Circulation

IN DEPTH

Vascular Aging

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ABSTRACT: Vascular aging is a central determinant of healthy life span, not only influencing the susceptibility to cardiovascular diseases but also shaping the risk of systemic decline across multiple organs. It is driven by a variety of age-related factors, including cellular senescence, chronic inflammation, loss of proteostasis, mitochondrial dysfunction, genomic instability, epigenetic remodeling, and stem cell exhaustion. These processes interact with the unique mechanical and metabolic environment of the vasculature to create a distinctive pathological trajectory, manifested in part as arterial stiffening, impaired barrier integrity, and dysregulated vasomotor control. Recent advances in single-cell omics and cross-organ molecular clocks have revealed the heterogeneity and organ specificity of aging, underscoring the need for integrative frameworks that connect vascular biology with overall health. Meanwhile, the development of diverse therapeutic strategies—ranging from senolytic and immune-mediated clearance to metabolic and mitochondrial interventions—highlights the translational potential of targeting the aging vasculature. Looking ahead, multimodal biomarkers and precision medicine may transform vascular aging from an inevitable process into a modifiable determinant of health span.

Key Words: aging ■ DNA damage ■ inflammation ■ mitochondria ■ stem cells

You are as old as your arteries.
—Thomas Sydenham (1624-1689)

The links between vascular aging and overall life span and health have been known since the time of the great English physician Thomas Sydenham. However, the nature of this relationship, namely whether it indicates a correlative versus causative link, has significantly evolved over the past several decades. In large part because of our deeper understanding of how and why we age, there is a growing framework to place the age-dependent susceptibility for myriad diseases within the context of the biology of aging. This shift in understanding can be traced back to observations in basic science laboratories that noted that in simple organisms such as *Caenorhabditis elegans*, manipulating a single gene could extend the overall life span of the organism.[1–3] Remarkably, many of the genes and pathways identified in lower organisms are well conserved. For instance, the first well-described pathway in worms outlined a pathway encompassing an insulin-like receptor, regulating the activity of a downstream kinase (eg, PI3K), and ultimately modulating the activity of the FOXO family of transcription factors.[2] The facts that genetic variants in FOXO family members appear to correlate with human longevity[4] and, perhaps more germane to this review, these longevity effects appear particularly relevant to those individuals with cardiovascular risk factors[5] suggest that aging is not random but rather, like all other biological processes, is under genetic and biochemical regulation. Dissecting these regulatory mechanisms thereby provides hope that a blueprint can emerge that will allow us to finally understand how to tackle the single greatest risk factor that underlies almost all major human diseases: age itself.

The characteristic phenotypes of vascular aging include deterioration of mechanical properties, disruption of barrier integrity, and dysregulation of vasomotor control (Figure 1). Vascular compliance and elasticity depend on the coordinated function of medial vascular smooth muscle cells (VSMCs) and elastic and collagen fibers. With advancing age, elastic fiber fragmentation and increased collagen deposition lead to arterial stiffening and reduced compliance. In large arteries, such alterations in mechanical properties result in a marked increase in pulse wave velocity and pulse pressure, both of which have been established as independent predictors of adverse cardiovascular outcomes.[6]

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Nonstandard Abbreviations and Acronyms

AGE	advanced glycation end-product
BBB	blood-brain barrier
CHIP	clonal hematopoiesis of indeterminate potential
COLCOT	Colchicine Cardiovascular Outcomes Trial
DAMP	damage-associated molecular pattern
EC	endothelial cell
ECM	extracellular matrix
IL	interleukin
LoDoCo2	Low-Dose Colchicine 2
NF-κB	nuclear factor-κB
ROS	reactive oxygen species
SASP	senescence-associated secretory phenotype
VSMC	vascular smooth muscle cell

The vascular endothelium is central to barrier function. In aged endothelial cells (ECs), reduced expression of intercellular junction proteins (eg, claudins and occludins) and cytoskeletal remodeling contributes to increased permeability.[7] Concurrently, basement membrane thickening and impaired endothelium-dependent vasodilation coexist, leading to reduced efficiency of molecular exchange along with increased nonspecific leakage. This bidirectional imbalance is particularly pronounced in high-barrier organs such as the blood–brain barrier (BBB), renal glomeruli, and pulmonary capillaries, thereby accelerating the progression of neurodegenerative disorders, chronic kidney disease, and pulmonary vascular pathologies.[8,9]

Precise regulation of vascular relaxation and contraction is essential for maintaining vascular tone and facilitating efficient exchange of substances. In aged ECs, reduced nitric oxide (NO) production and bioavailability impair endothelium-dependent vasodilation.[10] Meanwhile, in aged VSMCs, abnormal calcium channel signaling and actin cytoskeleton remodeling weaken contractile capacity.[11]

Given the rapid acceleration of global population aging, it is not surprising that vascular aging has emerged as a central determinant of healthy life span. It is now widely recognized not only as the fundamental pathological substrate of cardiovascular disorders such as hypertension and atherosclerosis but also as a shared contributor to organ-specific diseases, frailty, and multisystem aging. Indeed, at least in model systems, rates of vascular aging may in fact be rate limiting for the entire organism.[12]

DRIVERS OF VASCULAR AGING

As with other tissues and organs, vascular aging is driven by multiple interacting factors. However, owing to its unique structure and function, the vasculature exhibits distinctive responses to these influences. For instance, the vascular wall is continuously subjected to pulsatile pressure and shear stress, rendering it particularly sensitive to factors that affect the cytoskeleton and extracellular matrix (ECM).[13] Throughout the life span, blood vessels remain in direct contact with a multitude of circulating factors, thereby being persistently exposed to lipoproteins, inflammatory mediators, and sources of oxidative stress.[14]

In the following sections, we examine how the mechanistic pathways governing organismal aging from the simple worm to complex mammals also drive vascular aging and thereby the susceptibility to cardiovascular disease (Figure 2). We include among the pathways to be discussed cellular senescence, chronic inflammation,

