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Lung Ageing, Inflammation and Telomere Attrition – The Trilogy in Chronic Obstructive Pulmonary Disease

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Abstract – COPD is ranked as the third common cause of death and considered as a global epidemic, with increasing prevalence as populaces live longer as a result of decreased mortality from cardiovascular and infectious diseases. Cigarette smoking is considered to be the significant hazard factor for COPD worldwide, however in developing countries vulnerability to indoor air pollution and biomass smoke is also common especially in rural areas. Various studies have demonstrated that incidence and prevalence of COPD increase with age in all populations. These associations suggest that normal aging could contribute to the pathogenesis of COPD. Telomeres are the structure of repetitive nucleotide sequence which encompass the regions at the ends of chromosomes and aid in chromosomal stability by protecting the DNA against recombination and degradation. Telomere shortening is a well-known phenomenon in aging and decreased telomere length in circulating leukocytes in COPD has been exhibited in a few investigations. Aging and COPD are related with critical dysregulation of the immune system that prompts a chronic inflammatory response. The comparative genetic determinants and molecular mechanisms shared by COPD and aging propose that immunosenescence may add to the advancement of COPD.

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COPD is considered as a global epidemic, with increasing prevalence as populaces live longer as a result of decreased mortality from cardiovascular and infectious diseases. In developed countries, COPD is ranked as the third common cause of death and fifth positioned reason for disability, yet is expanding to a substantial extent in developing countries (Lozano et al. 2012). COPD is present in around 10% of population more than 45 years of age and it is equally common in men as in women in developing countries, reflecting the predominance of smoking in the population (Barnes et al., 2015). Cigarette smoking is considered to be the significant hazard factor for COPD worldwide, however in developing countries vulnerability to indoor air pollution and biomass smoke is also common especially in rural areas (Sood et al., 2018). COPD is represented by irreversible and continuous airway obstruction because of the destruction of the lung parenchyma (emphysema) and obstruction of small airways (Hogg and Timens 2009). This outcomes physiologically in dynamic hyperinflation, air trapping and hyper-expanded lungs catching, hyper-expanded lungs and dynamic hyperinflation that prompts shortness of breath on rigorous effort or exertion, the significant manifestation of COPD patients. Over time this outcomes in rapid decrease in lung function and even though only 50% of the COPD patients show accelerated decline, rest of the patients have a normal decline starting from low peak lung volumes because of the poor lung development during adolescence (Lange et al., 2015).

The underlying mechanisms of COPD are poorly understood but it is associated with chronic inflammation that is largely corticosteroid-resistant (Barnes. 2016). This inflammation is similar to that found in normal smokers, but appears to be amplified. The mechanisms underlying COPD are poorly understood however it is related with chronic inflammation that is to a great extent corticosteroid-resistant (Barnes. 2016). This inflammation is like that found in ordinary/normal smokers, however it appears intensified. This mechanism of intensification involves a decrease in the nuclear enzyme histone deacetylase-2 (HDAC2), which assumes a significant role in turning off activated inflammatory genes (Barnes 2009). Various mediators and cells are involved in COPD and

increased oxidative stress either endogenously from activated lung inflammatory cells or from inhaled noxious particles/gases results in a decrease in HDAC2 (Kirkham and Barnes 2013).

As COPD is a disease that mostly affects elderly, with peak pervasiveness around 65 years, the worldwide increase in COPD is probably going to be associated with the aging population. Age related acceleration of decline in lung function in COPD is represented by gradually continuous airway obstruction, which suggested that COPD involves acceleration of the normal lung ageing process (Ito and Barnes 2009; Mercado et al. 2015). There is an expanding evidence that COPD exhibits all hallmarks of accelerated ageing, as compared to non-smokers and smokers with normal lung function. Age is the most significant hazard factor for various chronic illnesses, including COPD, and drives mortality and morbidity (Kennedy et al. 2014).

AGING AND CELLULAR SENESCENCE

Aging or senescence has been characterized as the continuous decrease in homoeostasis which happens after the reproductive period of life and prompts increasing danger of ailment or death. Biological aging, even though normally connected to chronological age, can happen earlier in life and is thought to result from an organ failure or failure of repair or cell maintenance, especially an inability to protect DNA against oxidative damage (*Kirkwood T.B., 2005*). Thus aging is a consequence of amassing of molecular damage. The subsequent cellular deformities can in turn increase inflammation and thus aggravate existing damage. Senescence or cellular aging, brings about a progression of adjustments in cell morphology and capacity, including the loss of proliferative action, so-called replicative/proliferative senescence. Various cellular and molecular mechanisms are related with cell senescence, including amassing of DNA damage (*von Zglinicki T., 2001*), epigenetic changes in DNA (*Fraga, M.F., 2007*), impedance of DNA repair (*Lou Z & Chen J., 2006*), protein damage and elevated production of free radicals (*Friguet B., 2006*), and telomere attrition (*Boukamp P., 2001*). Cell arrest and cell senescence not only take place after exhaustion of a predetermined proliferative capacity, but also can be induced by external stresses, such as oxidative stress.

