Aging and Lung Disease

Clinical Impact and Cellular and Molecular Pathways

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Abstract

With the expected rapid growth of the aging population worldwide, there is a clear need to understand the complex process of aging to develop interventions that might extend the health span in this group of patients. Aging is associated with increased susceptibility to a variety of chronic diseases, and lung pathologies are no exception. The prevalence of lung diseases such as idiopathic pulmonary fibrosis and chronic obstructive pulmonary disease has been found to increase considerably with age. In October 2014, the Division of Pulmonary, Allergy, and Critical Care of the University of Pittsburgh cohosted the Pittsburgh-Munich Lung Conference focused in aging and lung disease with the Comprehensive Pneumology Center, Institute of Lung Biology and Disease, Ludwig-Maximilians University and Helmholtz Zentrum Munich Germany. The purpose of the conference was to disseminate novel concepts in aging mechanisms that have an impact in lung physiology and pathogenesis of pulmonary diseases that commonly occur in older populations. The conference included 28 presentations on diverse topics, which are summarized in this report. The participants identified priorities for future basic and translational investigations that will assist in the identification of molecular insights involved in the pathogenesis of age-related pulmonary diseases and the design of therapeutic interventions for these lung conditions.

Keywords: aging; lung disease; lung repair

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The Division of Pulmonary, Allergy, and Critical Care Medicine at the University of Pittsburgh School of Medicine has organized a highly attended lung conference since 2002 (https://www.dept-med.pitt.edu/paccm/conference_archive.html). The 2014 conference, which occurred October 23 and 24, could be described as a trial run for a new conference structure that merges two influential small international meetings: The Pittsburgh International Lung Conference and the Munich Lung Conference organized by the Comprehensive Pneumonology Center in Ludwig Maximilian University of Munich, Germany. This collaborative event, the Pittsburgh-Munich International Lung Conference, will hereafter be hosted by the two institutions in alternating years. The focus of the 2014 meeting was on aging, aiming to promote the interaction of academic leaders in clinical, translational, and basic research focused on the intersection of aging and lung disease. Six thematic sessions covered diverse aspects of the biology of aging with an emphasis on the age-related molecular mechanisms underlying lung diseases and the vulnerability of the aging lung to exogenous stress.

Independent of specific diseases, the process of aging sets an intrinsic limit on life span. Human life span (maximum number of years that a human can live) has remained consistently at ~125 years for the past 100,000 years. In fact, it is has been estimated that the control or elimination of major specific diseases, such as cancer or cardiovascular disease, will have modest effects on life span because we still face an intrinsic aging clock that drives multisystem breakdown at the limits of natural age. For instance, elimination of heart disease would increase life expectancy at birth by almost 4 years and elimination

of cancer by more than 3 years; the resolution of cardiovascular diseases, stroke, and cancer—the three major causes of death in old age—would result only in an increase of 15 years in human life span (1). However, life expectancy (average total number of years that a human expects to live) has expanded significantly in the last century predominately in developed countries with the improvement in the control of infectious diseases and public health measurements (2, 3). The increase in life expectancy has impacted the growth of the United States population of 65 years old and over. The most recent census shows that this age group increased from 35 million in 2000 to 41.4 million in 2011, and it is projected to increase to 79.7 million by 2040 (4).

As public health and medical advances prolong the human life span, the ever-increasing reality of population aging worldwide necessitates a more comprehensive study of age-related biological phenomena. Aging impacts health span (the years of disease-free living) based on specific age effects on disease susceptibility, progression, and therapy for many adult diseases. Fascinating new data suggest that, despite the apparent inevitability of this aging process, interventions such as intermittent fasting, sustained calorie restriction, exercise, and drugs such as rapamycin and metformin will extend life span in primitive organisms, such as *Drosophila*, *Caenorhabditis elegans*, and yeast, and even in mice (5–11). However, the picture remains less certain in primates and man (7). Thus, despite advances in the field of aging and specific diseases, many unknown age-related phenomena are likely drivers of disease. The fragmentary grasp we have currently on age-related factors among complex networks hinders man's ability to extend the human health span.

