ANTIOXIDANTS & REDOX SIGNALING
Volume 8, Numbers 3 & 4, 2006

Forum Editorial

Genetics, Redox Signaling, Oxidative Stress, and Apoptosis in Mammalian Aging

CHRISTIAAN LEEUWENBURGH[1] and TOMAS A. PROLLA[2]

THE FIELD OF AGING RESEARCH has now entered a rapid phase of discovery. The most dramatic findings have been associated with the extension of lifespan in simple organisms, such as *C. elegans*, *S. cerevisiae,* and *Drosophila*. The question that now permeates the field is "Can these findings be extended to mammals?" Only two interventions—caloric restriction and dwarfism—have achieved life extension to an extent that compares with findings obtained in the simpler organisms. However, there is tantalizing evidence that a deeper understanding of mammalian aging is at hand. Several interventions, such as overexpression of antioxidant enzymes (15), $p66^{Shc}$ deletion (9), and manipulations of insulin/IGF1 axis (1) have produced extension of lifespan in the absence of the overt changes in body composition observed in caloric restriction or dwarf animals. Interestingly, most of these interventions appear to be associated with an increase in stress resistance. In this forum issue of ARS, the relevance of genetics, redox balance, oxidative stress, and apoptosis to mammalian aging is examined through a spectrum of viewpoints.

Migliaccio *et al.* (10) discuss the important role of $p66^{Shc}$ protein in the regulation of cellular responses to oxidative stress, apoptosis, and aging. The $p66^{Shc-/-}$ mouse model provided support for the involvement of reactive oxidant species in aging, and also facilitated the discovery of a link between the p53 and $p66^{Shc}$ signaling pathways, which has provided support for a complex but exciting new area of research in apoptosis and aging. Suh and Vijg (18) discuss the critical balance between genomic instability, apoptosis, and cancer in relation to aging. As DNA damage accumulates as a function of age, so thus the induction of apoptotic pathways. Apoptosis eliminates potential precancerous cells, but the tradeoff may be the loss of critical cells. Aging, it seems, occurs at least partially due to the accumulation of such damage and resulting cell loss, as evidenced by progeroid symptoms in several animal models of genetic instability, including Ku80 and Xpa deficiency (4, 6, 18). Surprisingly, some models of genetic instability and oxidative stress, such as Xpa and SOD2 deficiency do not result in accelerated aging but do increase age-related tumorigenesis. Thus, the type of DNA damage may be critical in determining its overall contribution to the aging phenotype, and age-related cancer mortality. Although both factors contribute to age-related mortality, they can be uncoupled as demonstrated by these animal models. The recent discovery that mice that overexpress a mitochondria-targeted catalase display increased lifespan is intriguing, and Mele *et al.* (8) provide compelling evidence that cells derived from such animals are in fact resistant to oxidants. Surprisingly, whole animal resistance to paraquat is not observed in the transgenic animals, a finding that raises questions regarding the actual mechanism of longevity. As usual, conclusions are not straightforward in studies of mammalian aging, probably due to the complexity of the aging process.

One of the most disturbing findings for enthusiasts of the free radical theory of aging was the finding that mice that carry mutations in SOD2 display elevated oxidative stress but no decrease in lifespan (19). Also surprising were the recent findings that mice with a proofreading-deficient version of the mitochondrial DNA polymerase-γ (POLG), which accumulate mtDNA mutations in tissues and display features of accelerated aging, do not display increased markers of oxidative stress, but show induction of apoptotic markers (7). Given these remarkable findings, one is forced to ask if the oxidative stress theory of aging remains viable. Sanz *et al.* (14) review the critical evidence in models of normally aging animals, which suggest that the theory has support, but that the focus of investigation may need reevaluation. Comparative studies consistently show that long-lived mammals and birds have low rates of mitochondrial reactive oxygen species production and low levels of oxidative damage to their mitochondrial DNA. Furthermore, caloric restriction, which extends longevity, also decreases mitochondrial reactive oxygen

[1]University of Florida, Department of Aging and Geriatric Research, College of Medicine, Institute on Aging Genomics and Biomarkers Core, Biochemistry of Aging Laboratory, Gainesville, Florida.
[2]University of Wisconsin, Departments of Genetics and Medical Genetics, University of Wisconsin, Madison, Wisconsin.

species production at complex I and lowers mtDNA oxidative damage. Of novelty is the finding that positive changes can also be achieved with protein restriction without significant caloric restricting animals. Moreover, the authors show supporting data based on reduced levels of membrane unsaturation in long-lived birds, and reduced reactive oxygen species production in mitochondria from these species. Although correlative, such studies suggest that significantly reducing overall reactive oxygen species production may partly be achieved through alterations in mitochondrial composition. Closely linked to the oxidative stress theory of aging is the inflammation theory of aging. Chung *et al.* (3) discuss the growing evidence that inflammatory pathways play a key role in aging. Many believe that humans are ill-protected against self-induced inflammation through obesity, and that during evolution few mechanisms were put in place to protect us from the chronic inflammation associated with this metabolic state. Clearly, what we define as aging is a very complex collection of alterations at the molecular level, leading to impaired stress and disease resistance, and resulting in the ultimate demise of the organism.

