COACTION PUBLISHING

Pathobiology of aging: an old problem gets a new look

The pursuit of investigations into the science of aging is really designed to understand why cellular processes begin to fail with advancing age, and what molecular events contribute to this failure. In this regard, the distinction between aging and the diseases associated with aging becomes less clear, and they are most likely driven by the same or similar events related to biological decline. With the launch of *Pathobiology of Aging & Age-related Diseases*, we hope to enlighten the scientific community by recognizing outstanding pathobiology-based scientific contributions, allowing scientists to communicate data that might be of less interest in other journals more focused on generic aging or specific scientific disciplines. Aging is indeed an 'old' problem and is being studied in a variety of ways that use mammalian model systems to identify mechanistic pathways that can be targeted to maintain healthy living. In this regard, we are providing a 'new' venue for disseminating information that specifically focuses on the pathobiological aspects of aging and the chronic diseases directly associated with aging. There will be a commitment to publishing manuscripts that meet the highest standards of science, but the nature of the journal will allow highly detailed and image-intensive descriptions of the pathology of aging and disease conditions associated with aging. The aim is to provide an interdisciplinary venue for pathology-based manuscripts that focus on the physiological function of aging in preclinical mammalian models.

Pathology is the study of events associated with the gross, histological, and cellular conditions considered abnormal. Pathobiology can be defined as the study of abnormal morphological features and the biological events associated with cellular dysfunction. In this regard, the pathobiology of aging and age-related diseases is an entity that fits nicely under the pathology umbrella but not yet recognized by the scientific community as having any stand-alone impact on advancing healthy aging. This is not to say that it should be a stand-alone entity. On the contrary, integration with physiology and anatomy is a key component to a comprehensive assessment of abnormal versus normal. Data describing the pathobiology of aging and the diseases generally associated with aging have unique challenges. By design, it covers a wide range of disciplines and has an underlying focus of addressing mechanisms using a pathological basis to define the progression of age-associated lesions. These types of data are by nature quite descriptive but still can be highly informative even in the absence of mechanistic details.

Pathobiology of Aging & Age-related Diseases launches with six highly interesting articles:

Pathobiology data mining

Preclinical studies using mutant mouse models have been highly productive in identifying specific genes involved in the aging process. Lifespan studies have been conducted and published using a number of different mouse lines representing a variety of genes with different but, at times, overlapping functions (1). Most of these studies did not perform extensive pathological analyses, thus informative data on the progression of aging and presence of age-related lesions were lost. Our own studies serve as an example of how data can be mined from lifespan studies in mice. In 2005, we reported the lifespan extension of mice expressing mitochondrial-targeted catalase (mCAT) (2) but with only limited pathological description, so the comprehensive extent of age-related lesions was not known. Fortunately, we saved an extensive amount of tissues collected from mice at the end of their lifespan and described a broad array of tissue-specific lesions that were consistently attenuated in mCAT mice (3). In one of the articles with which *Pathobiology of Aging & Age-related Diseases* launches – Practical pathology of aging mice – using examples of lesions in wild-type control mice from this study as well as in other studies, Pettan-Brewer and Treuting (4) describe common tissue alterations associated with aging in the C57BL/6 inbred or F1 mouse. This informative paper can easily be used as a pathobiological guide by scientists using mice for aging studies. It is designed as an illustrative review to provide an introduction to age-associated diseases and lesion patterns in mice from clinical presentation to pathologic assessment.

Another example of pathology data mining from aging studies using mice comes from the Jackson Laboratories. In their article, 'The mouse as a model for understanding chronic diseases of aging: the histopathologic basis of aging in inbred mice,' Sundberg et al. (5) describe an overview of the lesions in middle-age and old-age mice representing 30 different strains. This is of great interest and relevance to aging because of the comprehensive coverage of so many different mouse strains. But just as important, it provides an in-depth insight into the extremely valuable contributions that the mouse can potentially contribute to the biology of aging research.

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These data provide tools that, when linked with modern *in silico* genetic mapping, can begin to unravel the complex genetics of many of the common chronic diseases associated with aging in humans and other mammals. In addition, novel disease models were discovered in some strains. This extensive data set is now available online and provides a useful tool to help better understand strain-specific background diseases that can complicate interpretation of studies using genetically engineered mice.

A third and more focused example of pathology data mining in mice is presented by Dollé and his team (6) in their article 'Broad segmental progeroid changes in short-lived Ercc1$^{-/\Delta 7}$ mice,' in which they describe lesions associated with a segmental progeria condition mediated by partial loss of the DNA repair gene Ercc1 (*Ercc1*$^{-/\Delta 7}$). They show that the short lived *Ercc1*$^{-/\Delta 7}$ mice develop a broad spectrum of aging-related changes that are also observed in wild-type mice, but at normal (chronological age), accelerated (biological age), or extreme rates. The segmental progeroid phenotype of *Ercc1*$^{-/\Delta 7}$ mice has two potential practical advantages for aging research. First, the accelerated segmental nature of the aging phenotype could bring research focus on those specific endpoints, and underlying causes and consequences that would be more difficult to discern in wild-type mice that dilute these endpoints with the full aging spectrum. Second, short lifespan and the explicit aging aspects could make a suitable short-term intervention model for lifespan extension and reduction of aging-related pathology.

