HIGHLIGHTED TOPIC | Physiology of the Aging Vasculature

Inflammation and endothelial dysfunction during aging: role of NF-κB

Anna Csiszar,1 Mingyi Wang,2 Edward G. Lakatta,2 and Zoltan Ungvari1

1Department of Physiology, New York Medical College, Valhalla, New York; and 2Laboratory of Cardiovascular Science, Gerontology Research Center, National Institute on Aging, National Institutes of Health, Baltimore, Maryland

CSIZAR A, WANG M, LAKATTA EG, UNGVARI Z. Inflammation and endothelial dysfunction during aging: role of NF-κB. J Appl Physiol 105: 1333–1341, 2008.—One of the major conceptual advances in our understanding of the pathogenesis of age-associated cardiovascular diseases has been the insight that age-related oxidative stress may promote vascular inflammation even in the absence of traditional risk factors associated with atherogenesis (e.g., hypertension or metabolic diseases). In the present review we summarize recent experimental data suggesting that mitochondrial production of reactive oxygen species, innate immunity, the local TNF-α-converting enzyme (TACE)-TNF-α, and the renin-angiotensin system may underlie NF-κB induction and endothelial activation in aged arteries. The theme that emerges from this review is that multiple proinflammatory pathways converge on NF-κB in the aged arterial wall, and that the transcriptional activity of NF-κB is regulated by multiple nuclear factors during aging, including nuclear enzymes poly(ADP-ribose) polymerase (PARP-1) and SIRT-1. We also discuss the possibility that nucleophosmin (NPM or nuclear phosphoprotein B23), a known modulator of the cellular oxidative stress response, may also regulate NF-κB activity in endothelial cells.

Dysfunction, senescence, resveratrol, caloric restriction, poly(ADP-ribose) polymerase, renin-angiotensin system; coronary artery disease; stroke; myocardial infarction

There are over 35 million Americans 65 yr of age or older, and the majority of them will suffer from age-associated cardiovascular disease (53–55). Understanding the critical mechanisms underlying cardiovascular aging and age-related arterial pathophysiologial alterations may hold promise in developing novel interventional treatments for promotion of cardiovascular health in older persons.

There is increasing evidence that inflammation in the absence of other risk factors, aging per se promotes development of atherosclerosis and increases the morbidity and mortality of myocardial infarction and stroke. The mechanisms by which endothelial oxidative stress and arterial inflammatory processes act as potent proatherogenic stimuli have been the subject of intense study. This review focuses on emerging evidence that reactive oxygen species (ROS) and activation of inflammatory pathways each play a central role in cardiovascular aging (52–55), and discusses the role of NF-κB in the endothelial oxidative stress response during aging.

OXIDATIVE STRESS AND ARTERIAL INFLAMMATION IN AGED ARTERIES: ROLE OF NF-κB INDUCTION

Since Harman originally proposed the free radical theory of aging (40), considerable evidence has been published that increased production of ROS underlies cellular dysfunction in various organ systems of aged humans and laboratory animals (19, 22, 32, 38, 88, 101). The oxidative stress theory of aging postulates that ROS induce a variety of macromolecular oxidative modifications, and accumulation of such oxidative damage is a primary causal factor in the aging process. There is also strong evidence that oxidative stress develops with age in the arterial system, both in humans (28, 30, 31, 33, 48) and laboratory animals (22, 32, 38, 88, 101). One of the consequences of increased oxidative stress in aging is a functional inactivation of NO by high concentrations of O2•−, resulting in enhanced ONOO− formation (1, 22, 28, 32, 48, 88). It is generally accepted that severe impairment of NO bioavailability during aging will decrease vasodilator capacity, thereby limiting tissue blood supply (19, 98). There is an emerging view that ROS, in addition to scavenging NO and causing oxidative damage, play important signaling roles during aging (Fig. 1), increasing production of ROS in arterial inflammation [reviewed recently elsewhere (15, 19, 52, 95, 96, 98)].

