HHS Public Access

Author manuscript

J Am Coll Cardiol. Author manuscript; available in PMC 2021 November 01.

Published in final edited form as:

J Am Coll Cardiol. 2020 March 03; 75(8): 931–941. doi:10.1016/j.jacc.2019.11.061.

Mechanisms of Vascular Aging, A Geroscience Perspective: JACC Focus Seminar

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Abstract

Age-related pathological alterations of the vasculature have a critical role in morbidity and mortality of older adults. In epidemiological studies age is the single most important cardiovascular risk factor that dwarfs the impact of traditional risk factors. In order to develop novel therapeutic interventions for prevention of age-related vascular pathologies it is crucial to understand the cellular and molecular mechanisms of vascular aging. In this review, shared molecular mechanisms of aging are considered in terms of their contribution to the pathogenesis of macro- and microvascular diseases associated with old age. The role of cellular senescence in development of vascular aging phenotypes is highlighted and potential interventions to prevent senescence and to eliminate senescent cells for prevention of vascular pathologies are presented. The evidence supporting a role for inter-organ communication and circulating pro-geronic and anti-geronic factors in vascular aging is discussed.

Condensed abstract:

Age-related pathological alterations of the vasculature have a critical role in morbidity and mortality of older adults. In this review, shared molecular mechanisms of aging are considered

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Disclosures: None

in terms of their contribution to the pathogenesis of macro- and microvascular diseases associated with old age. The role of cellular senescence in development of vascular aging phenotypes is highlighted and potential interventions to eliminate senescent cells for prevention of vascular pathologies are presented. The evidence supporting an important role for inter-organ communication and circulating pro-geronic and anti-geronic factors in orchestration of vascular aging processes is discussed.

Keywords

geroscience; senescence; endothelial dysfunction; microcirculation; atherosclerosis

Introduction: a man is as old as his arteries – and microvessels

The famous seventeenth-century physician Thomas Sydenham, known as the “English Hippocrates,” observed, “a man is as old as his arteries.” Modern medicine concurs: cardiovascular and cerebrovascular diseases are the leading causes of serious long-term disability and mortality among older adults in the developed world(1). Importantly, in population-based studies the effects of conventional risk factors (e.g., hypertension, hypercholesterolemia, etc.) on the prevalence of cardiovascular and cerebrovascular diseases are dwarfed by the single most important risk factor for these diseases: advanced aging (1).

In addition to recognized role of vascular aging processes in the genesis of age-related macrovascular diseases (e.g., atherosclerotic diseases of the large arteries (1)), there is also increasing appreciation of the importance of age-related microvascular pathologies (2). Aging causes multifaceted structural and functional microcirculatory impairment, which has deleterious effects on tissue oxygenation, nutrient delivery, waste removal and thus negatively impacts multiple organ functions (2). Aging also impairs local regulation of microvascular perfusion (e.g., by impairing endothelium-mediated, flow-induced arteriolar vasodilation), angiogenesis) and promotes pathological structural remodeling of the microvascular network, resulting in microvascular rarefaction (3). By altering the phenotype of endothelial cells, smooth muscle cells and pericytes, microvascular aging also negatively impacts the function of the immune system (e.g., white blood cell adhesion and chemotaxis) and endocrine system (e.g., insulin signaling), and impairs barrier function and stem cell physiology (e.g., altering stem cell niches and impacting endothelial cell-stem cell interactions during homing and engraftment) (2). Aging also alters the secretory phenotype of cells in the microcirculatory network, which results in deleterious changes in the production of a wide range of trophic factors, cytokines, chemokines, lipid mediators, exosomal factors, micropeptides and/or gasotransmitters(2). All of the aforementioned age-related microcirculatory alterations contribute to the age-related complex changes in the local humoral and cellular environment in the tissues. Aging-induced microvascular functional, structural and phenotypic alterations play a critical role in age-related dysfunction of multiple organ systems and contribute significantly to the pathogenesis of a diverse spectrum of age-related diseases (e.g., heart failure, Alzheimer’s disease, vascular cognitive impairment, age-related macular degeneration [AMD], sarcopenia and kidney disease)(2). The emerging concept is that shared molecular and cellular mechanisms

underlie both age-related macrovascular and microvascular pathologies, as well as other diseases associated with old age (Central Illustration).

Significant advances in geroscience in the 21st century have led to the identification of evolutionarily conserved pathways responsible for regulation of lifespan and health span (4). In the present review, the pathophysiological roles of these fundamental aging processes in the vascular system are considered in terms of their contribution to both micro- and macrovascular aging phenotypes and the pathogenesis of age-related vascular diseases (Central Illustration). The interconnectedness between the cellular and molecular mechanisms of vascular aging and the interaction among these aging processes, disease-specific pathways and cardiovascular risk factors is emphasized. We also provide an overview of emerging experimental evidence, which supports the existence and significance of diverse secreted/circulatory factors derived from distal organs that modulate vascular aging processes.

