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Review article

When GETomics meets aging and exercise in COPD☆

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ABSTRACT

The term GETomics has been recently proposed to illustrate that human health and disease are actually the final outcome of many dynamic, interacting and cumulative gene (G) – environment (E) interactions that occur through the lifetime (T) of the individual. According to this new paradigm, the final outcome of any GxE interactions depends on both the age of the individual at which such GxE interaction occurs as well as on the previous, cumulative history of previous GxE interactions through the induction of epigenetic changes and immune memory (both lasting overtime).

Following this conceptual approach, our understanding of the pathogenesis of chronic obstructive pulmonary disease (COPD) has changed dramatically. Traditionally believed to be a self-inflicted disease induced by tobacco smoking occurring in older men and characterized by an accelerated decline of lung function with age, now we understand that there are many other risk factors associated with COPD, that it occurs also in females and young individuals, that there are different lung function trajectories through life, and that COPD is not always characterized by accelerated lung function decline.

In this paper we discuss how a GETomics approach to COPD may open new perspectives to better understand its relationship with exercise limitation and the ageing process.

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a major public health problem [1] traditionally understood as a self-inflicted disease caused by tobacco smoking, occurring in old males and characterized by enhanced lung function decline over time [2], the latter being often interpreted as evidence of accelerated lung ageing in COPD [3]. Research over the past few years, though, has challenged this traditional understanding [4]. First, a substantial proportion of COPD patients around the world are never smokers [5], and many different environmental [6] and genetic risk factors for COPD [7] have now been uncovered. Second, it is now well established that there is a range of lung function trajectories through the life time, some of which lead to COPD in adulthood [8]. On the one hand, there are those characterized by accelerated lung function decline (the traditional understanding of COPD pathophysiology). On the other, however, now we know that those related to abnormal lung development early in life can cause reduced peak lung function in young adults and can lead to COPD later in life with a normal rate of lung function decline with age [4,8–11]. A direct consequence of this new pathogenic understanding of COPD [4] is that it is now accepted that there are COPD patients younger than 50 years of age (both males and females) [1,12], and that anticipating the diagnosis and treatment of the disease in these young patients can prevent disease progression and unhealthy ageing [13,14].

The term GETomics has been recently proposed to highlight the importance of the dynamic, complex and cumulative gene (G) – environment (E) interactions that occur during the lifetime (T) of an individual as a key pathogenic driver of COPD [10]. This approach proposes

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that the end clinical result of any G-E interaction (health or disease) depends on both the age of the individual at which that G-E interaction occurs (during phases of organ development or organ ageing), as well as the cumulative history of previous G-E interactions that the individual might have encountered before in her/his life [10]. Of note, this GETomics approach goes beyond COPD and can be applied to human health and disease at large [10]. In fact, aging is the main risk factor for major non-communicable chronic diseases [15] that accompany COPD almost invariably [16,17].

Ageing is characterized by a progressive impairment of tissue/organ/organism functions, resulting in increased vulnerability to environmental challenges and a growing risk of disease and death [18]. In a seminal paper published in 2013, Lopez-Otin et al. described nine hallmarks of aging [19]. Now, ten years later, as discussed below, these same authors extended these hallmarks to twelve and have also identified other hallmarks of health in what they describe as "an expanding universe" [20].

Exercise (or lack of) is a well-established environmental factor influencing human health and ageing [21]. Epidemiological studies have clearly shown that regular exercise improves human longevity [22,23]. Of note, however, the relationship between exercise and premature mortality follows a reverse J shaped curve, where premature mortality decreases in a dose-dependent fashion, until a threshold of physical activity is exceeded, and health benefits are attenuated [21]. Although extreme exercise can have detrimental health effects, regular moderate exercise can influence several of the hallmarks of aging mentioned above and contribute to maintain functional capacity, delay aging, and prevent or post-pone the onset of age-associated chronic diseases [21]. In fact, in patients with COPD regular exercise is encouraged and, in those with moderate-severe disease, participation in a formal rehabilitation program is strongly recommended [1].Whether regular exercise can stimulate lung regeneration in COPD is unclear but certainly an exciting possibility [24–26] that we address below.