Inflammation is considered to be a critical initial step in the development of atherosclerosis during aging. Our recent studies demonstrate that arterial aging, even in the absence of traditional risk factors for atherosclerosis (hypertension, diabetes, smoking, etc.), is associated with a proinflammatory shift in gene expression profile (19, 22–24, 95). Proinflammatory changes in endothelial phenotype, known as “endothelial activation,” involve upregulation of cellular adhesion molecules, an increase in endothelial-leukocyte interactions and permeability, as well as alterations in the secretion of autocrine/paracrine factors, which are pivotal to inflammatory re-

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Fig. 1. Proposed scheme for pathways contributing to cellular oxidative stress and NF-κB activation in aged endothelial cells. In aged endothelial cells, increased levels of O$_2$$^-$ generated by the electron transport chain and NAD(P)H oxidases [stimulated by elevated TNF-α levels and/or by the activated local renin-angiotensin system (RAS) in the vascular wall] are dismutated to H$_2$O$_2$. Increased cytoplasmic H$_2$O$_2$ levels and activation of toll-like receptors (TLRs) each contribute to the activation and nuclear translocation of NF-κB, which results in a proinflammatory shift in the endothelial gene expression profile, endothelial activation, and increased monocyte adhesiveness to the endothelium. The transcriptional activity of NF-κB is regulated by nucleosomin (NPM) and SIRT-1 (hatched arrows represent inhibition), and both pathways exhibit age-related alterations. In addition, poly(ADP-ribose) polymerase (PARP-1) activation also modulates transcriptional activity of NF-κB. Increased O$_2$$^-$ production and/or downregulation of endothelial nitric oxide synthase (eNOS) are mutually responsible for impaired bioavailability of NO and endothelial vasodilator dysfunction in aged arteries. The model predicts that upregulation of TNF-α may contribute to endothelial apoptotic cell death, which, along with increased oxidative stress and vascular inflammation, increases the risk for coronary artery disease. iNOS, inducible nitric oxide synthase; SOD2, superoxide dismutase.

MULTIPLE PATHWAYS CAN REGULATE NF-κB ACTIVATION PROMOTING ARTERIAL INFLAMMATION DURING AGING

In arterial cells, NF-κB is present as an inactive, IκB-bound complex in the cytoplasm. On stimulation NF-κB enters the nucleus and activates gene expression, a key step for controlling NF-κB activity via regulation of the interaction between IκB and NF-κB. Many signals that lead to activation of NF-κB converge on the ROS-dependent activation of a high-molecular-weight complex that contains an IκB kinase (IKK). Activation of IKK complex leads to the phosphorylation and degradation of IκB, consequently unmasking NF-κB. Pathways that converge on NF-κB may contribute to endothelial activation during aging, and include TNF-α signaling, mitochondrial ROS-induced pathways, the local renin-angiotensin system (RAS), and pathways associated with innate immunity (Fig. 1). NF-κB is also regulated by ubiquitination, acetylation, and prolyl isomerization, and the transactivation activity of NF-κB can be affected by phosphorylation and poly(ADP-ribose)ylation. In the present review, we discuss the potential role of three nuclear factors, PARP-1, SIRT-1, and nucleophosmin, in regulation of NF-κB activity during aging.

Role of TNF-α in arterial inflammation in aging. TNF-α is the prototypic proinflammatory cytokine and master regulator of endothelial activation via the NF-κB pathway. It has been repeatedly shown that circulating TNF-α levels are increased in aged animals and older humans (7, 84, 85, 111). We have demonstrated that in aged rodent coronary arteries, there is an upregulation of TNF-α (23, 24) associated with a gene expres-
sion profile suggestive of an inflammatory response (22–24, 32, 85, 95). Increased TNF-α production has been also demonstrated in the carotid arteries, aortic wall (6), and heart (58) of aged rodents. We have previously demonstrated that arterial endothelial and smooth muscle express the TNF-α-converting enzyme (TACE/ADAM17) (24), suggesting the presence of an autocrine/paracrine TNF-α-dependent regulatory pathway in the arterial wall. Because TNF-α can be secreted by arterial cells (due to the activity of TACE), it is likely that arterial TNF-α production contributes to elevated plasma concentrations of TNF-α in older organisms. It is also likely that, in addition to arterial cells and immunocytes, adipocytes are another significant source of circulating TNF-α (106). In this regard, it is significant that serum conditioned by adipocytes from aged mice can induce an inflammatory response in detector cells (106). Because an NF-κB binding site is present on the promoter region of the TNF-α gene (78), the possibility that increased circulating levels of TNF-α promote TNF-α expression in the arterial wall cannot be ruled out.