Our emerging understanding of vascular aging processes enable the identification of novel targets for therapeutic intervention to reverse the deleterious consequences of vascular aging and to improve cardiovascular and cerebrovascular health in older adults. In the present review we discuss the potential therapeutic benefits of a new class of treatment: prevention of cellular senescence and elimination of senescent cells. Related reviews in the same issue discuss in detail the vasoprotective effects of interventions that target sirtuin-regulated pathways and autophagy. For an overview of emerging therapies targeting other major processes involved in vascular aging (Table 1) and the effects of preventive measures already available and in clinical use (e.g., physical exercise, dietary regimens, smoking cessation, inhibitors of the renin-angiotensin system, statins) the interested reader is referred to recent comprehensive reviews (2,5).

Shared mechanisms of macro- and micro-vascular aging

The goal of geroscience research is to develop drugs and interventions for prevention and treatment of a range of chronic diseases of old age as a class, by targeting shared mechanisms of aging (4). It is expected that this strategy will also result in revolutionary novel interventions preventing, attenuating and reversing age-related vascular pathologies (5).

The relative contribution of cell autonomous and non-autonomous mechanisms to systemic aging in human subjects, laboratory animals and different model organisms is hotly debated. The model for vascular aging that we have recently proposed(2) predicts that a range of shared and interconnected cell-autonomous molecular mechanisms of aging contribute both to the genesis of vascular aging phenotypes and age-related pathologies of other organ systems (Central Illustration). These mechanisms of vascular aging are listed in Table 1. In general, many of these mechanisms are related to spontaneous, stochastic damage that activate evolutionarily conserved cellular programs (e.g., senescence, inflammatory responses, etc.) and the pathways determining the resilience of the cells to such damage/stress (e.g., loss of proteostasis, impaired Nrf2-driven antioxidant response and DNA repair, etc.). For a detailed discussion of the roles of these cellular and molecular mechanisms

in age-related vascular pathologies the interested reader is referred to recent reviews (2). In the present review the role of increased cellular senescence, a specific cell-autonomous mechanism of vascular aging, , and its potential therapeutic considerations are discussed in more detail (Figure 1).

It has also become apparent in recent years that cell-autonomous mechanisms alone(4) are inadequate to explain all aspects of vascular aging. The hierarchical regulatory cascade for vascular aging also involves modulation of cell-autonomous cellular and molecular aging processes by systemic/circulating factors (2). In addition, age-related cell autonomous changes also cause non-cell autonomous consequences (e.g., release of paracrine mediators from senescent cells) that affect vascular aging (2). According to the model proposed, circulating progeronic factors and anti-geronic factors derived from the central nervous system, endocrine organs, the immune system, the adipose tissue and other organs (including the gastrointestinal tract) orchestrate microvascular and macrovascular aging processes (Figure 2). An important prediction of the model is that conventional risk factors promote age-related cardiovascular and cerebrovascular pathologies by exacerbating one or more fundamental molecular and cellular (cell autonomous and non-cell autonomous) aging processes (Central Illustration).

Exacerbation of vascular aging processes by cardiovascular and cerebrovascular risk factors

From the standpoint of geroscience, conventional risk factors promote cardiovascular and cerebrovascular pathologies by inducing an ‘accelerated vascular aging’ phenotype, which account for the inter-individual variability in the rate of development and progression of age-related vascular diseases (Central Illustration). Each conventional cardiovascular and cerebrovascular risk factor exacerbates one or more fundamental cellular and molecular aging processes in the vasculature (2). Accordingly, hypercholesterolemia, hypertension, high fat diet consumption, hyperhomocysteinemia, obesity and diabetes mellitus promote increased inflammatory status, oxidative/nitrosative stress, mitochondrial dysfunction, endothelial apoptosis, macromolecular damage and/or increased senescence in the vascular wall (2,6). Smoking, environmental pollutants (e.g., diesel exhaust particles) and other toxicants promote oxidative/nitrosative stress, inflammation, induce DNA damage, and promote cellular senescence in the vasculature(2). Sedentary lifestyle (and the consequentially altered hemodynamic environment, including decreased shear stress) is associated with increased inflammatory status and oxidative stress(2). Whole brain radiation therapy of tumor patients promotes DNA damage and induces cellular senescence, which results in an accelerated cerebromicrovascular aging phenotype contributing to the genesis of cognitive decline(7,8). Importantly, a better mechanistic understanding of the interaction between cardiovascular risk factors and specific aging processes will enable the development of innovative combination treatments for prevention in elderly patients at risk for cardiovascular and cerebrovascular pathologies. It is expected that in the future preventive measures already available and in clinical use that target conventional risk factors (e.g., physical exercise, dietary regimens, smoking cessation, inhibition of the renin – angiotensin-aldosterone system, statins) will be combined with interventions that increase

the resilience of the vasculature to cellular stresses (e.g., by boosting the endogenous cell survival pathways, including SIRT1(9) and Nrf2 regulated pathways(6)) and target the cellular and molecular aging processes contributing to the pathogenesis of vascular diseases. One caveat to keep in mind is that therapies that increase microvascular blood supply and/or stimulate prosurvival pathways in transformed cells may also promote tumor growth in older individuals.