For those who are interested in lifestyle interventions, four original contributions in this issue strongly suggest that age-related increases in oxidative stress and apoptosis as well as decrease in redox status can be attenuated. Song *et al.* (17) demonstrates for the first time that treadmill exercise markedly reduces apoptosis signaling in aged muscle, whereas Molnar *et al.* (11) provides evidence that hydrogen peroxide production is reduced with exercise, a finding that may be linked to alterations in membrane composition. Seo *et al.* (16) show that both exercise and caloric restriction also attenuate age-related increases in oxidative stress and the induction of pro-inflammatory factors. An extremely interesting finding reported by these authors is that a very mild caloric restriction regimen of 8% was sufficient to reduce oxidant production and oxidative stress. DeRuisseau *et al.* (5) discusses the potential benefits of caloric restriction and exercise can provide for the diaphragm. Taken together, these findings provide further support to a large and growing body of evidence in favor of caloric restriction and exercise as the most practical interventions to retard aging and increase the quality of life in aged humans.

This forum issue of *ARS* also contains manuscripts that highlight novel players in the complex phenotype of aging. Park (13) proposes that caveolins may play an important role, given their complex regulatory role. Napoli *et al.* (12) discuss the role of frataxin and iron–sulfur clusters as modulators of oxidative stress and aging. Apparently heme defects in the electron transport chain of mutants are responsible for increased oxidative stress observed.

Finally, if our growing knowledge of the biology of aging is to be translated into increases in the length and quality of life, relevant biomarkers must be identified and monitored in humans. Cesari *et al.* (2) discusses the role of oxidative damage markers as new predictors of mortality and morbidity. Some of the findings, such as increased oxidized LDL in individuals more likely to become disabled, suggest that despite the controversy surrounding the free radical theory of aging, oxidative damage, and inflammation may be good prognostic markers for disability and future mortality.

ACKNOWLEDGMENTS

The authors thank Lindsay Stevens for her technical assistance with assembling this Forum and the referees for their critique and input.

ABBREVIATIONS

IGF1, insulin-like growth factor 1; Ku80, mice defective in nonhomologous endjoining; mtDNA, mitochondrial DNA; p53, tumor suppressor; $p66^{Sch-/-}$, $p66^{Shc}$ gene deficient; POLG, DNA polymerase-γ; SOD2, mitochondrial superoxide dismutase 2; XP, xeroderma pigmentosum.

REFERENCES

1. Bluher M, Kahn BB, and Kahn CR. Extended longevity in mice lacking the insulin receptor in adipose tissue. *Science* 299: 572–574, 2003.
2. Cesari M, Kritchevsky S, Leeuwenburgh C, and Pahor M. Oxidative damage and platelet activation as new predictors of mobility disability and mortality in elders. *Antioxid Redox Signal* 8: 609–619, 2006.
3. Chung HY, Sung B, Kyung JJ, Yani Z, and Byung PY. The molecular inflammatory process in aging. *Antioxid Redox Signal* 8: 572–581, 2006.
4. de Boer J, Andressoo JO, de Wit J, Huijmans J, Beems RB, van Steeg H, Weeda G, van der Horst GT, van Leeuwen W, Themmen AP, Meradji M, and Hoeijmakers JH. Premature aging in mice deficient in DNA repair and transcription. *Science* 296: 1276–1279, 2002.
5. DeRuisseau KC, Kavazis AN, Judge S, Murlasits Z, Deering MA, Quindry JC, Lee Y, Falk DJ, Leeuwenburgh C, and Powers SK. Moderate caloric restriction increases diaphragmatic antioxidant enzyme mRNA, but not when combined with lifelong exercise. *Antioxid Redox Signal* 8: 539–547, 2006.
6. Hasty P, Campisi J, Hoeijmakers J, van Steeg H, and Vijg J. Aging and genome maintenance: lessons from the mouse? *Science* 299: 1355–1359, 2003.
7. Kujoth GC, Hiona A, Pugh TD, Someya S, Panzer K, Wohlgemuth SE, Hofer T, Seo AY, Sullivan R, Jobling WA, Morrow JD, Van Remmen H, Sedivy JM, Yamasoba T, Tanokura M, Weindruch R, Leeuwenburgh C, and Prolla TA. Mitochondrial DNA mutations, oxidative stress, and apoptosis in mammalian aging. *Science* 309: 481–484, 2005.
8. Mele J, Van Remmen H, Vijg J, and Richardson A. Characterization of transgenic mice that overexpress both copper zinc superoxide dismutase and catalase. *Antioxid Redox Signal* 8: 628–638, 2006.
9. Migliaccio E, Giorgio M, Mele S, Pelicci G, Reboldi P, Pandolfi PP, Lanfrancone L, and Pelicci PG. The $p66^{shc}$ adaptor protein controls oxidative stress response and life span in mammals. *Nature* 402: 309–313, 1999.
10. Migliaccio E, Giorgio M, and Pelicci PG. Apoptosis and aging: role of $p66^{shc}$ redox protein. *Antioxid Redox Signal* 8: 600–608, 2006.