Importantly, our recent studies, as well as those conducted by other laboratories, have linked TNF-α to endothelial impairment during aging (4, 18). These studies have demonstrated that administration of exogenous TNF-α can induce oxidative stress by upregulating/activating NAD(P)H oxidase (18, 94), endothelial dysfunction (18), and endothelial apoptosis (18, 24). Importantly with respect to the present review, TNF-α is a potent activator of NF-κB in endothelial cells (18, 20). There is solid evidence that TNF-α activates NAD(P)H oxidase-dependent ROS generation, which then activates NF-κB. Accordingly, in endothelial cells (20), TNF-α treatment results in NF-κB-dependent upregulation of proatherogenic inflammatory mediators, such as iNOS and adhesion molecules, which can, in turn, be attenuated by NAD(P)H oxidase inhibitors. The effects induced by TNF-α closely mimic aging-induced functional and phenotypic alterations of the arterial endothelium (18, 22–24, 88, 101). Indeed, there are strong data suggesting that neutralization of TNF-α by chronic etanercept treatment improves endothelial function, attenuates oxidative stress, reduces arterial NADPH oxidase activity and expression, and attenuates expression of adhesion molecules (18). Etanercept (Enbrel) is an FDA-approved drug (composed of the extracellular ligand-binding portion of human TNF receptor 2) that binds and inactivates circulating TNF-α. Previous studies also suggest that increased endothelial apoptosis is a feature of advanced aging (16, 18, 22, 24). The results of both chronic etanercept treatment (16) and in vitro neutralization of TNF-α (24) decreased apoptotic cell death in aged vessels. This provides strong evidence that increased TNF-α levels during aging, in addition to promoting arterial inflammation, also initiate programmed endothelial cell death, which may likely contribute to age-related cardiovascular pathophysiology (95).

Role of mitochondrial oxidative stress in arterial inflammation during aging. The mitochondrial theory of aging (41) postulates that mitochondria-derived H$_2$O$_2$ diffuses readily through cellular membranes, thereby contributing to a variety of macromolecular oxidative modifications. Several lines of evidence suggest that mitochondria are a major source of H$_2$O$_2$ in aged blood vessels (99, 100), which, in addition to causing oxidative damage, play important signaling roles. The findings that inhibition of mitochondrial ROS production or scavenging of H$_2$O$_2$ attenuates NF-κB activation and NF-κB-dependent gene expression in aged vessels (100) suggest that mitochondrial H$_2$O$_2$ production is involved in regulation of endothelial NF-κB activity. In contrast, it is likely that mitochondria-derived O$_2^{•−}$ plays a lesser signaling role. First, O$_2^{•−}$ is membrane impermeable (except in the protonated perhydroxyl radical form, which represents only a small fraction of total O$_2^{•−}$ produced), whereas H$_2$O$_2$ easily penetrates the mitochondrial membranes. Second, because of efficient scavenging of O$_2^{•−}$ by high levels of superoxide dismutase (SOD) in mitochondria, it is likely that mitochondria-derived H$_2$O$_2$ is a major factor in initiating inflammatory signaling processes in endothelial cells. This view is in line with the finding that exogenous H$_2$O$_2$ substantially increases NF-κB activation in vessels of young rats, mimicking the aging phenotype (100). It is interesting to note that mitochondrial oxidative stress in the cardiovascular system during aging is also associated with increased lipid peroxidation (49), and end products of lipid peroxidation were shown to induce NF-κB activation in endothelial cells in vitro (59). In addition, mitochondrial ROS-induced NF-κB is likely to upregulate the expression of inflammatory cytokines (e.g., IL-6, TNF-α), which may further increase oxidative stress (e.g., by activating NADPH oxidases) and thereby NF-κB activation during aging. Collectively, these observations suggest that an associated decline in mitochondrial function is at least partially responsible for arterial inflammation in aging (100). Indeed, in aging mice that overexpress human catalase in the mitochondria (MCAT), cardiac pathology is delayed, oxidative damage is reduced, H$_2$O$_2$ production and H$_2$O$_2$-induced aconitase inactivation are attenuated, and the development of mitochondrial deletions is reduced (83). It would be of interest to elucidate whether inflammatory gene expression is also attenuated in the cardiovascular system of MCAT mice. Interestingly, mitochondria-derived H$_2$O$_2$ has been proposed as a vasodilator in coronary arteries in previous studies (67, 69). Yet, endothelial function in coronary arteries is significantly impaired during aging (22), suggesting that mitochondrial oxidative stress does not compensate for the loss of NO-mediated vasodilation.