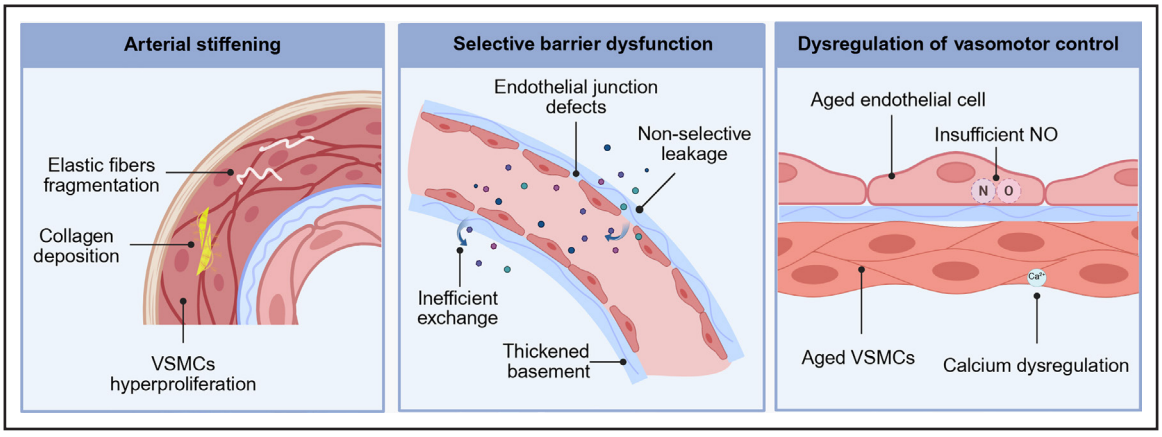

Figure 1. Characteristic phenotypes of vascular aging.
Arterial stiffening is characterized by fragmentation of elastic fibers, excessive collagen deposition, and vascular smooth muscle cell (VSMC) hyperproliferation. Selective barrier dysfunction with aging endothelial cells exhibiting impaired intercellular junctions and exchange and thickened basement membrane. Dysregulation of vasomotor control results in part from old endothelial cells exhibiting insufficient nitric oxide (NO) production, whereas aged VSMCs show calcium signaling dysregulation, together leading to impaired vascular tone regulation.

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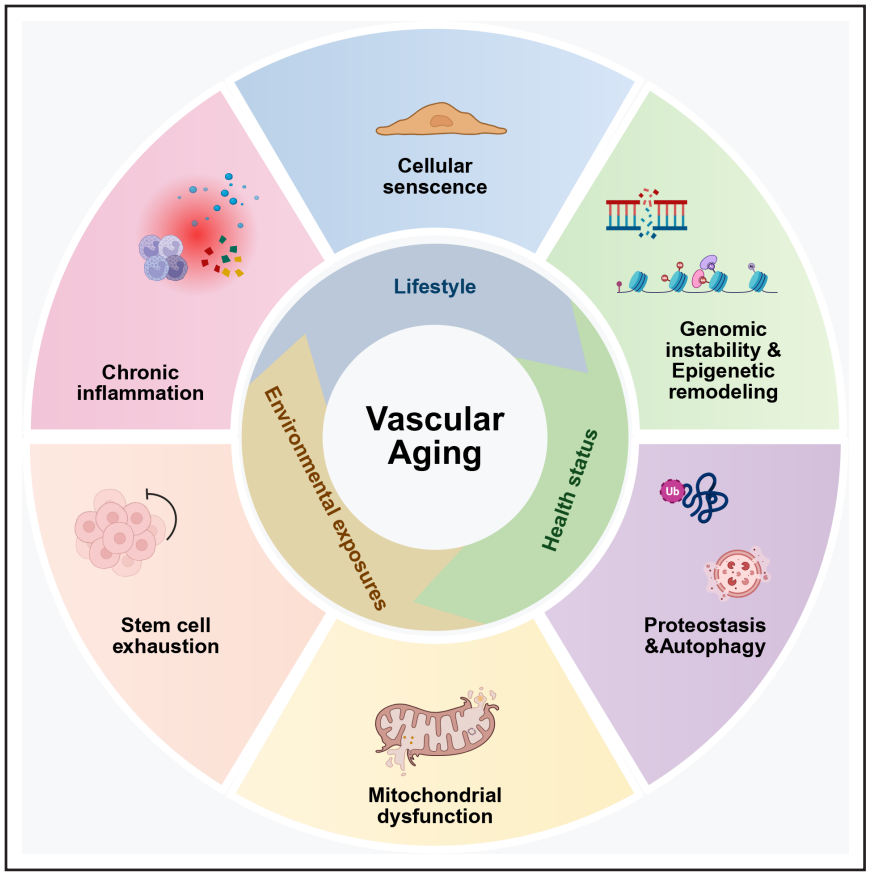

Figure 2. Risk factors and molecular drivers of vascular aging.
Identified cardiovascular risk factors modulate key molecular drivers to propel vascular aging. Individual health status (eg, insulin resistance, hypertension, and menopause), lifestyle (eg, diet, physical activity, smoking, and alcohol consumption), and environmental exposures (eg, geographic living conditions and pollution) all contribute to this process. These factors intersect with key molecular drivers, including cellular senescence, genomic instability and epigenetic remodeling, impaired proteostasis and autophagy, mitochondrial dysfunction, stem cell exhaustion, and chronic inflammation. Together, they orchestrate the complex progression of vascular aging. See text for additional details.

loss of proteostasis, mitochondrial dysfunction, genomic instability, epigenetic remodeling, and stem cell exhaustion.[15] Together with the unique mechanical and metabolic milieu of the vasculature, these processes shape the distinctive pathological landscape of vascular aging.

CELLULAR SENESCENCE

Cellular senescence is a stable and irreversible state of cell-cycle arrest induced by diverse set of endogenous and exogenous stresses (eg, DNA damage, telomere shortening, oxidative stress, mitochondrial dysfunction). Although senescent cells no longer divide, they remain metabolically active and display characteristic phenotypes, including upregulation of various cell cycle inhibitors (eg, p16INK4a and p21Cip1), heterochromatin reorganization (formation of senescence-associated heterochromatin foci), and acquisition of a senescence-associated secretory phenotype (SASP), that entail abundant secretion of inflammatory cytokines, chemokines, and matrix-degrading enzymes.[16]

Cellular senescence is believed to be a major driver of tissue homeostatic imbalance and the decline in organ function. With age, senescent cells accumulate across multiple tissues, leading not only to cell-intrinsic functional deterioration but also, through their elaborated SASP, to a chronic inflammatory milieu (inflammaging). Through paracrine signaling, SASP factors further induce senescence in neighboring cells, forming a potential self-reinforcing feedback loop.[17] The basis for this increase in senescent cell burden with age is incompletely understood and could reflect a combination of increased generation of senescent cells and impaired immune-mediated clearance. By whatever mechanism, numerous animal studies have shown that eliminating senescent cells (eg, through senolytics)[18–20] or suppressing their SASP (eg, through senomorphic agents) can delay aging in multiple organs, improve metabolic/functional indices, and extend overall health span.[17]

In the vascular system, senescent cells are prevalent in ECs and VSMCs and constitute core drivers of vascular aging and related diseases such as atherosclerosis.[21] Recent advances in single-cell and spatial transcriptomics have further delineated the heterogeneity and spatial organization of senescent vascular cells. In murine models of atherosclerosis, senescent ECs and VSMCs have been mapped during arterial remodeling, providing unprecedented resolution into how senescence potentially shapes vascular pathology.[22] These studies also attempted to define vascular-specific transcriptional signature of senescence, what is increasingly viewed as a "senotype." This reflects the growing realization that there is no universal senescent cell and that the signature of senescence depends on a variety of factors, including the cell type of origin and how senescence was induced.