Aging is associated with increased susceptibility to a variety of chronic diseases, including type 2 diabetes mellitus, cancer, and neurological diseases (12–14). Lung pathologies are no exception; the prevalence of lung diseases such as idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD), and acute lung injury have been found to increase considerably with age, but the involved mechanisms are not fully elucidated (15–18). IPF is the prototype of age-associated disease, because it usually occurs in individuals older than 50 years and increases remarkably with aging (16, 19, 20). Aging is the highest demographic risk factor for IPF. Similarly for COPD, the prevalence is reported to be two to three times higher in the elderly (persons older than 60 years of age), and it is considered that progressive graying of the global population is playing a role in the increase of the disease (21).

Aging may also have an impact in the outcome of acute lung diseases, such as acute lung injury, acute respiratory distress syndrome (ARDS), and asthma (22, 23). Elucidating the molecular mechanisms of lung aging is essential to understand the drastic decline in lung function with age and how aging relates to the development and progression of acute and chronic lung diseases. Although our understanding of the biology of aging has advanced remarkably in the last two decades, few molecular mechanisms linking aging to age-related pulmonary diseases have been identified. Thus, there is a recognized need to understand the effects of aging in the lung and to integrate aging in basic and translational studies in lung diseases. Thought leaders in both aging and lung biology presented their findings at the Pittsburgh-Munich conference with hopes to consolidate our understanding of these complex phenomena, which we discuss below (Table 1).

After the opening lecture by Kevin High (Wake Forest School of Medicine) detailing the relevance, challenges, and impact of the research on aging (24), the first session, Mitochondria and Aging, discussed the effects of aging on mitochondrial homeostasis and quality control. Mitochondrial proteins can be adversely modified by acetyl groups produced by fat and glucose metabolism. Mitochondrial deacetylase Sirt3 counteracts such acetylation events to protect against oxidative stress and aging (25, 26). In the absence of Sirt3, mitochondrial perturbation leads to the activation of the NLRP3 inflammasome and elevated IL-1β levels and inflammation. Calorie restriction induces Sirt3, leading to the amelioration of NLRP3-induced inflammation (Michael N. Sack, National Heart Lung and Blood Institute, NIH).

Oxidative stress and mitochondrial quality control were further discussed by Michael Lotze (School of the Health Sciences, University of Pittsburgh), focusing on the multifaceted high-mobility group box 1 (HMGB1) protein, which can regulate the cells' response from adaptive autophagy to immunogenic necrosis according to varying degrees of oxidative stress (27). He described a role for HMGB1 in natural killer (NK) cells and dendritic cells (DC) that enhances the metabolic activity of NK cells while promoting NK:DC crosstalk (28, 29). Valerian Kagan (Graduate School of Public Health, University of Pittsburgh), an authority in oxidative lipidomics, focused on cardiolipin as a dynamic signal that can trigger cell death programs or act as a clearance signal for dead cells and damaged mitochondria depending on the modification status of cardiolipin (30–32). Phosphatase and tensin homologue–induced putative kinase 1 (PINK1), a key protein related to mitochondria homeostasis, is affected by aging, and a deficiency of this single protein may contribute to the complex disease IPF (Marta Bueno, School of Medicine, University of Pittsburgh) (33).

The contribution of genetic background to age-related lung diseases was explored in the second session, Age, Genetics, and Lung Diseases. Familial IPF studies with asymptomatic first-degree relatives of symptomatic patients reveal lung and blood abnormalities, some of which cause severe childhood diseases in homozygous individuals (regulator of telomere elongation helicase 1 [RTEL1] mutations) with slower progression in heterozygotes (34). Longitudinal follow up of these asymptomatic at-risk subjects can enable risk stratification, development of prediction models, and insights into IPF pathobiology (Timothy Blackwell, Vanderbilt University School of Medicine). Telomere homeostasis and maintenance is one of the best-described parameters of aging (35). Telomere dysfunction underlies many diseases and may lower the threshold for a "second hit" to manifest disease attributes (36, 37).