The oxidative stress theory of aging predicts that longer-lived species should 1) produce less ROS and/or 2) exhibit superior resistance to the adverse effects of oxidative stress. In support of this theory, we have recently reported that successfully aging species, including the naked mole-rat (Heterocephalus glaber; maximum lifespan >28 yr), the white-footed mouse (Peromyscus leucopus; maximum lifespan >8 yr), and the little brown bat (Myotis lucifugus; maximum lifespan >30 yr), exhibit significantly lower arterial ROS production and/or superior cellular resistance to oxidative stress than the house mouse (Mus musculus; maximum lifespan ~3.5 yr) (16, 51, 92, 97). Presently, it is unknown whether lower cellular and mitochondrial ROS production (57) in longer-lived species is associated with an attenuated arterial inflammatory response during aging compared with that in shorter-lived species.

We have recently demonstrated that aging is associated with impaired mitochondrial biogenesis in the arterial system (99). There is also increasing evidence that alterations in mitochondrial biogenesis are associated with mitochondrial dysfunction in various organs during aging [reviewed recently elsewhere (5, 15)]. It is thought that mitochondrial proliferation reduces the flow of electrons per unit mitochondria (if cellular energy...
demand is unchanged), which, per se, attenuates mitochondrial ROS production. Thus it is likely that impaired mitochondrial biogenesis during aging may contribute to increased mitochondrial oxidative stress, thereby increasing H$_2$O$_2$-mediated NF-κB activation, as well as induction of inflammatory gene expression. In this regard, it should be noted that TNF-α has been linked to mitochondrial dysregulation in vitro. Whether upregulated TNF-α plays a role in mitochondrial dysregulation and mitochondrial oxidative stress in aged arteries, however, is yet to be determined.

**Role of the local RAS in arterial inflammation during aging.**
Previous studies called attention to the association of an upregulated tissue RAS with intimal thickening and remodeling in large arteries of aged animals and humans (86, 102–104). The aforementioned studies demonstrated that angiotensin-converting enzyme (ACE), ANG II, ANG II receptor type 1, matrix metalloproteinases 2/9 (which can degrade the major components of the arterial extracellular matrix, contributing to intimal growth and vessel wall remodeling), and monocyte chemoattractant protein-1 (which can promote leukocyte infiltration) increase within the arterial wall during aging (56, 65, 86, 92, 102–104). The data so far suggest that upregulation of RAS contributes to chronic arterial inflammation during aging, enhancing arterial response to injury while rendering the arterial wall susceptible to the development of arterial diseases (including atherosclerosis and hypertension). ANG II is known to regulate NF-κB activity (44, 91), likely via a redox-sensitive pathway involving NAD(P)H oxidases (34). It is thus possible that activation of local RAS contributes to NF-κB induction and endothelial activation during aging. Indeed, some studies suggest that older patients with overt atherosclerotic plaques may benefit from pharmacological disruption of the local RAS (81).

**Does innate immunity play a role in arterial inflammation during aging?** During the aging process, adaptive immunity significantly declines (“immunosenescence”). In contrast, recent data suggest that mechanisms related to innate immunity are upregulated/activated during aging (80). In their signaling, toll-like receptors (TLR) play a significant role in innate immune defense. TLR4 is activated by bacterial lipopolysaccharide and various endogenous ligands, including those produced in response to tissue injury. TLR4 activates NF-κB and mitogen-activated protein kinase (MAPK) signaling cascades, which leads to a proinflammatory shift in cellular gene expression profile (39). TLRs are expressed in the arterial system, and there is increasing evidence linking upregulation/activation of TLRs to atherogenesis (2, 9, 45, 61, 70, 71, 82). Interestingly, recent studies demonstrated that multiple TLRs (including TLR1, TLR2, TLR4, TLR5, and TLR7) are upregulated in the mouse brain during aging (62). Our recent data suggest that TLR4 can be upregulated in the cardiovascular system of aged rodents, as well (Ungvary and Csizsar, unpublished observations). Thus the possibility that activation of innate immunity may contribute to arterial NF-κB activation and inflammatory gene expression during aging warrants further investigation.