In ECs, cellular senescence and SASP factors (eg, interleukin [IL]-1β, tumor necrosis factor-α, C-reactive protein) can suppress endothelial NO synthase expression through nuclear factor-κB (NF-κB) signaling while elevating intracellular reactive oxygen species (ROS), thereby reducing NO signaling and impairing endothelium-dependent vasodilation.[23] Concurrently, these inflammatory mediators upregulate adhesion molecules such as vascular cell adhesion molecule-1 and intracellular cell adhesion molecule-1, promoting inflammatory cell accumulation in the vessel wall and further compromising barrier integrity.[24] In VSMCs, senescence drives phenotypic switching, characterized by downregulation of contractile markers (α-smooth muscle actin, SM22α) and upregulation of osteogenic markers (Runx2, BMP2 [bone morphogenetic protein 2], osteopontin), leading to medial calcification, loss of elasticity, and luminal stiffening.[25]

SASP-derived matrix-degrading enzymes and inflammatory cytokines also compromise ECM integrity, increase endothelial barrier permeability, and activate immune-cell adhesion and infiltration.[26] Infiltrating immune cells—including macrophages, T cells, and neutrophils—further drive ECM degradation, elastic fiber fragmentation, and wall thinning by releasing matrix metalloproteinases, elastases, and ROS.[14,27–30] Furthermore, senescent intimal foam cells have been shown to exert deleterious effects throughout all stages of atherosclerosis, underscoring the pathogenic role of senescence within immune-derived vascular cell populations.[31]

CHRONIC INFLAMMATION

In older individuals, a chronic inflammatory state, called inflammaging, often exists. This low-intensity, sterile induction of the innate immune system is closely linked to many age-related diseases.[15] The basis for inflammaging is not fully understood. Clearly, the accumulation of senescent cells with age and their accompanying SASP may be a contributor. Other contributors to inflammaging include immune senescence whereby both innate immunity and adaptive immunity show quantitative and qualitative decline (eg, restricted T/B-cell repertoire, proinflammatory skewing), often resulting in a reduced capacity to maximally respond to a challenge while maintaining a high basal inflammatory state.[32] In parallel, aging weakens gut barrier integrity and promotes dysbiosis, facilitating mucosal translocation of microbe-derived molecules/metabolites that chronically stimulate immunity and result in a systemic inflammatory burden.[33] Moreover, in ostensibly "sterile" contexts, tissue damage and metabolic derangements that increase with age result in the augmented release of damage-associated molecular patterns (DAMPs) that engage multiple pattern recognition receptors to sustain inflammatory signaling.[34]

Chronic inflammation is believed to be a core driver of age-related diseases and physiological decline. Persistent low-grade inflammation disrupts stem cell self-renewal, accelerates cellular senescence, and impairs regenerative niches while amplifying metabolic dysregulation and oxidative injury.[15] Cytokines such as IL-6, tumor necrosis factor-α, and IL-1β not only induce paracrine senescence but also modulate hematopoietic,[35] nervous,[36] and muscular systems,[37] potentially contributing to immunosuppression, cognitive decline, and sarcopenia.

Because the vessel wall is in direct contact with a host of circulating factors, chronic inflammation has particularly profound vascular effects. Inflammatory mediators impair vascular function through NF-κB, JAK-STAT, and related signaling pathways—mechanistically similar to senescence/SASP effects—and are not reiterated here. Advanced glycation end-products (AGEs) activate receptor for AGEs, activating inflammatory pathways, driving AGEs deposition, and accelerating ECM degradation.[38] DAMPs directly engage ECs, repeatedly triggering innate immune sensors such as the NLRP3 inflammasome and the cGAS-STING pathway. This leads to persistent upregulation of the IL-1β/IL-6 axis that is associated with reduced endothelial NO synthase activity and glycocalyx damage, thereby weakening barrier function and altering hemorheology.[39] It is important to emphasize that the cGAS-STING innate immune pathway, triggered by the presence of double-stranded DNA in the cytosol, plays a broad and central role in propagating cellular senescence and inflammation.[40] Increasingly, this pathway is being linked to aging[41] and to chronic inflammatory age-related diseases, including atherosclerosis.[42] Selective, small-molecule STING inhibitors are advancing to the clinic, suggesting the translational potential of this pathway to modulate a host of inflammatory-mediated diseases,[43] including a range of cardiovascular and metabolic conditions.[44] Besides cGAS-STING, immune activation of the vessel wall is also modulated by activated complement that can form the membrane attack complex, which in ECs induces the NLRP3 inflammasome and IL-1β signaling, resulting in upregulation of adhesion/proinflammatory molecules, further amplifying inflammation and matrix degradation.[45] Furthermore, neutrophil extracellular traps capture platelets and coagulation factors to promote thrombosis[46]; neutrophil extracellular trap–borne elastase, myeloperoxidase, and matrix metalloproteinases weaken fibrous-cap collagen and accelerate ECM degradation, and microthrombus deposition plus local stress concentration increases plaque vulnerability and the risk of rupture/erosion.[30] Last, aging is often accompanied by impaired production/signaling of specialized proresolving mediators, hindering timely termination of the inflammation-thrombosis cascade, prolonging immune-cell retention and delaying repair, and thus perpetuating a vicious cycle of inflammation-injury-reinflammation.[47]

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LOSS OF PROTEOSTASIS AND DECLINE OF AUTOPHAGIC FUNCTION

Proteostasis refers to the cellular capacity—through molecular chaperones, folding surveillance, the ubiquitin-proteasome system, and the autophagy-lysosome axis—to maintain proper protein configurations, localization, and turnover. During aging, there is a generalized decline in the overall capacity of chaperone networks, the ubiquitin-proteasome system, and autophagy, leading to accumulation of misfolded/aggregated proteins and damaged organelles across tissues. This is seen throughout the body; notable nonvascular examples include phosphorylated τ and α-synuclein aggregates in the nervous system; desmin-related aggregates in myocardium; damaged mitochondria in skeletal muscle/liver due to impaired PINK1-Parkin–dependent mitophagy; lipofuscin and undegraded autophagosomes in retinal pigment epithelium/neurons; and misfolded protein and mitochondrial aggregates in renal tubular epithelium.[48]

