Atherosclerotic cardiovascular disease is an intrinsically age-related process, and epidemiologic data support the idea that the milieu of the elderly body, rather than a diseased blood vessel’s age, determines this susceptibility to atherosclerosis and its consequences. This notion, if true, suggests that vascular senescence may be a reversible process and raises the possibility of rejuvenative therapies for cardiovascular protection in the elderly. A report by Haendeler and colleagues in this issue of Circulation Research addresses the mechanisms by which cultured vascular endothelial cells undergo senescence and suggests that both antioxidant mechanisms and statins, the pharmacologic 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors, may reverse at least some features of the vascular senescence phenotype. What can we learn about vascular aging from this impressive report?

Do Aging and Replicative Senescence Go Hand in Hand?

The title of this article indicates that the authors are interested in replicative senescence of endothelial cells in cell culture as a model for understanding the mechanisms that underlie vascular aging. In now classic experiments, Leonard Hayflick discovered that somatic cells in culture cannot divide indefinitely. Replicative senescence therefore refers to the process by which cells lose their ability to replicate after a finite number of cell divisions, and Hayflick (among many others) noted that somatic cells exhausted of their ability to divide in culture may have characteristics associated with aging. This led to the notion that replicative senescence might account for organismal aging in vivo and, conversely, that the phenomenon of replicative senescence in culture might be a practical model for understanding the mechanisms that determine aging.

It must first be noted that the studies of Haendeler and colleagues in this issue do not actually measure replicative senescence per se but instead use the accumulation of acidic β-galactosidase activity as a marker of senescence; thus, strictly speaking, the authors are primarily studying biochemical rather than replicative senescence. Although widely used as a marker for senescence, the accumulation of β-galactosidase activity in mammalian cells is not a specific marker for replicative senescence and is increased by a variety of conditions in cultured cells even without extensive passage, including oxidative stress. It is at least formally possible that the results of the present studies reflect the accumulation of oxidative species with passage (which should by definition be reversed with antioxidant treatments, as the authors here show) rather than an indication that replicative senescence is occurring. The broader question of whether true replicative senescence indeed reflects processes that occur during organismal aging is itself still a matter of open debate—certainly features such as cell type, culture conditions, and donor species affect the number of population doublings available to donor cells, and the inverse correlation between population doublings of cultured cells and donor age that forms the basis for replicative senescence as an aging model is a weak and inconsistent correlation. Thus, the data presented in this issue are solid, but their extrapolation to organismal aging should be made with care. It is also worth keeping in mind that many pathologies associated with aging, including abnormal responses to vascular injury, are associated with accelerated, rather than diminished, proliferation. Thus, one charge to the vascular biology community is to prove the suitability of in vitro models of vascular aging or to develop new ones.

Oxidative Stress and Aging: A Real Link or True, True, and Unrelated?

In the report by Haendeler and colleagues, an association is made between the accumulation of reactive oxygen species (ROS) and cellular senescence, and the biochemical activities they used as markers of senescence were reversed with antioxidant therapies, suggesting that oxidative damage and senescence go hand in hand within the vascular endothelium (Figure). The idea that free radical–mediated oxidative damage contributes to the aging process was proposed almost half a century ago by Harman, and accumulating evidence since then lends credence to this theory. Recent studies indicate that the anti-aging effects of caloric restriction might be due to decreased mitochondrial oxygen consumption and ROS production and mice deficient in p66Shc (a cytosolic signal transducer) are resistant to paraquat-generated ROS and have increased life span. A corollary to the free radical theory of aging is the “mitochondrial theory of aging,” which suggests that senescence may be linked to oxidative injury that affects the integrity of mitochondria. Circumstantial evidence for this theory includes the association between aging and decreased

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activity of mitochondrial respiratory complexes. However, it is not universally accepted that aging results in altered mitochondrial electron transport or oxidative phosphorylation. Evidence of mitochondrial injury in the studies by Haendeler and colleagues would have been stronger if their assays of mitochondrial DNA damage were performed according to rigorously accepted standards. A quantitative polymerase chain reaction for detecting mitochondrial DNA damage was initially developed by Van Houten and colleagues and is based on the premise that oxidative lesions in a DNA template will stop a thermostable polymerase, resulting in decreased amplification of the damaged DNA template compared with undamaged DNA. Amplification of the entire mitochondrial genome in toto is a requisite to avoid the confounding factor of DNA damage “hot spots,” and results must be corrected for mean mitochondrial copy number per cell, which can vary. In the absence of these corrections, the authors’ observations must be considered suggestive but not indicative of accumulated mitochondrial DNA damage during the course of endothelial senescence. It remains to be established whether a causative association between mitochondrial dysfunction and vascular aging exists.

Statins: A Vascular Fountain of Youth?
Anyone with access to the mass media cannot be faulted for inferring that HMG CoA reductase inhibitors can jump-start any failing vascular condition. Indeed, the effects of statins extend beyond their ability to reduce low-density lipoprotein levels, at least at the cellular level. Through their ability to inhibit geranylgeranylation, statins can affect more cellular events than are often appreciated. For example, statins can increase the bioavailability of nitric oxide, which has potential relevance in the context of aging insofar as nitric oxide has protective effects on mitochondrial integrity. Statins may also enhance nuclear TERT activity via stimulation of Akt derived from increased phosphatidylinositol 3-kinase (PI3-K) activity or increased nitric oxide synthesis. Dashed arrows represent the sites of direct deleterious effects of ROS and the solid arrows the restorative effects of statins.
that reverse components of the vascular aging process through mechanisms such as these, although of course this remains a tantalizing hypothesis to be tested in future studies.

Vascular Senescence: What We Know and What We Don’t Know

The provocative study in this issue of Circulation Research is a useful barometer of where vascular biologists stand in understanding why cardiovascular disease is the leading cause of death and disability in postindustrial societies. It is easy to argue that, among all risk factors for cardiovascular disease, age is the least well understood. Epidemiologic studies suggest that there is something about being old that accelerates the risk of cardiovascular disease: that is, it may not be that blood vessels themselves are old so much as that they live in an aged environment. The factors that contribute to this propensity to vascular injury and disease remain to be elucidated. The report by Haendeler and colleagues serves as a wake-up call that vascular aging is neither trivial, beyond the scope of investigation, nor unworthy of our rigorous analysis.

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