Many genes (e.g., hTERT, hTP, RTEL1) and cell types (alveolar epithelial or stem cells) are implicated in a diversity of disease patterns, each influencing the maturation of a recognizable disease phenotype (38). New developments have led to correlation of telomere length and attrition with several pathological conditions and may guide individualized therapy for lung disease (Mary Armanios, Johns Hopkins University School of Medicine). Endogenous regenerative biological "tools" may be

Table 1. 2014 Pittsburgh-Munich International Lung Conference: Aging and Lung Disease

Program Agenda
Opening lecture: Research in Aging: Relevance, Challenges, and Impact, Kevin P. High, M.D., M.S.
Session 1: Mitochondria and Aging
Mitochondrial Metabolism, Sirtuins, and Aging, Michael N. Sack, M.D., Ph.D.
Inside, Outside, Upside Down: DAMPs and Redox Regulate Immunity, Michael Lotze, M.D.
Cardiolipin and Mitochondrial Apoptosis, Valerian E. Kagan, Ph.D., D.Sc.
Age-related PINK1 Deficiency Impairs Mitochondrial Homeostasis and Promotes Lung Fibrosis, Marta Bueno Fernandez, Ph.D.
Session 2: Age, Genetics, and Lung Diseases
Genetics of Familial IPF, Timothy Blackwell, M.D.
Telomeres and Telomerase in Lung Diseases, Mary Armanios, M.D.
Is IPF a Stem Cell Disease? Piero Anversa, M.D.
The Aging ECM in Chronic Lung Diseases, Oliver Eickelberg, M.D.
Twist in the IPF Fibroblast, Daniel Kass, M.D.
Session 3: Molecular Drivers of Cell Aging, and Their Impact in the Respiratory System
Update on Clinical Trials in IPF, Kevin Gibson, M.D.
Aging and Wnt Pathway, Melanie Königshoff, M.D., Ph.D.
Malfolded Proteins, Proteostasis, Lung Disease, and Aging, William E. Balch, Ph.D.
Immunosenescence and Aging, Patty Lee, M.D.
Studying Lung Aging in Murine Models, Enid R. Neptune, M.D.
Session 4: The "OMICS" of Aging
Genetics and Genomics of Human Aging, Stuart K. Kim, Ph.D.
Metabolomics of Aging, Dean Jones, Ph.D.
Proteomics: State-of-the-Art to Assess Aging, Matthias Mann, Ph.D.
Session 5: Lung Diseases and Aging
COPD, an Early Aging Disease?, Frank C. Sciurba, M.D., F.C.C.P.
IPF and Aging, Moisés Selman, M.D.
Age and Susceptibility to ARDS, Gustavo Matute-Bello, M.D.
Cellular Senescence in the Aging Lung: Implications for Epigenetic Changes and Cancer, John Michael Sedivy, Ph.D.
Smoke Responses in Aging Mice, Ali Önder Yildirim, D.V.M.
Session 6: Aging Lung Cells and Repair
Fibroblast Activation Protein (FAP) Is an Endogenous Regulator of Pulmonary Fibrosis, Ming-Hui Fan, M.D.
Impact of Aging on Mesenchymal Stem Cells, Mechanisms and Therapeutic Implications, Mauricio Rojas, M.D.
Lung Endothelial Cells Adaptation to Apoptotic Stress, Irina Petrache, M.D.
Hyaluronan Interactions with TLR4 Regulate Type 2 Alveolar Cell Renewal and the Severity of Pulmonary Fibrosis, Paul Noble, M.D.
Keynote speaker: Aging and Chronic Disease – A View from the Aging Side, Brian K. Kennedy, Ph.D.