Preclinical aging intervention studies

In addition to gene-driven studies, *Pathobiology of Aging & Age-related Diseases* is also committed to publishing high-quality preclinical aging intervention studies that describe pathological outcomes. Caloric restriction (CR) is a well-documented procedure that extends lifespan and healthy aging in a number of mammalian species, including rats and mice. In their article, 'The anti-tumor effects of calorie restrictionare correlated with reduced oxidative stress in ENU-induced gliomas,' Mahlke et al. (7) describe their results using an ENU-induced glioma model in rats to test whether changes in tumor incidence and/or growth by CR are associated with corresponding changes in oxidative stress, or its physiological consequences, such as changes in redox-sensitive signaling. The results showed that the CR group had both reduced the number and size of gliomas, with less accumulation of oxidative damage, decreased formation of glycated end products, and a decreased presence of antioxidants compared to the *ad libitum* group. These results are exciting because they not only demonstrate the anti-tumor effects of CR in gliomas but also suggest that the underlying anti-tumor mechanisms are associated with reduced accumulation of oxidative damage, decreased formation of glycated end products, decreased levels of HIF-1α, and downregulation of anti-oxidants.

In contrast to CR, long-term caloric excess has been shown to have detrimental effects associated with enhancement of aging and age-related diseases. In their article, 'Curcumin suppresses intestinal polyps in APC Min mice fed a high fat diet,' Pettan-Brewer et al. (8) study a diet high in fat and calories enhanced tumorigenesis in a mouse model of colon cancer. Interestingly, the enhanced tumorigenesis was blocked in mice ingesting the high caloric diet when curcumin was added. The study is relevant because colon cancer is a disease that is especially prevalent in the older population of Western countries, so it is intriguing that inclusion of curry, which contains high levels of curcumin, in the diet may have not only anti-tumor effects but anti-obesity effects as well.

A third intervention study coming with the launch of *Pathobiology of Aging & Age-related Diseases* tested a popular anti-aging polyphenol designated as resveratrol. In their article, 'Resveratrol has protective effects against airway remodeling and airway hyperreactivity in a murine model of allergic airways disease,' Royce et al. (9) show that resveratrol attenuates airway disease associated with an allergic response to an inhaled allergen. Pulmonary dysfunction associated with aging is an understudied area of aging research. Allergy-based airway disease is associated with extensive inflammatory activity. Periodic episodes over a period of many years become a risk factor for severe lung conditions including cancer. Their data suggest that resveratrol might be a suitable compound for not only helping prevent airway diseases but also could likely be considered as an adjunctive or primary treatment option for chronic lung disease in the elderly.

Aging mice are good models for organ dysfunction

Similar to humans, aging mice develop organ dysfunctions such as pulmonary disease, cognitive decline, cardiovascular disease, muscle weakness, osteoarthritis, as well as other chronic conditions. A hallmark of successful intervention of aging has been extended lifespan in animal models including mice (1). Interestingly, attenuation of organ dysfunction is not always associated with lifespan extension. Cardiac dysfunction is a good example. Cardiac dysfunction in mice can be detected by echocardiography as early as one year of age (10) depending on the background strain. As mice get older, lesions consistent with fibrosis and vascular inflammation are observed in association with the dysfunction. Old mice expressing mCAT have a robust attenuation of

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cardiac pathology along with more normal echocardiographic readings consistent with healthy aging and an extended lifespan (2, 11). However, we have shown that old mice lacking the beta catalytic subunit of protein kinase A have cardiac function that is similar to that of younger mice and vastly superior to that of their old wild-type littermates, but these mice have no advantage in lifespan (10). Aside from the fact that we are comparing two different genes, it illustrates the point that pathology-driven phenotyping for physiological function is critical in assessing aging endpoints, and that using lifespan in isolation might mean missing some critical advantageous phenotypes. *Pathobiology of Aging & Age-related Diseases* embraces this concept and encourages the submission of manuscripts based on the association of pathological findings and physiological function.

Cognitive decline is another example of a chronic age-related condition that occurs in mice and humans, especially in the context of dementia. Dementia is a hallmark of Alzheimer's disease (AD) such that assessment of cognitive function is a key diagnostic procedure. A number of transgenic mouse lines have been shown to model some of the characteristics of AD in humans, but correlation of cognitive function with pathological lesions, e.g. plaque development, has not always been reported because cognitive assessment in the mouse can be challenging. We have recently shown that a novel radial maze paradigm can distinguish cognitive decline in AD double transgenic mice that is directly correlated with the development of neuronal plaques (12). Dementia also occurs in wild-type aged mice depending to some degree on the genetic background strain. Again, a simple but yet robust cognitive assessment procedure is needed to determine cognitive function. We have unpublished preliminary data suggesting that aging wild-type C57BL/6 mice maintain a competent level of cognition for a longer period of time than age- and sex-matched CB6 F1 mice using the radial maze paradigm described previously. These are the kinds of data that contribute to manuscripts well suited for *Pathobiology of Aging & Age-related Diseases*.

We are committed to publishing manuscripts that meet the highest standards of science, but the nature of our journal will allow highly detailed and image-intensive descriptions of the pathology of aging and disease conditions associated with aging. The aim is to provide an interdisciplinary venue for pathology-based articles that focus on physiological function of aging, especially in preclinical mammalian models; and with the Open Access model we can guarantee widespread dissemination. We look forward to receiving *your* best papers!

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