In this perspective paper we discuss the relationship of exercise and ageing in patients with COPD from a GETomics perspective.

2. Hallmarks of aging and health: An expanding universe

Fig. 1 presents these twelve hallmarks of aging very recently described by Lopez-Otin et al. [20], stratified by different levels of organismal organization. From bottom to top, these include *molecular* (telomere attrition, genomic instability, epigenetic alterations, and loss of proteostasis), *organelle* (disabled autophagy, mitochondrial dysfunction), *cellular* (senescence), *supracellular* (stem cell exhaustion), *organ* (chronic inflammation), *organ systems* (deregulated nutrient-sensing), *systemic circuitries* (altered intercellular communication) and *meta-organism* (dysbiosis [27]) hallmarks, which are functionally related among each other and also interconnected to eight hallmarks of health (Fig. 1), including *spatial compartmentalization* (integrity of barriers and containment of local perturbations), *maintenance of homeostasis* over time (recycling and turnover, integration of circuitries, and rhythmic oscillations), and an array of *responses to stress* (homeostatic resilience, hormesis (i.e., a biphasic dose response to an environmental agent characterized by a beneficial effect at low dose and a detrimental effect at high dose [28]), and repair and regeneration) thus creating a multidimensional space of interactions that contribute to better understand the aging process [20].

3. Exercise: a polypill to target ageing

Exercise can be considered a polypill because it confers pleiotropic benefits in multiple organ systems [29,30]. As an example, a single session of aerobic exercise changes the expression of about 10.000 molecular analytes in the systemic circulation, including transcripts, proteins, metabolites, and lipids [21,31], many of which can in turn influence several of the hallmarks of ageing described above.

Telomere attrition. Telomere attrition during somatic cell division relates to chronological aging [32]. Importantly (see below) telomere shortening induces cell senescence [19]. In experimental animals and in young healthy individuals, exercise upregulates endogenous telomere repair mechanisms, but no studies have yet demonstrated this in older humans [33].

Genomic instability. Genomic instability of both the nuclear and mitochondrial DNA is a key hallmark of aging since DNA damage may lead to apoptosis or cell senescence of stem-cells that compromise tissue homeostasis and renewal [20]. There is some evidence that exercise can reduce genomic instability in older people [34].

Epigenetic drift. The term "epigenetic drift" refers to the observation that epigenetic differences in monozygotic twins increase with age [31]. The accumulation of epigenetic modifications during the lifespan is a key component of the GETomic approach to health and disease [10]. To date, however, the evidence that lifetime exercise results in differential DNA methylation status is weak [35]or negative [36,37].

Loss of proteostasis. The term proteostasis refers to the regulation of *de novo* protein synthesis, folding, assembly, as well as its export, breakdown, and degradation [20]. A disruption in proteostasis is intimately linked to aging and age-related diseases [21]. Exercise activates several mechanisms involved in proteostasis, including the mitochondrial unfolded protein response (UPRmt), the unfolded protein response in the endoplasmic reticulum (UPRer) and the heat shock response (HSR) [38,39].