present as stem cells, which might prove a valuable therapeutic for many lung diseases. In a burgeoning and controversial discussion, multipotent human lung resident stem cells may regulate organ homeostasis and tissue repair after injury and could represent therapeutic potential (Piero Anversa, Harvard Medical School) (39, 40). Although the prevalence of chronic lung diseases like COPD, IPF, and lung cancer increases with age, each is uniquely affected by age-related events. Beyond the well-defined hallmarks of aging, age-related changes in the extracellular matrix (ECM) represent a dynamic modifier of lung aging (18, 41, 42). As sophisticated methods to profile the expression of ECM components develop, new questions arise regarding the specific contribution of single ECM components, the topology of ECM changes, and the identity of the molecular pathways involved, which may inform therapeutic or rejuvenating strategies (Oliver Eickelberg, Ludwig-Maximillians University and Helmholtz Zentrum München). The analysis of data from large collaborative lung research consortiums has generated multiple associations between genetic background and clinical phenotypes (43). Twist1 genetic expression is inversely correlated to inflammatory markers in patients with IPF (44), and the genetic deletion of twist1 in an *in vivo* model causes an enhanced inflammatory fibrotic phenotype, acting partly through increased expression of chemokine CXCL12 (Daniel Kass, University of Pittsburgh).

The next session, Molecular Drivers of Cell Aging and their Impact in the Respiratory System, explored many more biochemical pathways important for lung aging. Wnt signaling is up-regulated in human IPF, and proteins induced downstream of Wnt can recapitulate fibrosis in animal studies, suggesting a strong link between age-related diseases and Wnt signaling (Melanie Konigshoff, Helmholtz Zentrum München) (45–47). Organisms have developed protective mechanisms to overcome the effects of stressors such as oxidants, but advanced age or smoking can blunt these protections and predispose to diseases like COPD. Macrophage migration inhibitory factor is a naturally occurring lung-protective protein that can be manipulated with beneficial results in COPD (Patty Lee, Yale School of Medicine) (48).

In addition to age-related changes in gene expression, proteostasis is also affected with age and disease, causing a plethora of changes in the proteome (49). Manipulation of proteostasis can correct maladaptive stress responses in cystic fibrosis and may prove effective in combatting age-related conditions caused by protein aggregations like Huntington disease or inclusion body myositis (William Balch, Scripps Research Institute) (50). As research into pathways of aging matures, murine models of lung aging are being validated so that there can be consensus on criteria that control for age, experimental time courses, mouse strains, and organ versus systemic aging (Enid Neptune, Johns Hopkins University School of Medicine) (51).

In the next session, the "OMICS" of aging was explored. Genetic and genomic profiling of healthy individuals has revealed that despite their healthy state older subjects have a higher chance of developing a disease and that a specific organ can be more "aged" than the rest of the organism. The molecular drivers of this aging were identified as seven transcription factors in the kidney that control many of the genes involved (52). Further evaluation of each of these factors could elucidate their role in aging and may facilitate therapeutic intervention (Stuart Kim, Stanford School of Medicine). The development of high-resolution mass spectrometry has now enabled metabolomic studies to facilitate disease phenotypes (metabolome-wide association studies) and promote the discovery of clinical biomarkers that can

accurately profile complex diseases and their progression. Moreover, early studies show that aging greatly affects the metabolome (Dean Jones, Emory University) (53). Proteomics is also driven by high-resolution mass spectrometry, and a sensitive but quick "single shot" method could greatly advance both the study of lung biology and personalized clinical diagnosis and treatment of a disease (Matthias Mann, Max Planck Institute of Biochemistry) (43, 54).

