Chair's Summary: Lung Aging and Regeneration 2016 Transatlantic Airway Conference

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The Transatlantic Airway Conference is a multidisciplinary conference established in 1986 with the main objective of providing a forum to discuss the most relevant topics related to lung physiology and diseases. The 2016 Transatlantic Airway Conference took place from January 13th to January 15th in Lucerne, Switzerland, and the focus was on aging and regeneration in the lungs. The meeting was attended by a kaleidoscope of well-known pulmonologists together with scientists in the field of aging research, all of whom congregated to discuss the basic aspects of aging and its impact on the development of chronic lung diseases.

Given the expected increase of the aging population in the next 30 years, the principal objective of this conference was to increase the awareness and understanding of the physiologic mechanisms of aging in the lung. It is a major concern that the increase in the lifespan of the overall human population will enhance the vulnerability to develop morbidities associated with age. Compared with the enormous effort spent on the study of aging in cardiovascular-, metabolic-, and neurological-related fields, thus far the research in age-related lung diseases has been limited. Despite the increased incidence and prevalence of chronic lung diseases like chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF) with age, and the higher clinical severity and mortality of lung diseases such as asthma and acute respiratory distress syndrome in patients with advanced age, the physiologic process of aging in the lung and the pathobiology of age-related lung diseases remain poorly understood.

Mechanisms of Lung Aging

The keynote speaker this year was Brian Kennedy, head of the Bulk Institute in California. Dr. Kennedy discussed the molecular aspects of aging, focusing mostly on geroscience as the area dedicated to the development of new drugs that can have an effect on the process of aging (pp. S398–S401). New compounds in the pipeline that have been observed to have an effect on prolonging lifespan include metformin and rapamycin. Rapamycin, which targets the activation of mammalian target of rapamycin (mTOR) complex 1 (mTORC1), is one of the most promising candidates. There is evidence that rapamycin can improve the immune response to influenza vaccine. Studies have shown an increase in the activation of the mTORC1 pathway in chronic lung diseases such as COPD, and more recently in lung fibroblasts from IPF lungs. However, how mTOR activation plays a role in the pathogenesis of lung diseases is still unclear. The potential protective and/or therapeutic effect of rapamycin in age-related lung diseases was discussed, as was the need for studies in animal models of lung diseases.

One of the major consequences of aging is the development of cell senescence. Judith Campisi discussed the fundamental aspects of cell senescence and the predominant phenotypes (pp. S402–S406). There is accumulating evidence that senescence is a response to stress, including reactive oxygen species generation, DNA damage, shortening of telomeres, and mitochondrial dysfunction. One of the most fascinating

phenomena is senescence-associated secretory phenotype (SASP). Secretion of IL-6, IL-8, and matrix metalloproteinases by senescent cells creates a proinflammatory environment that contributes to the development of chronic diseases. Novel data show that successful elimination of senescent cells is critical in processes such as wound healing and the therapeutic potential of senolytic drugs to treat age-related lung diseases.

An important aspect associated with aging is the presence of chronic, low-grade inflammation, which represents a phenomenon called inflammaging. How inflammaging compromises epithelial barrier properties was presented by Roosmarijn Vandenbroucke (pp. S407–S410). The choroid plexus is a highly vascularized structure that protrudes into the brain ventricles. It has been demonstrated that aging can affect the choroid plexus functions, and that this dysfunction is a contributing factor in age-related diseases such as Alzheimer's. Some of the changes associated with age are alterations of epithelial morphology of the choroid plexus, which results in alterations of the secretory capacity and immune response.

A persistent discussion in the field of age-related lung diseases concerns the molecular differences between COPD and IPF that might explain the pathologically and clinically different phenotypes of these two entities despite their similar risk factors. Melanie Königshoff discussed the opposite activation status of the Wnt-signaling pathway in COPD and IPF, as well as the potential role of Klotho,

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an inhibitor of the Wnt pathway in COPD pathogenesis (pp. S411–S416).

Age-related Lung Diseases

Ana Maria Cuervo discussed new aspects of autophagy and how the process acts in the defense against cellular stress and aging. It is known that autophagy decreases with age; in particular, the chaperone-mediated microautophagy (CMA) associated with low expression of the lysosome-associated membrane protein type 2A (LAMP-2A) also decreases with age. Some of the activators of LAMP-2A include oxidative stress, DNA damage, hypoxia, starvation, and lipids. There is evidence that starving can act as a stimulator of LAMP-2A expression, resulting in a major formation of the complex chaperone–lysosome required for protein degradation. Defective CMA leads to multiple pathologic processes in the brain and liver, as well as development of metabolic syndrome. The role of CMA in the pathobiology of lung diseases is still under investigation.