Mitochondrial dysfunction. The control of mitochondrial quality

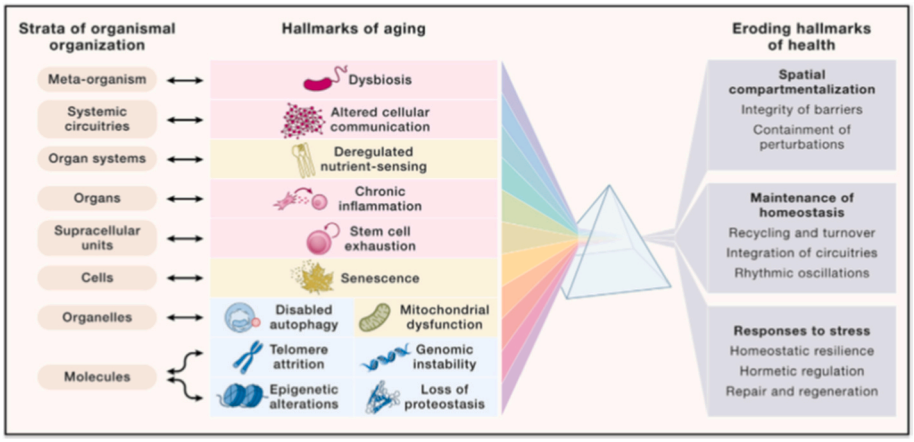

Fig. 1. The 12 hallmarks of aging are interconnected to the 8 hallmarks of health, creating a multidimensional space that may contribute to explain the aging process. For further information, see text. Reproduced with permission from Ref. [20].

and quantity (*mitostasis*) is tightly regulated in mammalian cells [21]. *Mitochondrial biogenesis* and mitochondrial adaptations (*mitohormesis*) require the crosstalk between the master transcriptional factor, PGC-1α, and the redox-sensitive transcription factor, NRF-2 [40]. Aerobic exercise upregulates PGC-1α phosphorylation and activation in skeletal muscle thus stimulating mitochondrial biogenesis [21]. On the other hand, age-related increases in ROS production, and poor scavenging of ROS due to diminished antioxidative capacity can result in mitochondrial damage with age. Damaged mitochondria can fuse with healthy counterparts to alleviate stress and continue to supply the ATP needed by the cell or, if irreparable, be degraded through the autophagosome-lysosomal pathway (*mitophagy*) [41]. The effects of exercise on mitophagy are less well-understood [42].

Sarcopenia is characterized by reductions in muscle mass and strength and frequently occurs in older individuals [43] and COPD patients, particularly those with emphysema [44]. Mitochondria dysfunction seems to be a key pathogenic process in sarcopenia and exercise can attenuate sarcopenia through still unclear mechanisms that regulate mitochondrial function including mitochondrial biogenesis, fusion, fission and mitophagy [43].

Stem cell exhaustion. Stem cell exhaustion is a well-recognized hallmark of aging (Fig. 1). Exercise can potentially mobilize hematopoietic stem cells (HSCs) and other progenitor cells (e.g., endothelial progenitor cells —EPCs) and, as discussed in more detail below, potentiate tissue repair and remodeling [45].

Cellular senescence. Cellular senescence is a cellular state characterized by irreversible growth arrest and secretion of the so-called senescence associated secretory phenotype (SASP) [46]. Cellular senescence plays a role in organ development and ageing [46]. Senescent cells can arise throughout the lifespan (not only in the elderly) and, if persistent, can have deleterious effects on tissue function due to SASP [47]. Unhealthy lifestyles, such as physical inactivity, unhealthy diet, and cigarette smoking, are associated with the accumulation of senescent cells in human tissues, independent of chronological age [48]. By contrast, a systematic review of published literature indicates that exercise can have senolytic effects in healthy humans [49].

Immunosenescence and inflammaging. The term *immunosenescence* describes the deterioration of the immune system with age [15,50]. It is often accompanied by low-grade, persistent, systemic inflammation (*inflammaging*) [51]. The latter contributes to sarcopenia of the elderly through the ubiquitin proteosome pathway and the mammalian target of rapamycin (mTOR)-Akt signaling pathway, which controls protein synthesis and stress response pathways [52]. Conversely, circulating concentrations of anti-inflammatory cytokines, such as IL-10, decrease with age [53]. Chronic low- and moderate-intensity physical exercise reduces inflammaging and enhance immune function through the involvement of toll-like receptors (TLR)s, particularly TLR2 and TLR4, which modulate phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mTOR signaling causing the release of anti-inflammatory cytokines, including IL-10 [54]. Immunosenescence and inflammageing are reduced in elderly adults who cycle regularly [55].