TELOMERES

Telomeres are the structure of repetitive nucleotide sequence (TTAGGG) which encompass the regions at the ends of chromosomes (*Chan S.R and Blackburn E.H. 2004*), and aid in chromosomal stability by protecting the DNA against recombination and degradation (*d'Adda di Fagagna F et al. 1999*). In majority of somatic cells, telomeres abbreviates/shorten with each cell cycle because of the difficulty of DNA polymerase to prime DNA synthesis at the end of the chromosome. At the point when telomeres arrive at a critical length, cell senescence is instigated (*Aviv A. 2004*). Chronic inflammation and oxidative stress increases telomere shortening (*Saretzki G and von Zglinicki T. 2002*). Therefore, telomere length (TL) reflects the length at birth and continues to shorten thereafter. The telomere shortening is because of replication history, but can also be attributed to chronic inflammation and accumulation of oxidative stress acting on progenitor cells (*Aviv A. 2004*). At cellular level, telomere length (TL) provides a marker of biological age, shorter telomeres depicting increased biological age. TL in humans is often measured using PBL (peripheral blood leucocytes), and TL in blood leucocytes likewise concurs with that in different tissues (*Cawthon R.M. 2003*). PBL telomere length lessens with age, on average by 20–60 bp per year (*Valdes A.M et al. 2005*). Poor survival correlates with shorter telomeres in blood leucocytes (*Cawthon R.M. 2003; Brouilette S.W. 2007*). Interestingly, there is a dose-dependent relationship between years smoked and leucocyte telomere length (*Morla M. 2006*). Besides, endothelial cells and alveolar epithelial (*Tsuji T. 2006*) and fibroblasts (*Muller K.C et al. 2006*) in emphysematous patients' lungs display shorter telomeres contrasted with those from non-emphysematous subjects. Recent evidences also demonstrate that COPD patients have shorter telomeres in their circulating leucocytes compared with control subjects in any age range (*Savale L. 2009; Houben J.M. 2009*).

TELOMERE SHORTENING

Telomere shortening is a well-known phenomenon in aging and a significant inducer of cell senescence. Decreased telomere length in circulating leukocytes in COPD has been exhibited in a few investigations (Rutten EP et al. 2016; Savale L. 2009; Houben JM. 2009; Lee J. 2012), in spite of the fact that information about telomere shortening in structured cells is still scant. Shorter telomere length has been demonstrated in pulmonary artery smooth muscle cells and pulmonary vascular endothelial cells among COPD patients when compared to cells derived from smoking controls (Amsellem V et al. 2011; Noureddine H et al. 2011). TSUJI et al. (Tsuji T. 2006) utilized fluorescent in situ hybridisation to evaluate telomere length in alveolar type II and endothelial cells and exhibited diminished telomere length in COPD patients when contrasted with non-smoking controls, but not compared to smoking controls. A study from AHMAD et al. (Ahmad T. 2007) evaluated telomere length in lung tissue and revealed a relationship with levels of telomere protection protein 1 (TPP1). Both telomere length and TTP1 levels were diminished in lung homogenates from COPD patients contrasted with non-smoking controls, but not compared with

smoking controls. This was additionally supported by reduced TTP1 levels and telomere length in lung fibroblasts and CSE-treated airway epithelial cells (Ahmad T., 2007). These findings of TSUJI et al. (Tsuji T. 2006) and AHMAD et al. (Ahmad T., 2007) propose an association of telomere length with smoking as opposed to be COPD specific, albeit given that majority of COPD patients are ex-smokers, this may be a contributing factor to disease risk and development.