11. Molnar AM, Servais S, Guichardant M, Lagarde M, Macedo DV, Pereira-Da-Silva L, Sibille B, and Favier R. Mitochondrial H_2O_2 production is reduced with acute and chronic eccentric exercise in rat skeletal muscle. *Antioxid Redox Signal* 8: 548–558, 2006.
12. Napoli E, Taroni F, and Cortopassi GA. Fraxatin, iron-sulfur clusters, heme, ROS, and aging. *Antioxid Redox Signal* 8: 506–516, 2006.
13. Park SC. New molecular target for modulation of aging process. *Antioxid Redox Signal* 8: 620–627, 2006.
14. Sanz A, Pamplona R, and Barja G. Is the mitochondrial free radical theory of aging intact? *Antioxid Redox Signal* 8: 582–599, 2006.
15. Schriner SE, Linford NJ, Martin GM, Treuting P, Ogburn CE, Emond M, Coskun PE, Ladiges W, Wolf N, Van Remmen H, Wallace DC, and Rabinovitch PS. Extension of murine life span by overexpression of catalase targeted to mitochondria. *Science* 308: 1909–1911, 2005.
16. Seo AY, Hofer T, Sung B, Judge S, Chung HY, and Leeuwenburgh C. Hepatic oxidative stress during aging: effects of 8% long-term calorie restriction and lifelong exercise. *Antioxid Redox Signal* 8: 529–538, 2006.
17. Song W, Kwak H-B, and Lawler JM. Exercise training attenuates age-induced changes in apoptotic signaling in rat skeletal muscle. *Antioxid Redox Signal* 8: 517–528, 2006.
18. Suh Y and Vijg J. Maintaining genetic integrity in aging: a zero sum game. *Antioxid Redox Signal* 8: 559–571, 2006.
19. Van Remmen H, Ikeno Y, Hamilton M, Pahlavani M, Wolf N, Thorpe SR, Alderson NL, Baynes JW, Epstein CJ, Huang TT, Nelson J, Strong R, and Richardson A. Life-long reduction in MnSOD activity results in increased DNA damage and higher incidence of cancer but does not accelerate aging. *Physiol Genomics* 16: 29–37, 2003.

Address reprint requests to:
Christiaan Leeuwenburgh
1329 SW 16th Street, Room 5277
Gainesville, FL 32610-0107

E-mail: cleeuwen@aging.ufl.edu

Received for publication September 23, 2005; accepted October 3, 2005.

This article has been cited by:

1. Benjamin L. Predmore, Maikel J. Alendy, Khadija I. Ahmed, Christiaan Leeuwenburgh, David Julian. 2010. The hydrogen sulfide signaling system: changes during aging and the benefits of caloric restriction. *AGE* **32**:4, 467-481. [CrossRef]
2. Adeel Safdar, Justin deBeer, Mark A. Tarnopolsky. 2010. Dysfunctional Nrf2–Keap1 redox signaling in skeletal muscle of the sedentary old. *Free Radical Biology and Medicine* **49**:10, 1487-1493. [CrossRef]
3. Arnold Y. Seo, Jinze Xu, Stephane Servais, Tim Hofer, Emanuele Marzetti, Stephanie E. Wohlgemuth, Mitchell D. Knutson, Hae Young Chung, Christiaan Leeuwenburgh. 2008. Mitochondrial iron accumulation with age and functional consequences. *Aging Cell* **7**:5, 706-716. [CrossRef]