of Nrf2 in atherosclerosis remains ambiguous.

Several possible explanations for a role of Nrf2 in exacerbation of atherosclerotic phenotype were given, such as Nrf2 dependent activation of NLRP3 inflammasome and IL-1 production [212], regulation of lipogenic genes [207], decreased uptake of AcLDL [208] and oxLDL-induced upregulation of CD36 [207,208,213].

CD36 and CD38 role in atherosclerosis and maintenance of contractile phenotype are well established [195,214]. CD36 negatively regulates Nrf2 signaling during vascular injury, and it leads indirectly to Nrf2 nuclear export and degradation. In the absence of CD36, Nrf2 efficiently decrease ROS level during vascular injury [194]. The role of Nrf2 in VSMC phenotype switching was intensely studied. Some of the groups attribute the beneficial effect on maintenance the low proliferating phenotype of VSMC to induction of its target genes and decrease in ROS level [196,199]. The signaling through CD38 plays a crucial role in the induction of NOX4 and superoxide production, which, in turn, leads to Nrf2 activation and maintenance of contractile phenotype of SMC [195].

Apart from excessive lipid accumulation and macrophage influx into the media layer, accelerated calcification and coagulation within the arterial wall are important factors contributing to the development of atherosclerosis [215–217]. A recent study showed that activation of Nrf2 significantly inhibited sulfide-mediated calcification in human vascular SMCs. Importantly, those beneficial effects are mediated by the activation of NQO1 [135].

Role of Nrf2 in the pathogenesis of atherosclerosis is not only narrowed to VSMCs. Nrf2 was shown to be activated in ECs only by laminar shear stress, which is considered to be antiatherogenic [218]. Accordingly, Nrf2 was reported to be activated in atherosclerosis resistant regions of the aorta through the PI3K/Akt pathway. Its activation decreases ROS level and protects ECs against oxidative stress-related injury [66]. PI3K/Akt-dependent response to cyclic stretch and subsequent Nrf2 activation was shown to be triggered by EGFR [219]. Nrf2 activation in atheroprotected regions of aorta counteracts p38-VCAM-1 signaling by enhancing the activity of MKP-1 [70]. Moreover, Nrf2 deficiency leads to higher expression of pro-inflammatory adhesion molecules and chemokines on ECs [220]. Additionally, H_2S attenuated onset of atherosclerosis in Nrf2-dependent manner, through reduction of ROS and inflammation [136]. Collectively, Nrf2 protects ECs from inflammatory state [70,136,220].

The role of Nrf2 in atherosclerosis in humans remains unclear. However, the data from Vlagtwedde-Vlaardingen study, on 1,390 cohort of exclusively Caucasian individuals of Dutch descent where the relation between *NFE2L2* and all-cause, cardiovascular mortality and its associations with triglyceride and cholesterol levels were studied, found that *NFE2L2* is associated with reduced risk of all-cause, cardiovascular mortality in humans and minor allele carriers of SNP rs13001694 in *NFE2L2* had a 20% reduced mortality risk during the 18 years of follow-up in the general population [221]. Similarly, the Tampere adult population cardiovascular risk (TAMRISK) study on Finnish 50-year-old cohort (n = 6000; hypertensive subjects of 336 subjects with diagnosed hypertension and 480 normotensive controls) where a SNP in the Nrf2 gene region was studied, indicated that polymorphisms in rs6721961, rs1962142, rs2706110 of *NFE2L2* were associated with cerebrovascular disease, rs6721961 showed association with hypertension and Nrf2 rs6706649 (C > T) genotype CC was associated significantly with increased serum cholesterol values compared to the TC genotype [222].

2.8. Nrf2 and aortic aneurysm

Atherosclerotic lesions form at specific regions of the arterial tree, such as in the vicinity of branch points, the outer wall of bifurcations, and the inner wall of curvatures, where disturbed flow occurs [223]. According to the law of Laplace, the enlargement of aortic diameter leads to the higher mechanical stress acting on the vessel wall, thus activating mechanoreceptors and cytoskeleton on the endothelial layer or resident cells. Therefore, atherosclerosis may lead to dilatation of the aortic wall causing an aortic aneurysm [224].

Age constitutes a major risk for aneurysm formation. Aneurysm incidence doubles every 5 years in men who are > 65 years old [225]. It may be connected to age-related reduction of SIRT1, what eases onset of senescence and increases vascular inflammation [226]. Additionally, inflammation and ROS play an essential role in the appearance and development of aortic dissection that may lead to life-threatening acute aortic dissection. Oxidative stress causes a disturbance between regeneration and destruction of the vascular wall through several processes: increasing SMCs apoptosis, reinforcing matrix proteolysis, changing mechanical forces and increasing inflammation (reviewed in [227]). All of those processes are dependent on Nrf2, as it was described in this review. However, there are not many studies which directly link Nrf2 and aneurysm formation. In one of them, the authors indicated that ursodeoxycholic acid (UDCA) protects against acute aortic dissection caused by infusion of AngII to *Apoe* knockout mice. UDCA, acting through Nrf2, decreased ROS level in VSMC and infiltrating immune cells and prevented SMCs apoptosis [228]. Moreover, disturbed flow causes ligand-independent activation of VEGFR2, what indirectly leads to stabilization of unspliced XBP1 and HDAC3, activation of Akt1, increasing Nrf2 stability and transcription of *HMOX1* [229]. It is in accordance with previous researches indicating that unspliced XBP1 can induce the antioxidant response (summarized in [230]).

2.9. Concluding remarks

To summarize, fine-tuning of the redox balance in the cardiovascular system seems to be pivotal for the maintenance of a healthy cardiovascular system. The activity of Nrf2 may counteract aging and related diseased on many levels, primarily by driving the expression of detoxifying and cytoprotective genes. Furthermore, Nrf2 can decrease the detrimental effects of acute injuries, such as myocardial infarction. On the other hand, high activity of Nrf2 in macrophages may lead to enhanced atherosclerosis. Therefore, we conclude, that although the Nrf2 system exerts mostly beneficial effects concerning aging and CVDs, its effects are complex and strongly depend on the cell type.

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