Elimination of senescent cells: an emerging approach for prevention of age-related vascular pathologies

Cellular senescence is regarded as a fundamental aging process characterized by irreversible growth arrest, functional impairment and profound pro-inflammatory secretome changes (10) (Figure 1). Various endogenous and exogenous stressors (e.g., reactive oxygen and nitrogen species, DNA damage, mitochondrial dysfunction, telomere dysfunction, paracrine signals) can exacerbate cellular senescence in aging (11,12). Strong preclinical data show that depletion of $p16^{INK4A}$ expressing senescent cells can significantly extend lifespan and health span in mouse models (11). These data support the concept that increased presence of senescent cells have important roles in age-related physiological decline and vulnerability to diseases. In previous studies senescent cells have been implicated in the pathogenesis of a wide range of age-related diseases, including chronic obstructive pulmonary disease, sarcopenia, liver fibrosis, obesity, diabetes mellitus, chronic kidney disease, Alzheimer's disease, Parkinson's disease, cataracts, AMD, diabetic retinopathy, cardiac fibrosis, heart failure, osteoporosis, osteoarthritis and cancer(13). There is also growing evidence that both aging and pathophysiological conditions associated with accelerated vascular aging associate with increased presence of senescent cells in the vasculature (14,15). Though the ratio of senescent cells is usually low, multiple mechanisms have been identified by which they may impair vascular function and promote development of age-related vascular pathologies (Figure 1). Senescent vascular cells exhibit increased production of ROS and acquire a senescence-associated secretory phenotype (SASP), which is characterized by increased production of inflammatory cytokines and chemokines and altered synthesis of lipid mediators (16). There are multiple ways by which senescent cells may affect the function and phenotype of neighboring cells in the vascular system. Endothelial cells are connected by gap junctions and function as a syncytium. Thus, it is possible that signals that induce senescence may be transmitted between cells (Figure 1). Secretion of SASP factors may also induce paracrine senescence and/or impair the function of neighboring cells. Through the aforementioned mechanisms senescent cells may contribute to endothelial dysfunction (14), impaired barrier function, heightened inflammatory status and pathological remodeling of arteries and/or microvessels in aging (17). In senescent cells the biosynthesis of components of the extracellular matrix (ECM), secretion of ECM degrading matrix metalloproteinases (MMPs) and expression of growth factors that regulate remodeling of the ECM are also altered. Thus, it is also possible that presence of senescent cells in the arterial wall may also contribute to decreased elasticity, increased stiffness and impaired resilience of the vascular wall to mechanical damage. Replicative senescence may also be potentially important for age-related impairment of regenerative and angiogenic capacity of the microvascular endothelial cells. These hypotheses should be experimentally tested. Proof-of-

concept for the important pathological role of cellular senescence in accelerated vascular aging has been provided by investigations using a mouse model of y-irradiation-induced, DNA damage-dependent senescence(16) showing that experimentally induced senescence in cells of the neurovascular unit promotes dysregulation of cerebral blood flow, neurovascular dysfunction, disruption of the blood brain barrier, microvascular rarefaction and cognitive deficits, mimicking the brain aging phenotype (7). Studies on genetic murine models of accelerated cellular senescence (e.g., $BubR1^{H/H}$ mice) extend these findings demonstrating that induction of senescence in vascular endothelial cells and pericytes associates with blood brain barrier disruption(18). Importantly, increased presence of senescent cells has been shown in advanced atherosclerotic lesions(10). Elimination of senescent cells in $Ldlr^{-/-}$mice by genetic and pharmacological approaches exerts anti-atherogenic effects, implicating senescent cells both in exacerbation of vascular inflammatory processes(19) and plaque instability (10). Future studies also should investigate the possibility of paracrine transmission of senescence from vascular cells to perivascular and parenchymal cells (11).

It is expected that therapeutic strategies that increase the stress resilience of vascular cells would prevent vascular senescence. The Nrf2-dependent homeostatic antioxidant defense pathway plays a central role in vascular stress resilience by regulation of both cellular DNA repair and elimination of ROS. Importantly, genetic depletion of Nrf2 exacerbates age-related vascular senescence(20). Treatment with pharmacological activators of Nrf2, including resveratrol, which attenuates ROS-induced DNA damage is expected to prevent ROS-induced senescence in vascular cells(2). Importantly, senescent cells can also be eliminated pharmacologically(21). There are several experimental senolytic strategies extant, including treatment with dasatinib, the polyphenols quercetin and fisetin and the Bcl-2/Bcl-XL inhibitor navitoclax (ABT263), which result in effective and selective removal of senescent cells in a number of organs, including the vasculature(10,21). Initial studies demonstrate that chronic treatment with senolytic drugs can attenuate atherogenesis(10) and improve endothelial function in aged mice(14). Future studies should test the protective effects of a wide range of translationally relevant senolytic treatments in animal models of various age-related macro- and microvascular pathologies. The exact cause of increased cellular senescence in the vasculature, including the role of increased oxidative stress, impaired stress resilience pathways and increased DNA damage should be further explored. The contribution of exogenous stressors (e.g., toxicants, dietary factors) and the role of factors released from senescent cells residing in other organs (e.g., the adipose tissue(12)) in older individuals towards induction of vascular senescence should also be elucidated. The potential unwanted/unexpected side effects of senolytic treatments should also be considered. For example, it should be methodically tested whether senescence cell removal may cause temporary microvascular damage (e.g., blood brain barrier disruption). Future studies also should explore variations in the senescent phenotype within the vascular cells. Studies using single cell sequencing methods will be quite informative in that regard. Finally, new biomarkers for senescence are needed that could be used in translational studies. These may include analysis of a wide range of SASP factors and exosomes derived from senescent cells, among others.