**Does PARP-1 play a role in arterial inflammation during aging?** One of the consequences of increased oxidative stress during aging is a functional inactivation of NO by high concentrations of O$_2$$^•$-, resulting in an enhanced peroxynitrite formation (1, 22, 32, 88). The possible downstream targets of peroxynitrite are multiple (for an excellent review, see Ref. 73). Both peroxynitrite and H$_2$O$_2$ in large concentrations can induce DNA single strand breaks, which may contribute to the endothelial damage during aging (35, 73, 76). DNA damage induced by oxidative/nitrosative stress may lead to the activation of the nuclear enzyme PARP-1 and its homologs (8, 76). PARP-1 belongs to the DNA damage surveillance network, and its catalytic activity is markedly stimulated on binding to DNA strand interruptions (8). There is increasing evidence that PARP-1 activity increases during aging (74, 75, 77). We have recently reviewed the role of nitrosative stress and the potential contribution of PARP-1 activation to cardiovascular aging (19). In brief, on its activation PARP-1 transfers 50–200 molecules of ADP-ribose to various nuclear proteins, including transcription factors and histones. As a result, PARP-1 activation has been shown to modulate the transcriptional regulation of various inflammatory genes (10, 36). Important for the present review are the findings that PARP-1 can regulate NF-κB activation (3, 42, 115). Future studies are definitely needed to elucidate the role of PARP activation during age-induced cardiovascular dysfunction and inflammation.

**Role of SIRT1 in regulation of arterial inflammation during aging.** Studies from the past few years have revealed that the SIRT2/SIRT1 (silent mating type information regulation 2 homolog 1) gene promotes a longer lifespan in evolutionarily distant organisms and may underlie the effects of dietary restriction to extend healthy lifespan (14, 46, 105). Recently, we found that resveratrol, the most potent naturally occurring SIRT1 activator compound (STAC) (46, 105), effectively attenuates TNF-α and H$_2$O$_2$-induced endothelial activation by inhibiting NF-κB (17, 20). SIRT1, a nicotinamide adenine dinucleotide-dependent protein deacetylase, is likely to directly regulate the transcriptional activity of NF-κB (112). Indeed, SIRT1 was reported to physically interact with the RelA/p65 subunit of NF-κB and to inhibit transcription by deacetylating RelA/p65 (112). Whether age-associated alterations of SIRT1 activity play a role in arterial inflammation during aging has yet to be determined. SIRT1 is thought to mediate, at least in part, the effects of caloric restriction (98). In this regard it is important to note that caloric restriction abrogates arterial NF-κB activation during aging (98). Resveratrol was shown to extend longevity in lower organisms while mimicking the effects of caloric restriction (46, 105), and there is good reason to believe that it also exerts antiaging activity (including attenuation of arterial inflammation) in mammals (recently reviewed in Ref. 52). In this regard, it should be noted that there are also studies showing that higher concentrations of resveratrol exhibit direct antioxidant properties (47, 60, 87), which may further enhance the cytoprotective effects of SIRT1 induction.

**Does nucleophosmin regulate NF-κB activity in endothelial cells during aging?** Nucleophosmin (NPM or nuclear phosphoprotein B23) is a ubiquitously expressed multifunctional nuclear phosphoprotein that constantly shuttles between the nucleus and cytoplasm (109, 113). Although the role of NPM in arterial pathophysiology is almost completely unknown, it is important to note that many of the known functions of NPM are related to oxidative stress response, the maintenance of genomic stability, transcriptional gene regulation, and control of cellular senescence and apoptosis, all of which are of interest to arterial biologists and researchers of aging. NPM takes part in various cellular processes by shuttling between
cellular compartments, orchestrating cellular repair pathways and modulating cellular stress responses [including the responses to UV irradiation (68, 107, 108, 110) and hypoxia (64)]. NPM participates in DNA repair processes (68), and it also seems to control pathways regulating cellular senescence and apoptotic cell death (12, 63). There is also evidence that NPM is overexpressed in cancer cells, and it has been shown to be involved in both positive and negative regulation of transcription (116). It is thought that, by regulating histone acetylation (116), NPM plays an important role in the regulation of transcription through modulation of chromatin condensation and decondensation events (90). Indeed, NPM enhances the acetylation-dependent chromatin transcription and becomes acetylated both in vitro and in vivo (90).