INFLAMMATION IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Inflammation is a perplexing sequence of events, involving numerous cell types (monocytes, macrophages, neutrophils, mast and dendritic cell), and their fundamental molecular products, for example, cytokines, chemokines, angiogenic factors, nuclear factor k B (NF-k B) and prostaglandins (*Provinciali M. 2010*). These components, which are created initially in the reaction to different stresses, are significant in being associated with both host protection and disorder. On one hand, there is expanding proof that for an immune reaction to be adequately established, an inflammatory reaction is required to aid the process along, and, specifically, for the enactment of the acquired immune response. On the other hand, there is likewise significant literature demonstrating that inflammation in abundance is harmful and that excess production and release of cytokine may lead to disorder. Even though inflammation is a vital reaction to clear the infections, fix tissue damage, and suppress initiation or progression of tumor growth, increased risk of developing diseases is also correlated with chronic inflammation. Development of inflammatory response is the common feature of COPD, described by the activation of macrophages and epithelial cells which in turn drives the activation and recruitment of monocytes, neutrophils, lymphocytes and eosinophils (*Barnes PJ. 2008*). The enactment of immune cells give rise to reactive oxidative species (ROS), which are embroiled in the pathogenesis of COPD. T lymphocytes, with a dominance of the CD8+ subtype, and macrophages are found in the parenchyma and in the walls of peripheral and central airways (Saetta M. 1998). The degree of airflow impediment in COPD correlated with the levels of CD8+ cytotoxic T lymphocytes, suggesting a significant role of CD8+ cell type in the pathophysiology of the COPD (*O'Shaughnessy TC. 1997*). A large number of systemic manifestations of COPD are an outcome of the inflammatory process and the unusual systemic inflammation in COPD were observed not only at the systemic level but also at the pulmonary level. Several mechanisms have been suggested so as to explain the systemic effects of inflammation: cigarette smoking, the systemic spread of inflammation mediators from the pulmonary compartment, the reaction induced by the bacterial product lipopolysaccharide during exacerbations, the inflammatory reaction to tissue hypoxia, bone marrow involvement and skeletal muscle dysfunction (*Wouters EF. 2005*).

Different cytokines have been appeared to play a role in the arrangement of inflammation in COPD through the activation, enrolment, and survival of inflammatory cells. Specifically, during intensifications, increased levels of various inflammatory markers such as TNF-alpha, interleukin 8 (IL-), and circulating activated macrophages, lymphocytes, neutrophils and eosinophils have been reported (*Decramer M. 2008*). These significant levels of inflammatory markers correspond with severity of exacerbation and increased oxidative stress (*Oudijk EJ. 2006*). The levels of inflammatory proteins appear to be increased in systemic circulation even through stable COPD. Muscle weakness, change in muscle metabolism and weight loss are some of the systemic manifestations induced by inflammatory mediators in COPD patients. Consequently, COPD has been viewed as a systemic disease. Various investigations have indicated that systemic inflammation distinguish aging and inflammatory markers are a noteworthy indicators of mortality in old people (*Kundu JK and Surh YJ. 2008*). Many age-associated diseases have been correlated with chronic inflammation. In fact, it is broadly acknowledged that a large number of the most significant age-related ailments for example cardiovascular diseases, Alzheimer's disease, atherosclerosis, diabetes, arthritis and sarcopenia share a common background. Increased levels of number of acute-phase proteins including TNF-alpha and IL-6 represent the age-related elevated concentrations of inflammatory mediators in the blood. Numerous investigations have concentrated on IL-6, proposing that aging independently of any specific illness is related with low-grade increments in the plasma levels of the inflammatory markers. Increased levels of IL-6 have been related with many age-related sicknesses, for example, diabetes, arthritis, cardiovascular illness and osteoporosis (*Ahmad A et al. 2009*). IL-6 elevated levels may then be an impression of an increased inflammatory state brought about by underlying illness even in the normal healthy older people. Apart from IL-6, the increased levels of TNF-a associate with functional status and diminished possibility of long-life endurance in the elderly. In addition, dysregulation and, specifically, overproduction of TNF-a has been implicated in various human illnesses including malaria, sepsis, autoimmune diseases like systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis as well as in cancer (*Franceschi C. 2007*).

CONCLUSION

There has been a recent focus of interest on the mechanisms of aging and cellular senescence and their role in the development of chronic diseases, including COPD. There has been an ongoing

interest on cellular senescence and mechanisms of aging and their role in the progression and development of chronic ailments including COPD. There are striking interfaces between indications of aging in smokers and COPD patients, especially those with emphysema. In patients with COPD, both circulating leucocytes and lung cells depict the markers of accelerated aging and cell senescence. Anti-aging molecules have moreover been demonstrated to be in the decreased levels in the lung of patients with COPD. Therefore there is impelling evidence that supports the fact that mechanism involved in pathogenesis of COPD are involved in accelerated aging too. There is in this way convincing proof that systems associated with quickened maturing forms are engaged with the pathogenesis of COPD. Thus focusing on these processes will lead to new therapeutic interventions for this condition.

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