In the vasculature, ECs and VSMCs inhabit a microenvironment of sustained mechanical stress, high metabolic demand, and intensive signaling, making them particularly vulnerable to proteostasis imbalance with age. Chronic hemodynamic forces (shear and pulsatile pressure) require continual renewal/repair of membrane and cytoskeletal proteins; vascular cells also participate broadly in immune responses, synthesizing and secreting abundant membrane and soluble proteins for immune-cell adhesion and positioning, together imposing a substantial load on the protein synthesis and degradation machinery.[21]

With aging, molecular chaperones such as BiP/GRP78 decline in function, predisposing to misfolded-protein accumulation.[21] During atherogenesis, chaperone-mediated autophagy activity in macrophages drops markedly, principally as a result of reduced lysosomal LAMP-2A expression, compromising proteostasis, promoting misfolded/damaged proteins and proteotoxicity, activating inflammation, and accelerating vascular pathology.[49] In addition, reduced ubiquitin-proteasome system activity allows oxidized/glycated proteins to persist and aggregate; such aggregates, together with AGE deposits, significantly alter arterial biomechanics, increasing stiffness and accelerating vascular aging.[50]

Aging vessels also exhibit lysosomal dysfunction that further lowers clearance efficiency. Age-related defects in lysosomal acidification resulting from impaired v-ATPase activity and dysregulated proton/metabolite transport shift organelle pH and inhibit hydrolase maturation/activity.[51] Lipid microenvironment disturbances (eg, bis[monoacylglycerol]phosphate imbalance) in aged cells destabilize lysosomal membranes and further impair enzyme function.[52] Loss of proteostasis can aggravate lysosomal defects by making damaged lysosomes refractory to various quality control processes, including ESCRT-mediated repair and ubiquitin-dependent lysophagy.[53] In this context, directly increasing lysosomal number or activity in the vessel wall appears to prevent the development of age-related diseases such as atherosclerosis.[54]

In addition, certain misfolded proteins accumulate specifically in aged vessels. Medin amyloid (derived from the C-terminal fragment of MFG-E8) deposits in the vasculature of nearly all individuals >50 years of age and is the most common vascular-associated amyloid. Medin binds directly to elastin and collagen, promoting ECM cross-linking and stiffening while inducing VSMC phenotypic switching and inflammatory signaling, thereby accelerating structural and functional vascular aging.[55,56] Another example of vascular proteostasis failure is the accumulation of progerin, a truncated lamin A isoform originally linked to the accelerated aging syndrome Hutchinson-Gilford progeria.[57] As a misprocessed protein, progerin is inefficiently cleared by the ubiquitin-proteasome system and the autophagy-lysosome pathway, thereby imposing chronic proteotoxic stress on vascular cells. Progerin also appears in normal aging cells and tissues, linking nuclear envelope dysfunction to physiological aging.[58] Last, somatic lamin A mutations were shown to generate mosaic progerin-positive VSMC clones in human arteries, directly implicating defective proteostasis in early vascular aging.[59]

MITOCHONDRIAL DYSFUNCTION

Mitochondrial dysfunction denotes a constellation of changes that lead to a persistent imbalance in energy metabolism, redox homeostasis, calcium dynamics, or quality control. In older individuals, impaired mitochondrial functions result from cumulative mtDNA and nuclear DNA damage, imbalances in fusion/fission dynamics, impaired mitophagy, reduced NAD^+ levels, and damage induced by chronic inflammation. These changes collectively reduce respiratory chain activity and membrane potential while elevating ROS, thereby disrupting intracellular signaling and driving metabolic reprogramming.[60]

Mitochondrial dysfunction is a key driver of organismal aging, promoting DNA damage, inflammatory responses, and cellular senescence through energy insufficiency and excess ROS. Damaged mitochondria can release mtDNA fragments and other mtDAMPs that activate innate immune pathways such as cGAS-STING, inducing chronic inflammation and SASP-like phenotypes.[61] In multiple animal models, enhancing mitochondrial quality control, boosting NAD^+, or promoting mitochondrial biogenesis delays organ functional decline, whereas inhibiting mitophagy or disturbing dynamics accelerates tissue aging and dysfunction.[62]

The vascular system, especially ECs, is particularly sensitive to mitochondrial dysfunction. Beyond general effects, elevated mitochondrial ROS reduces NO

bioavailability and impairs vasodilation. With aging, increased electron leak from complexes I/III elevates mtROS; excessive ROS reacts with NO to form peroxynitrite, oxidizing proteins, lipids, and mtDNA, thereby diminishing endothelium-dependent relaxation and amplifying inflammation.[63] Concomitantly, reduced oxidative phosphorylation efficiency and ATP supply aggravate vasomotor dysfunction. With an energetic deficit, ECs/VSMCs struggle to maintain membrane potential and calcium homeostasis; when mitochondrial membrane potential and calcium uptake decline, the imbalance between mitochondrial calcium uniporter-mediated influx and Na^+/Ca^{2+} exchanger–mediated efflux produces abnormal cytosolic Ca^{2+} transients, impairing endothelial relaxation and driving excessive VSMC contraction.[64–66] Mitochondrial calcium overload further activates calcium-dependent proteases and phospholipases, promoting injury and apoptosis and accelerating degenerative changes in the vascular wall.[67]

Physiologically, moderate mtROS levels participate in regulating vasodilation, gene expression, and antioxidant responses. Aging-related mtROS excess likely upends this balance, subverting ROS physiological signaling and instead acting as a damaging agent that activates proinflammatory pathways and drives sustained SASP release.[68] As mentioned, mtDNA fragments and other mtDAMPs further activate cGAS-STING; similarly, leakage of mitochondrial dsRNA into the cytosol can activate NF-κB and SASP through other specific intracellular sensors, further promoting systemic inflammaging.[40,61]

As a key mechanism maintaining mitochondrial homeostasis, mitophagy often declines with age.[69] The basis for this decline may relate to alterations in lysosomal function, as discussed previously, and to alterations in mitochondrial dynamics, a process closely linked to mitophagic clearance.[70] Impaired mitophagy, in turn, acts as a contributor to a host of pathological processes, including hypertension, atherosclerosis, and pulmonary hypertension.[71–73]

