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Editorial

Making Airway Immunology Disease-Relevant

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Introduction

With aging population and increased life expectancy in many of the industrialized countries, burden of disease is inevitably on the rise. Respiratory tract infection is a leading cause of illness in the elderly [1], and primary source of infection in 47% of severe sepsis cases [2]. Sepsis is another major disease of the aged, where over 60% of sepsis incidence and 80% of death arise from patients over the age of 65 [3,4]. Interestingly, more than 50% of sepsis patients also develop acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) with higher disease severity compared to non-sepsis cases [5,6], implicating the lung as a central organ system associated with morbidity in the elderly. Therefore, better understanding of age-related changes in the lung immune defense is imperative to improve the quality of life in the elderly population.

In the U.S., the number of deaths from sepsis exceeds that from prostate cancer, breast cancer and AIDS combined, and treatment cost for sepsis mounts up to $17 billion a year [3,7]. However, despite extensive research and over 100 Phase II and III clinical trials [8], there has been a disturbingly limited success in improving patient survival. While efforts continue to develop targeted immunomodulatory therapies [9], past failures signal a necessity to examine sepsis beyond the overpowering immune response. A closer look at the preclinical research studies reveals several discrepancies between the sepsis experimental approaches and the most-affected population, such as the use of young animals equivalent to under 20 years of human age to model endotoxemia, inadequate optimization of animal models for respiratory microbial infection that more closely resemble the human condition, and inadequate attention to identifying effective diagnostic tools to enable earlier detection of infection in the elderly. A number of recent studies have already demonstrated an age-dependent increase in mortality during systemic inflammation [10,11], and age-specific factors involved are just starting to be uncovered [12]. Yet unlike in polymicrobial peritonitis, systemic endotoxemia, or acute pancreatitis models, age-dependent increase in mortality has not been consistently observed in bacterial pneumonia models [10]. While differences in bacterial and animal strains and the inoculation techniques may largely be responsible for this variability, it is likely that fundamental differences in the airway structure, cell composition, and the process of airway epithelial senescence between mouse and human [13] are also accountable. Thus greater understanding of age-related changes in the regulation of airway immune response is critical, to better replicate human disease in in vivo studies. It is now time to place more emphasis on studying the real-life context of airway diseases with enhanced integration of lung physiology and effects of its age-related structural changes on the airway immune function. With advancing age, the elastic recoil of the lung decreases and the chest wall becomes more rigid, with reduced inspiratory capacity [1,14]. In the bronchoalveolar lavage (BAL) of healthy older individuals, there is also an age-associated increase in neutrophils, IgA, IgM, and CD4+/CD8+lymphocyte ratio, and an overall decline in immune cell function due to immunosenescence [14]. Recent evidence suggests that premature airway epithelial cell senescence by genotoxic agents slows tissue regeneration and exacerbates airway inflammation upon injury [15]. Nonetheless, how epithelial senescence exactly alters the airway immune response remains to be determined, as mouse models of aging lung indicate that the aging alone is not a direct cause of

airway diseases such as emphysema or chronic obstructive pulmonary disease (COPD), but a predisposing factor by enhancing susceptibility to extrinsic insults [16]. Detailed analysis of immunological changes in the mouse models of senile lung such as senescence-accelerated mouse (SAM), Klotho mouse, and SMP30 knockout mouse [16] and applying them in systemic disease models may provide insights into the contribution of structural changes in the lung to specific alterations in the immune function, which have been looked at in only very rare cases [17]. Furthermore, much of focus so far has been on the specific immune cells such as alveolar macrophages, neutrophils, dendritic cells and lymphocytes and their secreted mediators that play a discernible role in airway inflammation. However, airway epithelial cells themselves are an indispensable part of the immune defense, both as a physical barrier and as a microbial recognition receptor and source of proinflammatory cytokines [18]. Removal of foreign materials by mucociliary escalator and oral clearance by salivary flow [1,19], for example, normally clear over 90% of gram-negative bacteria from the oropharynx [1], and impairment of these mechanisms due to age-associated reduction in ciliary beating [19] or damaged epithelial integrity comprises 32% of attributable risk of contracting community-acquired pneumonia [20]. Aging also increases the mucosal expression of microbial ligands that provide adhesion sites for pathogens and reduces their efficient clearance [21]. Therefore, there must be more attention to developing potential preventative measures for the maintenance of healthy physical barrier, and further investigation on the effect of airway senescence on the immune activation and immune cell function in addition to the studies on the immunosenescence process itself. Another area needing promoted interest is increased incorporation of immune parameters in pneumonia and sepsis diagnostics. Diagnosis of airway infection in the elderly is particularly difficult due to blunted or even absence of inflammation-specific symptoms such as fever, while non-specific clinical presentations such as altered mental state, delirium, weakness, anorexia, malaise, falls, and urinary incontinence are comon [22,23]. Thus in addition to heightened vigilance by healthcare workers, more objective and accurate indicators of disease progression are required for effective earlier detection, to allow sufficient time for intervention and maximize patient survival. Past geriatric studies have identified a "immune risk phenotype" as the inversion of the CD4/CD8 T-cell ratio, which was associated with higher mortality in the elderly with a successful prediction of 2 to 4 year decrease in survival [24] and an increased incidence of nosocomial pneumonia [25]. Building on from these findings and from our current understanding of aging in the pulmonary system, further identification of specific immunological changes that are indicative of early infection and which can be incorporated into the routine blood check and sputum tests may help to more rapidly and reliably diagnose illness in elderly.

This will require large-scale longitudinal follow-up studies of elderly populations to monitor changes in their immune cell composition and analytes in relation to their health outcomes, as well as more strategic approaches to compare values of known inflammatory mediators as potential biomarkers [26]. Many diseases are associated with the elderly given the intrinsic decline in body function, making older individuals more susceptible to infections, autoimmune diseases, and cancer. As the old saying goes, being forewarned is being forearmed and prevention is better than cure. It is time to fill the knowledge gap on the specific effects of age-related airway epithelial cell alterations on the overall effectiveness of airway immune response, and emphasize more on prevention and early detection of infection in the elderly. While science may not be able to completely reverse aging, it can certainly help to make it manageable, and possibly avoid getting bed-ridden in the ICU near the end of one's life.

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