Regulation of vascular aging by pro-geronic and anti-geronic circulating factors

Increasing evidence suggests that organismal aging is associated with complex changes in inter-organ communication, which play a critical role in orchestrating/modulating cellular and molecular aging processes in the vasculature (Figure 2). Factors derived from the brain, the endocrine system, immune system, the adipose tissue and other organs (including the gastrointestinal tract and the symbiotic microbiota) can alter the rate of vascular aging. Our proposed model predicts that circulating pro-geronic factors (whose production increases with age and which impair vascular homeostasis; e.g., inflammatory mediators) and anti-geronic factors (which reverse/prevent development of aging phenotypes; e.g., IGF-1, mediators of caloric restriction, vasoprotective hormones) orchestrate cellular and molecular aging processes in the entire vascular system, including macrovascular and microvascular endothelial and smooth muscle cells, pericytes and cells of the neurovascular unit (including astrocytes). Changes in the balance of these circulating factors result in generalized functional alterations in both the large vessels and the microcirculation affecting structure and vasomotor, barrier, secretory and transport functions of the vasculature, promoting adverse structural remodeling and the development of a spectrum of age-related vascular pathologies.

In that regard, age-related changes in vasoprotective endocrine factors are of great significance, including altered interactions among the brain (hypothalamus), anterior pituitary gland, their target organs (gonads, liver) and the vasculature. Age-related changes in the gonadal and growth-hormone/insulin-like growth factor (GH/IGF-I) axes are associated with significant decreases in circulating levels of GH, IGF-1 and estrogens, which contribute to impairment of endothelial vasodilation, impaired autoregulation of cerebral blood flow, pathological vascular remodeling, atherogenesis, impaired vascular stress resilience, impaired angiogenic processes and microvascular rarefaction (2,3).

The critical role of circulating pro- and anti-geronic factors on cellular aging phenotypes was demonstrated by investigations using mouse models of heterochronic parabiosis (when a young mouse is surgically joined to an aged partner connecting their circulatory systems (22)) and mice with heterochronic blood apheresis(23) (which enables heterochronic blood exchange between young and old mice without sharing other organs). There is preliminary evidence that circulating anti-geronic factors derived from young mice can rejuvenate both endothelial function in large arteries (Ungvari, Csiszar, Huffman and Tarantini, unpublished observation 2019) and microvascular network architecture in aged heterochronic parabionts (22). Pro-geronic circulating factors, whose levels increase with age, may also contribute to impairment of vascular homeostasis(23). There is initial evidence that inflammatory cytokines (e.g. TNFα) may serve as pro-geronic circulating factors(2). Importantly, many of these factors are secreted by senescent cells in distant organs (e.g. the adipose tissue(12,13)).

Further evidence to demonstrate a key role of circulating anti-geronic factors orchestrating vascular aging processes is derived from investigations on animal models of calorie restriction, a dietary regimen, which extends health span and/or lifespan. Calorie restriction in rodents is associated with vascular rejuvenation, including rescue of endothelial function

and attenuation of oxidative stress and inflammation(2). Importantly, *in vitro* treatment of endothelial cells in culture with sera derived from caloric restricted rodents and non-human primates recapitulates cellular rejuvenating effects (including anti-inflammatory and pro-angiogenic effects) observed *in vivo* in caloric restricted animals(24,25).

The exact nature of the anti-geronic and pro-geronic circulating factors responsible for regulation of vascular aging processes and the vascular rejuvenating effects observed in the aforementioned studies, is a focus of current investigations. Figure 2 depicts potential candidates whose role can be inferred from indirect evidence. In addition to proteins, peptides, steroid hormones and other lipid mediators the roles of micropeptides, metabolites, NAD+ precursors, bacterial breakdown products and circulating exosomes, which contain many types of biomolecules, including cellular proteins, miRNAs and mRNAs, should be elucidated. Future studies should identify cellular origins of newly discovered circulating pro-geronic and anti-geronic factors that modulate vascular aging processes and determine their specific pathogenic roles in atherogenesis, endothelial dysfunction, blood brain barrier disruption and microvascular pathologies. Further studies are also warranted to better understand the role of circulating cells (immunocytes, endothelial precursor cells, platelets) in vascular rejuvenation. Human studies are needed to confirm that the role of these circulating factors in regulation of vascular aging is not species-specific and identify relevant pathological conditions that alter their levels in the circulation. Mechanistic studies characterizing the cellular effects of circulating pro-geronic and anti-geronic factors in the vascular cells are warranted. Pathways modulating cellular energy metabolism, including mitochondrial pathways and cellular nutrient sensing pathways, emerge as critically important areas for understanding vascular aging. Importantly, many putative circulating pro-geronic and anti-geronic factors (from TNFα to IGF-1 and mediators of caloric restriction) appear to modulate cellular energetics and mitochondrial function in vascular cells (2).