Annie Pardo discussed the phenotypic differences of fibroblasts isolated from aging patients and from patients with IPF compared with their younger counterparts (pp. S417–S421). Fibroblasts from lungs of patients with IPF have a profibrotic phenotype with disturbed expression of multiple signaling proteins including PTEN, WNT5A, PI3K, and Cyclin D1, and soluble factors like pGE2a, IL-8, HGF, and others. Novel studies support the concept that the phenotype of the fibroblasts is strongly modulated by their interactions with the extracellular cell matrix. It is also now well established that the composition of the extracellular matrix and its stiffness varies with age and disease.

Confirming the interaction between the different cell perturbations in the aging cell, Cornelia Weyand discussed how premature erosion of telomeres in T cell populations from patients with rheumatoid arthritis was associated with insufficient induction of telomerase, dysfunctional DNA damage responses, and metabolic alterations that

lead to insufficient glucose utilization, lactate production, and ATP generation (pp. S422–S428). Deficiency in phosphofructokinase-2 has been identified as the potential molecular mechanism that impacts the metabolism in these cells. Current studies are focused on defining whether such metabolic deficiencies impact T cell function and the accelerated aging phenotype in rheumatoid arthritis T cells.

Lung Regeneration

Chronic exposure to cigarette smoke has been defined as the most important ethological factor in the development of emphysema. Andy Bush proposed a new theory in which early alterations in pulmonary function, by a reduction in the ratio of forced expired volume in 1 second (FEV₁) to forced vital capacity (FVC) lower than 80% before age 40, can be used as indicators of a high risk for the development of COPD (pp. S438–S446). The factors that can drive the reduction in pulmonary function can be divided into three different stages: Stage 1, before birth (maternal nicotine exposure, maternal hypertension, previous pregnancies, and prematurity); Stage 2, childhood and lung growth (tobacco, pollution, asthma, and nutrition); and Stage 3, aging lung (reactivation of development genes). The data presented suggested that public health policies directed at decreasing smoking and air pollution can have a big impact in the development of COPD later in life.

Telomeres and lung diseases were discussed by Mary Armanios (pp. S447–S451). Much progress has been achieved in the unraveling of molecular signals for cellular senescence, as indicated by the 2009 Nobel Prize in Medicine being awarded to those who discovered telomere function. It has been established that telomere attrition can lead to cellular senescence or apoptosis in accordance with the turnover capacity of the cell. Short telomeres have been found in a percentage of cases of IPF and COPD, and mouse models with telomerase deficiency in lung epithelial cells demonstrate the critical role of telomeres in

maintaining lung structure and protecting against lung injury.

Despite the limited number of studies, there is an increased interest in the lung microbiota and how it is modulated by age and disease. Pioneering work by Susan Lynch supports the importance of diversity of endogenous lung microbiota in disease resolution (pp. S462–S465). Studies in allergic diseases and asthma support the concept that microbial exposure in early life, and colonization of the respiratory and gastrointestinal tract by certain commensal microbes, influences the generation of immune responses and the vulnerability to allergic sensitization and viral lung respiratory infections. In addition, studies in older adults show that microbiota correlates with age and might link with clinical morbidities, supporting the concept that manipulation of the microbiome of elderly patients might be an innovative strategy against age-related diseases.

The environment plays a major role during aging and disease. Dean Jones presented a novel concept: The exposome is the measure of cumulative environmental influences and associated biological responses during the lifespan (pp. S452–S461). The integration of specific environmental exposures or behaviors with genomic, transcriptomic, epigenomic, and metabolomic alterations might allow the elucidation of signaling pathways that control adverse environmental exposures and improve prediction and therapeutics of diseases.

On personalized medicine and lung repair, Alvar Agusti challenged the traditional concept that COPD is a uniform chronic lung disease characterized by airflow limitation (pp. S466–S470). He proposed the need to understand that, on the contrary, COPD is a complex and heterogeneous disease that requires a personalized medicine approach for a better management. For instance, network analysis of lung transcriptomics shows that the molecular signature of emphysema and bronchiolitis in COPD is different, reflecting potentially diverse pathogenic mechanisms. ■

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