GENOMIC INSTABILITY

Genomic instability represents the accumulation of errors and imbalance in maintaining DNA structure, sequence, and chromosomal integrity, encompassing base damage, single-/double-strand breaks, chromosomal rearrangements, replication stress, and telomere dysfunction. In aging, chronic exposure to oxidative stress, inflammation, metabolic abnormalities, and environmental toxins increases DNA damage burden, and the efficiency of various repair pathways (nucleotide excision repair, base excision repair, homologous recombination, nonhomologous end joining) declines. Replication stress plus telomere dysfunction renders chromosome ends prone to misrecognition as double-strand breaks, initiating a DNA damage response.[74]

Persistent genomic instability drives aging through multiple mechanisms. First, DNA damage activates the DNA damage response, triggering the p53-p21 and p16-Rb axes to potentially induce irreversible senescence and SASP.[17] Second, mutational burden and chromatin architectural drift disrupt transcriptional homeostasis and stem cell self-renewal, undermining regenerative potential.[75] Furthermore, nucleic acids released by DNA damage can be sensed by cGAS-STING and other innate immune pathways, triggering chronic inflammation and immune reprogramming and amplifying systemic inflammaging through inflammatory-metabolic positive feedback.[40,76]

Within the vasculature, ECs must continually proliferate/regenerate to withstand shear, pulsatile pressure, and metabolic stress, rendering them especially vulnerable to DNA damage and telomere dysfunction. In aged vessel walls, ECs at disturbed-flow regions show elevated markers of DNA double-strand breaks (γH2AX, 53BP1, etc) and increased telomere-associated damage foci, which collectively impair endothelial NO synthase–NO signaling and endothelium-dependent dilation, increase barrier permeability, and promote inflammatory cell infiltration.[23,74] While in VSMCs, DNA damage can activate p53 and NF-κB signaling, promoting a procalcific phenotype.[25,77]

EPIGENETIC REMODELING

Epigenetic remodeling encompasses sustained alterations in DNA methylation, histone modifications, chromatin structure, and noncoding RNA regulation without changes to the underlying DNA sequence. In aging, cumulative replication errors, oxidative/inflammatory stress, metabolic shifts (eg, NAD^+ decline, imbalance between methyl donors and demethylase activity), and changes in cellular composition collectively drive DNA methylation drift, histone-modification imbalance, and chromatin reorganization.[78]

Age-related epigenetic changes correlate strongly with frailty phenotypes, chronic disease risk, and mortality across systems; in population and longitudinal cohorts, accelerated epigenetic aging was robustly associated with cardiovascular outcomes and metabolic/inflammatory phenotypes, suggesting that epigenetic remodeling not only may be a readout but also may actively contribute to functional decline.[79] Emerging evidence suggests that manipulating certain epigenetic proteins (eg, SIRTs/HDACs) or DNA methylation regulators (eg, DNMT/TET) or using the Yamanaka factors to induce epigenetic reprogramming can ameliorate aging phenotypes in animal models. However, the reversibility and safety of these approaches in humans will require additional and more rigorous validation.[80]

In the vasculature, epigenetic remodeling alters chromatin accessibility and thus the transcriptome, directly

driving aging phenotypes of ECs and VSMCs such as increased calcification propensity in VSMCs,[81] reduced sensitivity of the NO pathway leading to vasodilatory dysfunction, and induction of endothelial-mesenchymal transition.[82] Epigenetic changes can also establish epigenetic preconditioning; for example, H3K27ac-mediated enhancer landscape remodeling sensitizes cells to exaggerated responses to various secreted cytokines, thereby subsequently predisposing them to endothelial-mesenchymal transition and inflammatory activation.[83] Hemodynamic shear also modulates the epigenome in an age-dependent fashion. For instance, under physiological laminar flow, the transcription factor KLF4 recruits the SWI/SNF chromatin remodeling complex to beneficially reshape the enhancer landscape, increasing the accessibility of protective enhancers, whereas with aging plus disturbed flow, ECs more readily assume proinflammatory/adhesive phenotypes and lose vasodilatory capacity.[84]

STEM CELL EXHAUSTION

Stem cell exhaustion reflects the progressive loss of number and function of adult tissue stem/progenitor cells, including diminished self-renewal, reduced differentiation potential, and delayed responsiveness. This undermines tissue repair and homeostasis, accelerating aging. Stem cell exhaustion markedly compromises regenerative and reparative capacity and is a key mechanism driving functional deterioration across organ systems. Declining stem cell function not only impedes tissue repair but also alters the microenvironment, aggravating inflammation and metabolic abnormalities. Concurrent epigenetic changes and amplified heterogeneity within stem cell pools lower regenerative quality and may cause aberrant differentiation or fibrosis, thereby accelerating overall aging and chronic disease.[15]

The most characterized vascular-related stem cells are $CD133^+$ endothelial progenitor cells, originating from bone marrow and peripheral blood, which differentiate into ECs, home to injury sites, and promote vascular regeneration.[85] With aging, endothelial progenitor cell numbers and function decline overall and are considered biological indicators of reduced vascular repair capacity. In addition, the $CD34^+/KDR^+$ endothelial progenitor cell subpopulation is widely used to assess vascular regenerative capacity in populations; reduced levels associate closely with vascular aging and adverse hemodynamic phenotypes, including reduced endothelial function, increased arterial stiffness, and abnormal blood pressure risk.[86–88]

Another key cell type is the mesenchymal stem cell, located in perivascular regions (eg, adventitia and glandular basal layers), providing structural support, modulating immunity, and contributing to vascular stability. Aging reduces mesenchymal stem cell chemotaxis and immunomodulation and biases differentiation toward fibrotic/osteogenic fates.[89] Moreover, pericytes and vascular wall–resident stem cells decline with aging and critically affect capillary regeneration.[90]

Aging induces a myeloid-biased shift in hematopoietic stem/progenitor cells, characterized by enhanced myelopoiesis accompanied by relatively reduced lymphopoiesis.[91] This altered hematopoietic pattern skews the immune microenvironment toward a proinflammatory state, manifested by exacerbated vascular inflammation, accelerated endothelial injury, and increased macrophage infiltration and foam-cell formation.[92] Collectively, these changes act as amplifiers in the progression of atherosclerosis, arterial stiffening, and hypertension, particularly by elevating SASP factors and oxidative stress within the vascular wall.