Perspectives

The aforementioned studies established the paradigm of the plasticity of vascular aging, demonstrating that vascular aging phenotypes can be reversed (6,14,15,26). The concept presented here (Table 1, Central Illustration) implies that several interrelated cell-autonomous cellular and molecular aging processes, also modulated by systemic/circulating factors, contribute to vascular aging. Thus, we predict that effective interventional strategies will use combination treatments targeting multiple vascular aging processes simultaneously. We propose that senolytic strategies (14) can be combined with treatments that prevent senescence induction (e.g., free radical and peroxynitrite scavengers, Nrf2 activators(6)), exert anti-inflammatory effects mitigating the impact of the SASP factors(26), improve mitochondrial function(27), activate AMPK(28) and sirtuin pathways(9), inhibit mTOR(29) and/or restore cellular NAD^+ levels(30,31). Anti-aging treatments that prove to be effective in preclinical studies should be also tested in translational studies(26). Importantly, a wide range of relevant vascular endpoints should be studied, from large artery health to microvascular physiology of the brain, heart, skeletal muscle (e.g. intermittent claudication), eye (e.g. AMD), kidney and ear (e.g. microvascular contributions to tinnitus). Critical areas of vascular aging research include mechanistic investigations into the microvascular

contributions to cognitive decline, neurodegeneration and heart failure as well as complex geriatric syndromes such as frailty in older adults. Interventions that improve the microcirculation are expected to exert pleiotropic therapeutic effects in these syndromes. Future studies should investigate cellular heterogeneity in the aging vasculature and its role in focal development of micro- and macrovascular pathologies, ranging from amyloid angiopathy and perivascular development of amyloid plaques in Alzheimer's disease (32), through atherosclerotic lesions to stroke, aneurysm and microhemorrhages (33). We also expect to see important breakthroughs in the near future in the fields at the intersection of microbiology, aging research and vascular biology. These will include better understanding of the role of the microbiota and the leaky gut in older adults in vascular pathologies and the contribution of infectious agents to the pathogenesis of age-related vascular diseases (including viruses with endothelial cell tropism, such as the human cytomegalovirus (34), fungi and bacterial pathogens penetrating the central nervous system though the lamina cribrosa). Public health research should shed light on the influence of the determinants of unsuccessful vascular aging (including genetic, environmental, dietary and socio-economic factors). Investigation of the mechanisms and consequences of macro- and microvascular aging evidently requires a multidisciplinary approach. We believe that universities with integrated translational geroscience programs bringing together expertise in cardiovascular and microvascular research, biogerontology, translational and public health research are the best positioned for this task.

Acknowledgment:

This work was supported by grants from the American Heart Association (ST), the Oklahoma Center for the Advancement of Science and Technology (to AC, ZU), the Presbyterian Health Foundation (to ZU, AC), the NIA-supported Geroscience Training Program in Oklahoma (T32AG052363), and the Cellular and Molecular GeroScience CoBRE (1P20GM125528).

Abbreviations:

SASP	senescence-associated secretory phenotype
AMD	Age-related macular degeneration
ROS	Reactive oxygen species
MMP	matrix metalloproteinase
ECM	Extracellular matrix
RAS	renin-angiotensin system
DAMPs	damage-associated molecular patterns
EPCs	endothelial progenitor cells
GH	growth hormone
IGF-1	Insulin-like growth factor-1

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Highlights

- Shared molecular mechanisms of aging promote macro- and microvascular pathologies associated with old age.
- Elimination of senescent cells is a promising approach for prevention of vascular diseases.
- Circulating pro-geronic and anti-geronic factors (e.g., IGF-1) regulate cell-autonomous processes of vascular aging.
- Future studies should elucidate how conventional cardiovascular risk factors exacerbate molecular mechanisms of vascular aging.