COPD, IPF, ARDS, and lung cancer are a few examples of lung diseases for which incidence increases with age; in the penultimate session, Lung Disease and Aging, these topics were explored. Many physiologic, anatomic, and cellular perturbations are similar between COPD and normal aging, and several lines of evidence suggest that premature cell senescence and early aging facilitate the pathology in patients with COPD (Frank Sciurba, University of Pittsburgh) (55). Smoking causes functional and structural changes more robustly in aged mice through inflammation, as measured by iBALT formation, lymphocyte count, Th17 cell count, and transcriptional profiles (Ali Onder Yildirim, Helmholtz Zentrum München) (56). In the field of IPF, one prevailing theory is that in addition to aging, loss of epithelial integrity due to injury and an epigenetic reprogramming affecting epithelial cells and fibroblasts cause fibrosis (57, 58). As such, drivers of disease progression may be represented by disease modifier genes, environmental factors, or epigenetic changes (Moises Selman, Mexican National Institute of Respiratory Diseases). Similarly, age is an independent predictor of ARDS in patients with trauma and an independent predictor of mortality in ARDS, and the functional status of ARDS survivors also worsens with age (Gustavo Matute-Bello, University of Washington) (59).

The final session of the conference discussed aging lung cells and repair. The severity of the impact of cellular senescence varies between cell types, organs, and individuals. Age-related cellular dysfunction may be the result of unappreciated phenomena such as the de-repression of deleterious retrotransposable elements by mechanisms of decreased heterochromatinization in aging somatic cells (John Michael Sedivy, Brown University) (60, 61). Not even stem cells can escape aging, and the phenomenon of stem cell exhaustion carries severe consequences for the repair of tissues and organs. Older animals are more susceptible to fibrosis and can be partially rescued by mesenchymal stem cell therapy from young animals only, and stem cell therapy may have promise (Mauricio Rojas, University of Pittsburgh) (62). Aging is often associated with chronic exposure to environmental factors such as cigarette smoke. Endothelial cells are profoundly affected by exposure to smoke, and chronic exposure leads to apoptotic stress adaptation, endoplasmic reticulum stress, and autophagy, probably through epigenetic mechanisms (Irina Petrache, Indiana University) (63). Regarding tissue repair, type-2 epithelial cells (AEC2) play an important role in recovering from alveolar epithelial injury, and their renewal protects against fibrosis. Hyaluronan is part of the extracellular matrix and helps maintain the AEC2 population. Several lines of evidence now suggest that hyaluronan ligates TLR4 on the AEC2 cell surfaces to induce IL-6 expression and AEC2 regeneration (Paul Noble, Cedars-Sinai Medical Center) (64, 65).

It has been challenging to summarize the overwhelming amount of work presented during the conference, and we apologize to our presenter colleagues for any omissions from this brief article. Certainly great strides are being made in the field of aging in lung disease, and we hope that we will someday claim that although aging is inevitable, disease and disability are not.

For 2015, the Pittsburgh-Munich international lung conference will be held in Munich, Germany on October 2 and 3. The theme this year is Precision Medicine: From Molecular Mechanisms to Targeted Therapy. Many experts from around the world are scheduled to give presentations, and we are sure that it will be another outstanding meeting. All interested parties are invited to attend. Details can be found at http://www.mlc2015.de/.

Conclusions

Aging is a natural and inevitable process that represents a progressive loss of physiological integrity, leading to impaired function and lower adaptive capacity to stress. The aging process of the lung involves every tissue compartment and may influence the response to environmental stresses. Studies in animals have shown different responses and increased injury of old compared with young lungs in various challenges, indicating that the cellular process is likely to impart the capacity to repair the lung. Several lung diseases have aging as a risk factor, including IPF and COPD, and hallmarks of cellular aging are associated with the pathobiology of age-related lung diseases. For instance, patients with IPF have short telomeres regardless of telomerase mutations, and type II epithelial cells from IPF lungs have alterations in the mitochondrial dynamics and function. Cellular senescence, another hallmark of aging, has been implicated in chronic inflammatory and pulmonary distress in COPD and IPF. Deregulated nutrient sensing with alterations of the mTOR pathway has been found in the aging lung and lung fibrosis. Efforts to understand mechanisms of aging in the pathobiology of lung disease are required to develop novel therapeutic approaches for age-related lung diseases and expand the health span, a critical challenge with the current increasing longevity of the population. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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