Clonal hematopoiesis of indeterminate potential (CHIP) represents another aging-associated hematopoietic abnormality. Its central mechanism involves the acquisition of somatic driver mutations in hematopoietic stem cells (eg, *DNMT3A*, *TET2*, *ASXL1*), leading to the expansion of mutant clones.[93] Unlike simple myeloid bias, CHIP not only alters lineage determination but also enhances the proinflammatory responsiveness of myeloid cells, for instance, through upregulation of IL-1β and IL-6, thereby contributing to systemic inflammation and vascular pathology.[94] Clinical and population-based studies have demonstrated that CHIP is significantly associated with increased risk of cardiovascular events, particularly atherosclerosis and ischemic heart disease.[95] Notably, this association is unidirectional: CHIP promotes the development of atherosclerosis, whereas atherosclerosis does not increase the incidence of clonal hematopoiesis.[96]

THERAPEUTIC INTERVENTION STRATEGIES

Given the pivotal role of vascular aging in age-related diseases, interventions targeting the drivers of vascular aging have become an increased focus in the treatment of age-associated vascular disorders (Figure 3). However, substantial interindividual variability influences the onset, progression, and therapeutic responsiveness of vascular diseases, highlighting the need to incorporate more precise and tailored interventions.[97,98] Accordingly, this section summarizes current clinical advances from 3 perspectives: (1) interventions targeting the drivers of aging, (2) repair of damaged vascular structure and function, and (3) personalized diagnosis and treatment.

CLINICAL INTERVENTIONS TARGETING AGING DRIVERS

Eliminating or reprogramming senescent cells is a potential direction for clinical intervention. Early studies

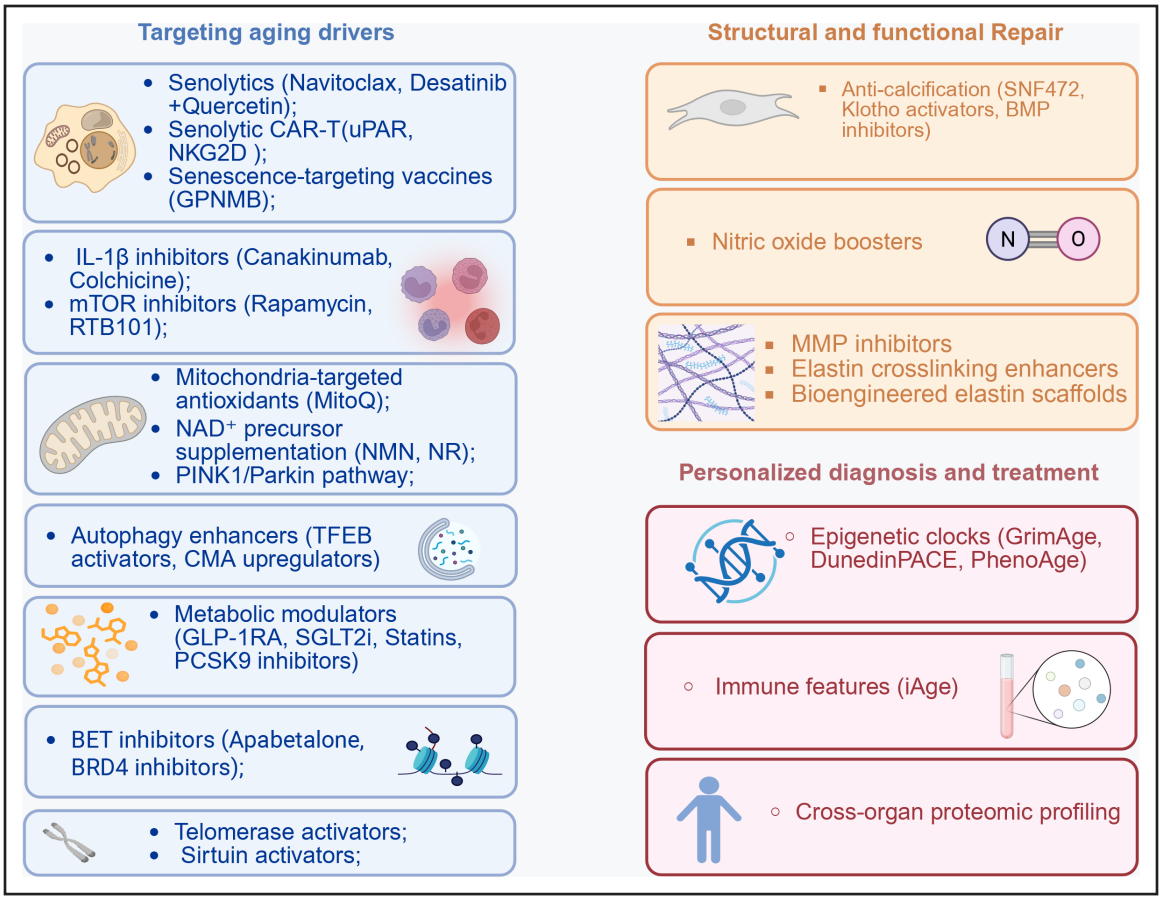

Figure 3. Therapeutic strategies and precision approaches for vascular aging.
Multiple strategies include targeting the drivers of aging, directed therapies aimed at the vascular wall, and in-depth molecular phenotyping. See text for additional details. BMP indicates bone morphogenetic protein; CAR-T, chimeric antigen receptor T cell; CMA, chaperone-mediated autophagy; GLP-1RA, glucagon-like peptide-1 receptor agonist; IL-1β, interleukin-1β; MMP, matrix metalloproteinase; mTOR, mechanistic target of rapamycin; PCSK9, proprotein convertase subtilisin/kexin type 9; SGLT2i, sodium-glucose cotransporter 2 inhibitor; and uPAR, urokinase-type plasminogen activator receptor.