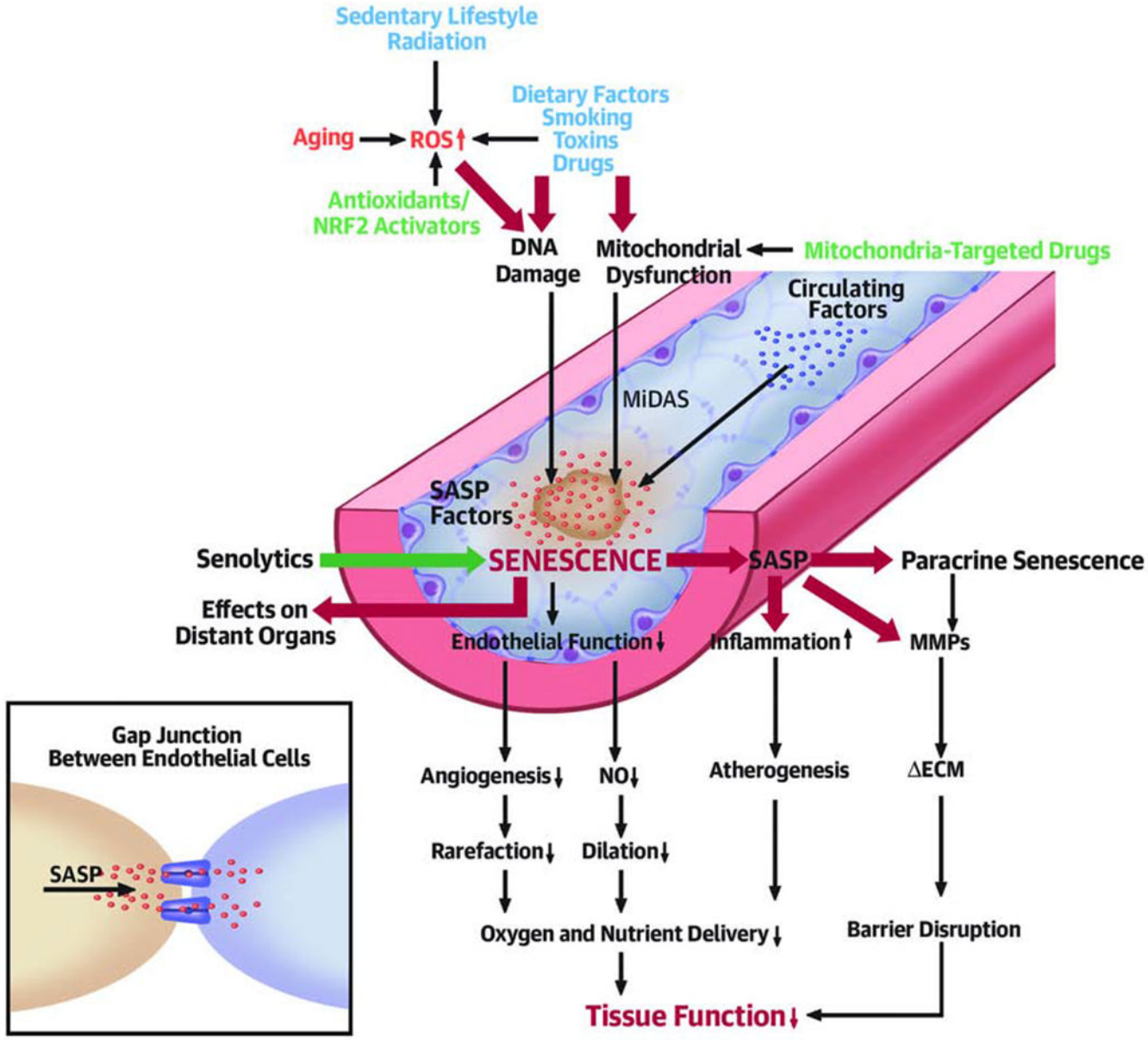


Figure 1. Conceptual model for the causes and pathological consequences of cellular senescence in vascular aging.

The model predicts that increased presence of senescent cells in the aged vasculature and their proinflammatory secretome (SASP: senescence-associated secretory phenotype) contributes to impaired angiogenesis and microvascular rarefaction, impaired vasodilation, chronic inflammation, pathological remodeling of the extracellular matrix (ECM), barrier disruption, and/or atherogenesis, all of which contribute to age-related tissue dysfunction. It is predicted that signals that induce senescence may be transmitted between cells (vis gap junctions). Secretion of SASP factors may also induce paracrine senescence and/or impair the function of neighboring cells. The model predicts that in aging increased ROS, DNA damage and/or mitochondrial dysfunction promote cellular senescence in the vasculature (MiDAS: mitochondrial dysfunction-associated senescence). Exogenous stressors/risk

factors (blue) exacerbate vascular aging by induction of senescence. Interventions for targeting senescence-related mechanisms include prevention of ROS-mediated DNA damage (by antioxidants and Nrf2 activators), mitochondria-targeted treatments and removal of senescent cells by senolytic treatment.