Our recent findings indicate that NPM can regulate NF-κB activity in endothelial cells (Fig. 2). Specifically, TNF-α-induced NF-κB activation is significantly reduced in cultured human coronary arterial endothelial cells following knockdown of NPM (Fig. 2A). In contrast, overexpression of NPM per se increased endothelial NF-κB activity (Fig. 2A). In accordance with our findings, a recent study demonstrated physical interaction between NPM and NF-κB and provided evidence that overexpression of NPM leads to increased MnSOD gene transcription in a dose-dependent manner (25). MnSOD, a mitochondrial antioxidant enzyme regulated by NF-κB, is essential for providing the functional integrity of mitochondria during aging. Consistent with this, expression of small interfering RNA (siRNA) for NPM leads to inhibition of MnSOD gene transcription (25). Based on immunoprecipitation experiments, NPM was also found to be associated with NF-κB in U1 bladder cancer cells (66). Interestingly, on siRNA-mediated knockdown of intracellular NPM, inhibition of NF-κB with consequent target gene inactivation has been observed in this model as well (66). Using chromatin immunoprecipitation (ChIP) analysis, Dhar et al. (26) have recently demonstrated that Sirt1 and NPM interact in vivo to enhance NF-κB-mediated gene induction. Interaction between NPM and NF-κB at the promoter and enhancer of the MnSOD gene in vivo was verified by the presence of PCR products from the promoter and enhancer elements in the ChIP assay (26). Interestingly, the transcription factor p53 also appears to be a component of the NPM-containing complex (26). Our studies also demonstrate that SIRT1 activator resveratrol effectively inhibits NF-κB activation in endothelial cells induced by NPM overexpression (Fig. 2A). It seems that neither resveratrol nor SIRT1 regulates NPM at the transcriptional level (Fig. 2B), but we hypothesize that SIRT1 may prevent NPM-induced NF-κB activation by directly deacetylating NF-κB. A possible SIRT1-NPM interaction, however, cannot be ruled out. Importantly, expression of NPM seems to increase in carotid arteries of aged F344 rats (Fig. 2C). Accordingly, recent studies also suggest that expression of NPM tends to be upregulated during aging in skeletal muscle (29) and during heart aging (27). It is tempting to speculate that these age-related alterations in NPM expression/activity would promote NF-κB activation in older cells. This idea is further supported by the finding that caloric restriction, which inhibits arterial NF-κB activation during aging (98), reduces NPM expression in aged vessels (Fig. 2C).

Additional studies are needed to elucidate the role of NPM in regulation of gene expression in cardiovascular aging and pathophysiological conditions associated with accelerated arterial aging.

**Perspectives**

In conclusion, aging per se, in the absence of other risk factors [hypertension (21), hypercholesterolemia, hyperhomocysteinemia (93, 94), diabetes mellitus, smoking (72)] is associated with oxidative/nitrosative stress and inflammatory changes in the phenotype of blood vessels. Age-associated induction of NF-κB activation is especially interesting, since it seems to contribute significantly to endothelial activation in aged vessels, which is a critical initial step in the development of atherogenesis. Several proatherogenic pathways converge on NF-κB (Fig. 1), including the local TACE-TNF-α system, the local RAS, and pathways involved in innate immunity. In
addition, there is strong evidence suggesting a link between mitochondrial oxidative stress and NF-κB activation during aging. Whether novel treatments targeting the factors that regulate NF-κB activity (e.g., SIRT1 activators, PARP-1 inhibitors) or attenuating mitochondrial oxidative stress are able to reverse or delay the age-induced arterial inflammation and the functional decline of the cardiovascular system remains a subject of current debate. It also remains to be seen whether animals genetically deficient in (or who show an overexpression of) TNF-α, TLRs, SIRT-1, and PARP-1 exhibit arterial phenotypic alterations during aging.

Future studies need to elucidate the link between age-related oxidative stress and arterial inflammation in successfully aging species and explore interspecies differences in NF-κB signaling and action of SIRT-1 and NPM. Finally, studies on humans and nonhuman primates are evidently needed to better understand the generality of age-related arterial phenotypic changes observed in laboratory animals.

Overall, to the benefit of older patients, we can expect recent advances in our understanding of oxidative/nitrosative stress and redox-sensitive inflammatory mechanisms to yield novel therapeutic approaches in the study of cardiovascular aging.

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