demonstrated that BCL-2 family inhibitors such as navitoclax can reduce senescent cell burden in experimental models and improve vascular barrier integrity and function.[99] Ultimately, the clinical use of such drugs may be limited by side effects such as myelosuppression. Within this evolving landscape, increasing attention has shifted toward endothelial- and vascular-targeting senolytics that potentially modulate aging of the vascular wall with greater specificity. For instance, preclinical studies show that fisetin may selectively eliminate senescent ECs and VSMCs, suppresses SASP output, and ameliorates vascular inflammation. In mouse models of cardiac and vascular aging, fisetin restores endothelial NO bioavailability, improves vasomotor responses, and reduces arterial stiffening.[100] Independently, fisetin has also been shown to protect the aging vasculature by reducing NF-κB–driven cytokine production and strengthening antioxidant defenses, thereby mitigating age-related vascular permeability and inflammatory remodeling.[101] In addition to small molecule approaches, chimeric antigen receptor T cells targeting potential senescent cell surface antigens such as the apparent increased expression of the urokinase-type plasminogen activator receptor on senescent cells have shown improvement when deployed in various cardiovascular and metabolic disease models.[102] Similarly, vaccines targeting other "senescence antigens" such as the transmembrane protein GPNMB appear to effectively reduce plaque burden in atherosclerosis models.[103] Notably, beyond senolytics and immune-based approaches, commonly used metabolic drugs have recently been implicated in senescence regulation. Sodium-glucose cotransporter 2 inhibitors, initially developed as antidiabetic agents, have been reported in preclinical studies to modulate cellular senescence and to attenuate pathological aging phenotypes across multiple tissues.[104] It is important to note that not all senolytic interventions appear beneficial. Recent evidence suggests that in preclinical pulmonary hypertension models, senolytics may actually have a deleterious effect.[99] Similarly, in the liver, removal of senescent ECs can also be detrimental.[105] These observations highlight the need for careful evaluation of senescence-targeting

interventions within complex physiological environments, as well as the necessity for outcomes-level validation.

Inflammatory amplification loops are important drivers of vascular aging, with a particularly prominent role in atherosclerosis progression. The CANTOS trial (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study; canakinumab is an IL-1β inhibitor) provided perhaps the first clinical evidence that anti-inflammatory therapy can reduce cardiovascular event risk independently of lipid levels.[106] Subsequently, COLCOT (Colchicine Cardiovascular Outcomes Trial) and LoDoCo2 (Low-Dose Colchicine 2) confirmed that low-dose colchicine reduces cardiovascular risk in patients with myocardial infarction or chronic coronary disease.[107,108] In contrast, the recent large, multinational CLEAR SYNERGY OASIS-9 trial (Colchicine and Spironolactone in Patients With Myocardial Infarction/SYNERGY Stent Registry–Organization to Assess Strategies of Ischemic Syndromes 9) reported no reduction in major cardiovascular events when colchicine was initiated within 72 hours of a percutaneous coronary intervention in the setting of an acute myocardial infarction.[109] These neutral findings contrast with the positive results of COLCOT and LoDoCo2 and suggest that the efficacy of colchicine may depend on clinical scenario, the underlying inflammatory state, or potentially the patient's genotype. In that context, gene-inflammation interaction studies have revealed that carriers of CHIP mutations (eg, TET2) may derive the most benefit from IL-1β inhibition,[110] suggesting that future anti-inflammatory therapies, be it colchicine or canakinumab, could be tailored to individual inflammatory-genetic profiles.

Preclinical studies have shown that mTOR (mechanistic target of rapamycin) inhibitors (eg, rapamycin) can improve vascular pathology and delay stiffening by suppressing inflammation and promoting the clearance of damaged cellular components.[111] Similarly, strategies that activate chaperone-mediated autophagy or enhance autophagy by stimulation of the master transcription factor TFEB have demonstrated benefits in atherosclerosis and remodeling models. As previously noted, in the endothelium, TFEB activation restrains inflammatory signaling and reduces atherosclerosis[54]; in mouse macrophages, TFEB-driven autophagy–lysosome biogenesis, achieved by genetic TFEB augmentation or pharmacologically by the addition of trehalose, enhances cargo clearance, lowers IL-1β, and attenuates plaque progression.[112] In a similar vein, chaperone-mediated autophagy enhancement reduces atherosclerotic burden and improves lesion phenotypes affecting both VSMCs and macrophages.[113] Mitochondria-targeted antioxidants such as MitoQ have been shown to improve endothelial function in aged animals.[114] Recent studies suggest that NAD^+ precursor supplementation may confer vascular or systemic benefits, although to date, most evidence is derived predominantly from small clinical trials and preclinical models. For example, in a small randomized controlled study, the NAD^+ precursor NMN appeared to improve endothelial function and reduce arterial stiffness, but larger outcome-driven trials are needed.[115] Recent studies have also emphasized the role of regulating mitochondrial dynamics and mitophagy (PINK1/Parkin pathway) in cardiovascular aging interventions.[116]

Telomerase activation has demonstrated vascular benefits in animal and other preclinical models, in which it delays arteriosclerosis and improves endothelial function; likewise, epigenetic modulation through sirtuin activation has been shown to enhance endothelial function and to reduce arterial stiffness in experimental systems.[117,118] However, there is no clinical evidence for either approach; therefore, their translational relevance requires further validation. Furthermore, epigenetic targeting can suppress VSMC phenotypic switching. For example, in mice, BET inhibitors, which block epigenetic reader proteins that recognize acetylated histones, can suppress smooth muscle phenotype conversion, representing a potential antiremodeling agent for vascular disease.[119]

STRUCTURAL AND FUNCTIONAL REPAIR

During aging, blood vessels progressively accumulate structural and functional damage. Once established, such damage can amplify upstream pathological processes if left unaddressed. Therefore, reparative therapies targeting preexisting vascular structural and functional decline constitute an essential component of strategies to slow vascular aging.

Endothelial dysfunction is one of the earliest hallmarks of vascular aging. Previous evidence indicates that improving NO bioavailability and suppressing ROS production can partially reverse endothelial impairment.[21,23] High-dose statins and proprotein convertase subtilisin/kexin type 9 inhibitors have been well documented to improve endothelial function, in addition to their lipid-lowering effects.[120] Several randomized trials have demonstrated that glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter 2 inhibitors significantly improve flow-mediated dilation and reduce arterial stiffness in patients with diabetes or high cardiovascular risk.[121] Of note, although these agents can enhance surrogate indices of vascular function—most notably flow-mediated dilation and arterial stiffness—such parameters serve as physiological proxies rather than definitive clinical outcomes. Consequently, the extent to which improvements in endothelial or hemodynamic measures translate into durable reductions in cardiovascular events remains to be established.

Vascular calcification is highly prevalent in the elderly and strongly associated with increased cardiovascular event risk. Early studies have shown that inhibiting

osteogenic phenotypic switching can delay progression of calcification. More recent findings indicate that activators of Klotho, an antiaging protein that also regulates mineral metabolism, and BMP signaling inhibitors can partially reverse calcium deposition in animal models of arterial calcification.[122] In humans, a phase II trial of SNF472 (myo-inositol hexaphosphate), an intravenous inhibitor of hydroxyapatite formation, demonstrated significantly reduced progression of coronary artery calcification and aortic valve calcification in patients with end-stage kidney disease compared with placebo.[123] These findings suggest that targeted anticalcification therapies are approaching clinical relevance, although further trials are needed to assess effects on cardiovascular outcomes.