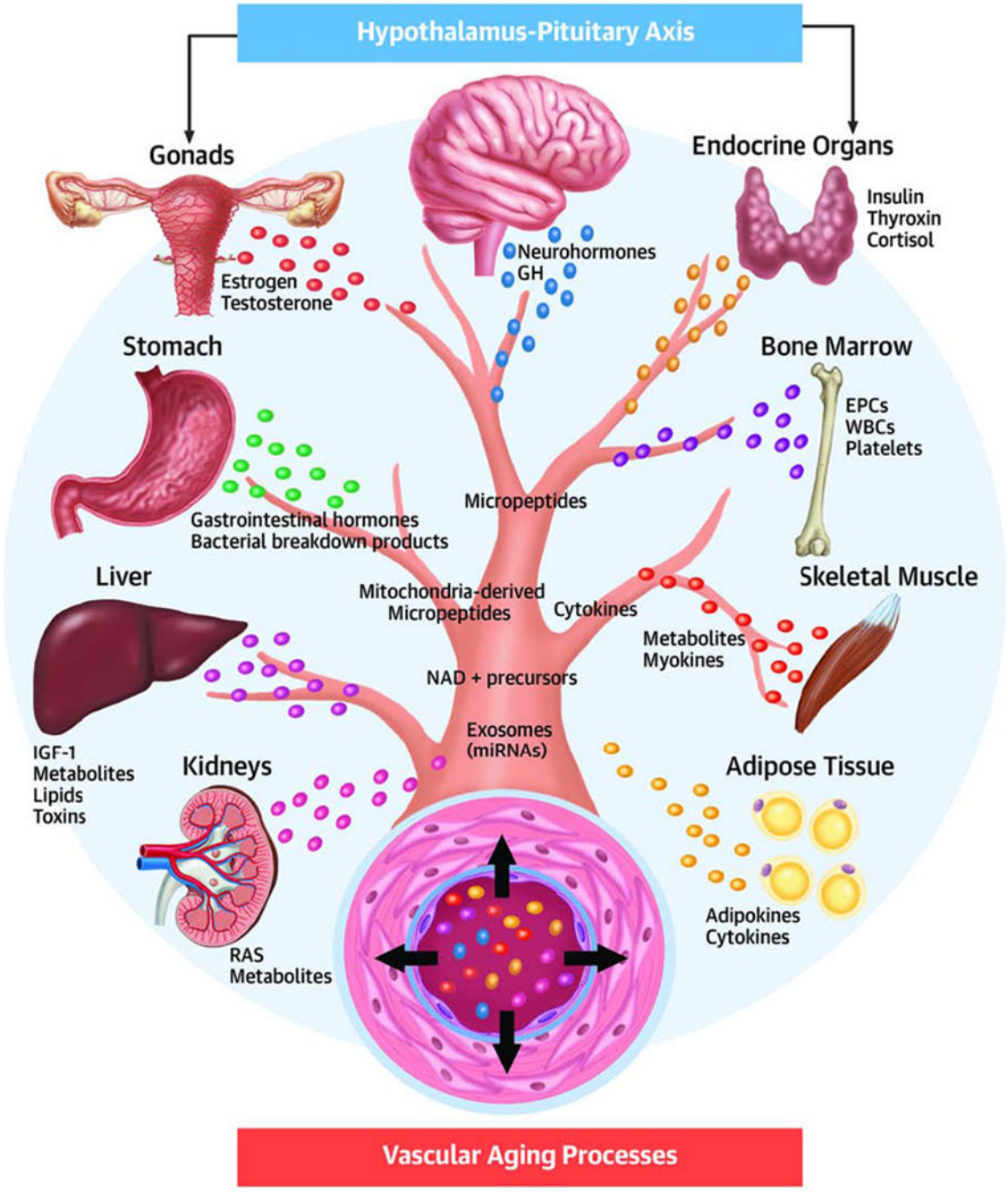
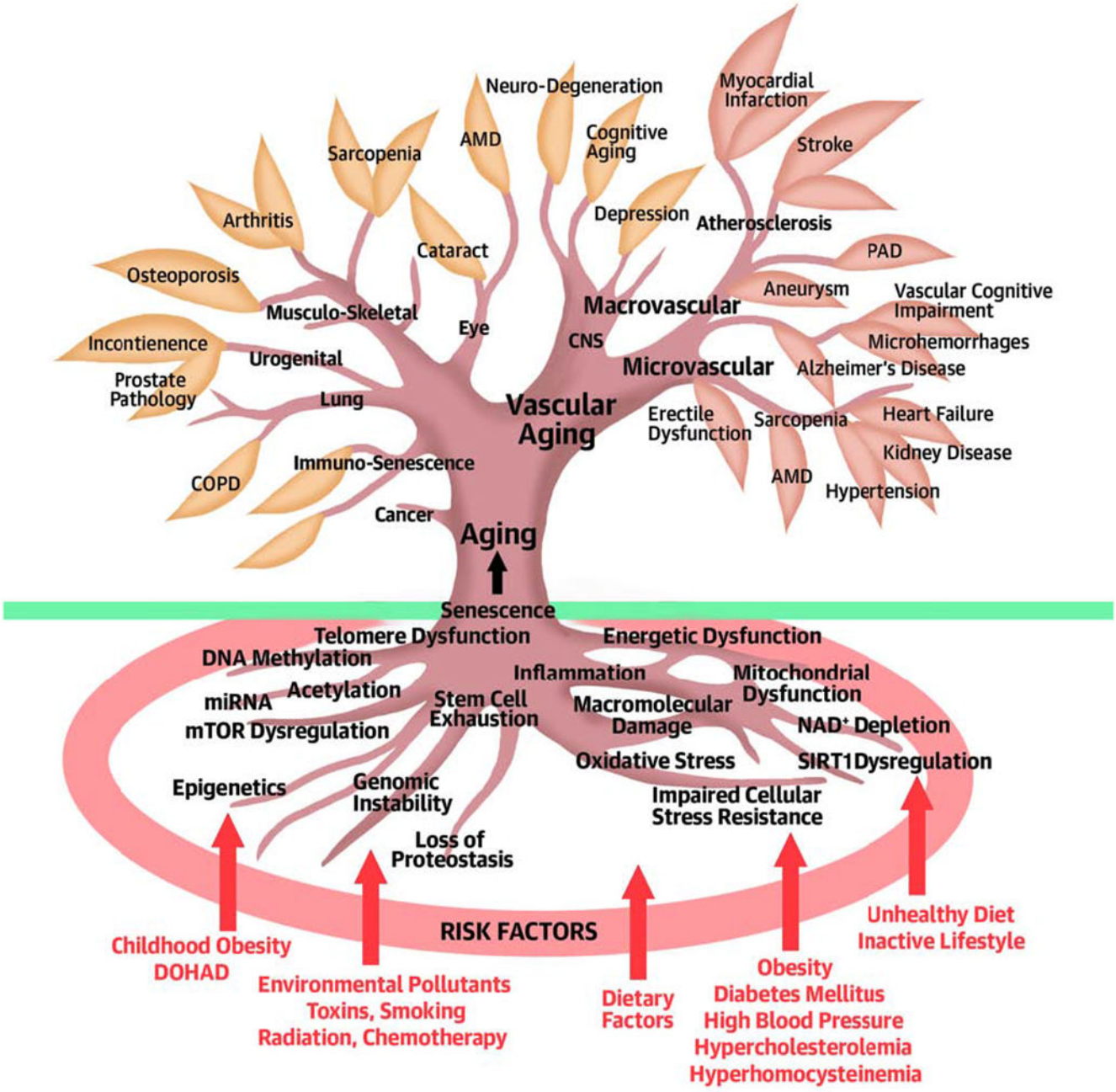


Figure 2. Regulation of vascular aging by pro-geronic and anti-geronic circulating factors.

The model depicts the role of inter-organ communication in the hierarchical regulatory cascade for vascular aging. Cell-autonomous cellular and molecular aging processes in the vascular wall are modulated by circulating pro-geronic (e.g., inflammatory cytokines) and anti-geronic factors (e.g., IGF-1, mediators of caloric restriction, estrogen) derived from the central nervous system, endocrine organs, the adipose tissue and other organs. RAS: renin-angiotensin system; MMPs: matrix metalloproteinases; DAMPs: damage-associated molecular patterns; EPCs: endothelial progenitor cells; GH: growth hormone.



Central Illustration. Multiple shared mechanisms of aging contribute to the pathogenesis of diverse age-related diseases in each organ system, including the vasculature, simultaneously.

Consequences of vascular aging lead to the genesis of micro- and macrovascular pathologies, ranging from atherosclerotic vascular diseases to Alzheimer's disease. Conventional risk factors (purple) promote age-related cardiovascular and cerebrovascular pathologies by exacerbating one or more fundamental molecular and cellular (cell autonomous and non-cell autonomous) aging processes (roots). Clinical disciplines, biogerontology and public health research separately focus on the individual age-related diseases (leaves), the mechanisms of aging (roots) and the risk factors, respectively.

Geroscience is an integrative scientific field that considers the interaction of all of these levels.

Table 1.

Mechanisms of vascular aging

Cellular and molecular mechanisms of aging(2)	Putative role in vascular pathologies(2)	Preclinical evidence	Translational evidence	Potential target for intervention (examples(5))
Oxidative and nitrative stress	Atherogenesis, inflammation, endothelial dysfunction, blood flow↓, ECM remodeling, hypertension, microhemorrhages, aneurysm formation	yes	yes	yes (antioxidants, peroxynitrite scavengers, upstream activators of antioxidant pathways)
Impaired oxidative stress resistance (including Nrf2 dysfunction)(35)	Impaired response to injury, exacerbated effects of vascular risk factors (hypertension, metabolic diseases, smoking), inflammation, atherogenesis, aneurysm formation, microvascular damage, impaired angiogenesis	yes	?	yes (Nrf2 activators, caloric restriction)
Chronic low grade sterile inflammation (NF-κB activation, cytokine dysregulation, DAMPs)	Atherogenesis, paracrine effects on tissue function (including stem cell niche impairment), barrier dysfunction, white blood cell extravasation	yes	yes	yes (inhibitors of NF-κB, upstream activators of anti-inflammatory pathways)
Mitochondrial dysfunction	Impaired endothelial vasomotor, transport and barrier functions(36), inflammation(37), atherogenesis(38) (39)	yes	?	yes (mitochondria-targeted antioxidants(27))
NAD+ depletion(40)	Endothelial dysfunction(30), cellular energetics↓, impaired angiogenesis, atherogenesis (?)	yes	yes	yes (nicotinamide mononucleotide(30), nicotinamide riboside, nicotinamide; PARP1 inhibitors(31))
SIRT1 dysregulation	Endothelial dysfunction, inflammation, atherogenesis, microvascular dysfunction(9,41)	yes	?	yes (SRT1720(9))
mTOR dysregulation	Microvascular rarefaction, inflammation, atherosclerosis, vasomotor dysfunction(29), blood-brain barrier disruption(42)	yes	?	yes (rapamycin, rapalogs(29))
AMPK dysregulation	Endothelial dysfunction, vascular inflammation	yes	yes	yes (metformin(28))
Δ DNA methylation	Vascular inflammation, aneurysm formation(43)	yes	?	?
miRNA dysregulation	Angiogenesis↓, atherogenesis(2)	yes	?	?
Loss of proteostasis (ubiquitin-proteasome↓, lysosome-autophagy system↓.	atherosclerosis, vascular inflammation(44,45), Alzheimer's disease, amyloidosis	yes	?	?
Apoptosis↓, necroptosis↓	Microvascular rarefaction, inflammation (?) (6), aneurysms (?)	yes	?	?
Progenitor cell exhaustion	Microvascular rarefaction (?), impaired angiogenesis and collateralization(?)(46)	yes	?	?
Genomic instability	Endothelial dysfunction, increased vascular stiffness, increased presence of senescence cells, hypertension(47), atherosclerosis(48)	yes	?	?
Cellular senescence↑ (10) (15)	Atherogenesis, Angiogenesis↑, endothelial dysfunction, inflammation↑, blood brain barrier dysfunction, microvascular rarefaction	yes	yes	yes (senolytics)