Elastin fragmentation and collagen imbalance are major contributors to reduced arterial compliance with age. Early in vitro studies demonstrated that reconstructing ECM architecture could improve vascular biomechanical properties. Animal studies using matrix metalloproteinase–specific inhibitors and elastin cross-linking enhancers have shown improved arterial compliance and delayed hypertension progression.[124] In addition, bioengineered elastin replacements and endoluminal regenerative scaffolds have entered the preclinical stage, offering potential for localized vascular repair in high-risk patients.[125]

The central nervous system is particularly sensitive to changes in vascular perfusion capacity and barrier function.[8] Large-scale proteomic analyses have revealed that vascular integrity loss associated with aging leads to BBB dysfunction, disruption of the cerebrospinal fluid–plasma protein balance, and subsequent cognitive impairment.[126] In recent years, notable progress has been made in strategies aimed at restoring BBB integrity. For example, activation of the Wnt signaling pathway has been shown to repair damaged BBB, whereas restoration of the endothelial glycocalyx in aged mice improved barrier integrity, reduced microhemorrhages, and enhanced cognitive function.[127,128] In parallel, regression of cerebral microvessels has been demonstrated to directly reduce neuronal activity, providing mechanistic evidence that vascular rarefaction itself can impair brain function.[129] It is important to note that age-related decline in vascular endothelial growth factor signaling has been identified as a critical driver of vascular rarefaction, impaired BBB repair, and neurovascular dysfunction. Restoring vascular endothelial growth factor activity can counteract these age-associated changes, thereby promoting healthy aging and, remarkably, extending life span in experimental mouse models.[12]

PERSONALIZED DIAGNOSIS AND TREATMENT

Even among individuals of the same chronological age, there are striking differences in the extent of aging. This has motivated the development of molecular clocks to more accurately capture an individual's true biological age. Moreover, aging is heterogeneous not only between individuals but also within a single individual in that different organs exhibit divergent rates of decline. In recent years, organ, pathway, and proteome level–based clocks have been devised.[130,131] Molecular clock biomarkers can also serve as indicators of disease prognosis.[132] Longitudinal studies have confirmed associations between organ-specific aging signatures and multisystem outcomes, underscoring the translational potential and public health value of these strategies.[133]

In the cardiovascular system, plasma proteome–derived aging signatures demonstrate that accelerated heart aging is associated with a 250% increased risk of heart failure, whereas accelerated vascular aging is linked not only to cardiovascular disease but also to the progression of Alzheimer disease.[134] Likewise, large-scale population studies using the epigenetic GrimAge clock reveal that accelerated aging is associated with increased cardiovascular age and a greater subclinical atherosclerotic burden, highlighting a close relationship between blood DNA methylation clocks and vascular aging.[135]

Other, noninvasive, nonmolecular techniques can also be applied to monitor vascular aging, including retinal vascular caliber,[136,137] vascular ultrasound, pulse wave velocity, coronary artery calcium scoring, and artificial intelligence–enabled ECGs.[138] Looking forward, integrating molecular clocks with these noninvasive techniques and cross-organ biomarkers into multimodal, multiorgan predictive models may enable precise evaluation of cardiovascular biological age and provide a foundation for early intervention in high-risk populations.

SUMMARY, DISCUSSION, AND FUTURE PERSPECTIVES

As discussed, in recent years, multiple laboratories have identified key molecular mechanisms that individually drive vascular aging. Increasingly, there is evidence that these pathways intersect and potentially amplify each other. For example, mitochondrial dysfunction can cause mtDNA leakage, that which the cGAS-STING pathway, thereby promoting chronic inflammation[61]; epigenetic remodeling acting in concert with inflammation can regulate phenotypic switching of VSMCs.[139]

In addition to these molecular drivers, dietary and lifestyle interventions have emerged as important modulators of vascular aging.[140] Caloric or dietary restriction improves endothelial function, reduces arterial stiffness, and activates longevity mediators such as AMPK and SIRT1, thereby lowering oxidative and inflammatory stress. Regular aerobic exercise similarly enhances NO bioavailability and attenuates systemic inflammation, whereas plant-based or Mediterranean dietary patterns

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improve metabolic profile and reduce vascular oxidative burden. Together, these nonpharmacological strategies provide practical and evidence-supported approaches that complement emerging molecular interventions aimed at slowing vascular aging.[140]

Beyond lifestyle and metabolic influences, additional exogenous and biological modifiers shape vascular aging trajectories. Environmental and circadian disruptions have been shown to accelerate vascular dysfunction, inflammation, and rates of vascular aging,[141,142] whereas well-established sex-specific hormonal differences contribute to differential susceptibility to endothelial dysfunction and arterial stiffness between men and women.[143]

In the future, beyond continued discovery of new drivers and mapping of complex interaction networks, mechanistic studies should also strive to "distill complexity into essentials" by pinpointing core nodes at which multiple drivers converge, thereby increasing the feasibility of clinical intervention. Indeed, unlike most areas in biology, aging lacks a single coherent theory, and the precise epistatic relationship between the drivers we have discussed remains unclear.

In the clinic, a range of emerging technologies are steadily translating into practice. Next-generation molecular biomarkers are being integrated with traditional modalities for early identification of vascular aging and risk stratification for cardiovascular events[144]; multiomics approaches are enabling personalized intervention strategies,[145] and several aging drivers have already become drug targets. Looking ahead, additional cutting-edge strategies are poised to enter the clinic, including bioengineering technologies (such as milli-spinner thrombectomy),[146] tissue engineering, targeted nanodelivery, and mRNA-based therapies.

All these mechanistic insights and potential therapeutic advances combine to lead to a sense of justified enthusiasm. However, in truth, skeptics might provide a counterargument that perhaps all we will have achieved with these myriad efforts is to finally understand what Thomas Sydenham intuitively knew nearly 400 years ago.

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Dr Finkel is a cofounder and stockholder in Generian Pharmaceuticals and Coloma Therapeutics. Dr Chan has served as a consultant for Merck, Janssen, and United Therapeutics; is a director, officer, and shareholder in Synhale Therapeutics and Amlysion Therapeutics; holds research grants from United Therapeutics, Bayer, and WoodNext Foundation; and has filed patent applications on the targeting of metabolism and inflammation in pulmonary hypertension and the targeting of circadian rhythm. Dr Wang reports no conflicts.

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