Metabolic dysregulation. Metabolic dysregulation (e.g., hyperglycemia and insulin resistance) increase with age, likely in relation to defective mitochondria [56]. Deregulated nutrient sensing in ageing involves altered growth signaling via the evolutionary conserved IGF-1/AKT/mTOR axis [21]. Exercise mitigates metabolic dysregulation, with aerobic and resistance exercise targeting specific but also overlapping molecular pathways [21].

Dysregulated stress response. The stress response is an evolutionarily conserved, adaptive mechanism that mobilizes a variety of cellular processes to counteract different stressors and promote cell survival [21]. The stress response declines with age and augmenting stress adaptation correlates with lifespan extension across species [19]. Importantly, while mild stressors increase resilience, strong acute (or mild chronic) stressors exhaust or alter an efficient stress response (hormesis). Exercise-induced oxidative stress fits the hormesis paradigm since regular moderate-intensity exercise training upregulates cellular concentrations of antioxidants enzymes and their activity, which mitigates exercise-induced oxidative stress, whereas prolonged intense exercise can increase oxidative stress that damage skeletal muscle fibers as well as their cellular components [21]. The efficacy of long-term treatment with antioxidants is unclear [21].

4. Hallmarks of ageing in COPD

There is evidence that some hallmarks of ageing are abnormal in (some) patients with COPD [57]. Further, many of the features of aging in the lungs closely resemble those seen in the lungs of COPD patients, but at a relatively younger age, supporting a role for accelerated aging in the pathogenesis of COPD [58]. These changes are discussed in more detail below.

Telomere attrition. In patients with COPD, telomere length is reduced in alveolar, endothelial, and smooth muscle cells, as well as in circulating lymphocytes, and relates to disease severity, smoking status and lung function decline [57,59,60]. Telomere shortening is seen both in old and young (<50yr.) patients with severe COPD [61]. Whether these changes are cause or consequence of COPD is unclear [57].

Genomic instability. There is little evidence that genomic instability is an important pathogenic driver of COPD [57] although some papers have shown that COPD patients have increased DNA-double strand breaks in lung and blood cells and that this increases their risk of lung cancer [62].

Epigenetic alterations. Epigenetic alterations, including DNA methylation, histone modification and noncoding RNAs, have been described in COPD [10,63]. Epigenetic changes induced by smoking lead to hyperplasia of basal and goblet cells, squamous metaplasia, loss of club and ciliated cells, decrease in the periciliary layer, ciliary damage, junctional barrier loss and reduces pIgR expression which, in turn, leads to a deficiency in localized secretory IgA, bacterial colonization and chronic airway inflammation [64].

Loss of proteostasis. In COPD patients due to α1-antitrypsin deficiency there is loss of protein quantity and function, and misfolded proteins also accumulate in the endoplasmic reticulum, triggering an unfolded protein response (UPR) and promoting lung inflammation and damage [57]. In smoking-related COPD there is also loss of proteostasis because oxidated cellular proteins from cigarette smoke suffer accelerated degradation by the proteasome or autophagy pathways [57].

Mitochondrial dysfunction. Cigarette smoke alters mitochondrial structure and function [57] and can induce mitochondrial fragmentation in bronchial epithelial cells in patients with COPD [65], which then lead to enhanced ROS production and induces cellular senescence. Likewise, mitochondria induced skeletal muscle apoptosis has been shown in patients with COPD and low body mass index and is associated with lower exercise tolerance despite similar degree of lung function impairment [66].

Stem cell exhaustion. Lung basal epithelial cells and endothelial progenitor cells have reduced regenerative capacity in COPD [57]. It has been shown that bone marrow derived MSCs express decreased levels of cytokine and chemokine receptors affecting their capacity of activation and mobilization to the site of injury [67]. Some studies have also reported decreased circulating hematopoietic progenitors in COPD patients [68]. Finally, a study on bone marrow tissue showed that impaired repair capacity in COPD patients, particularly in those with more emphysema and/or higher circulating eosinophils [69].

Cellular senescence. There is evidence of at least two mechanisms by which cell senescence, can contribute to COPD: loss of cell proliferation impairs renewal of epithelial and endothelial cells resulting in loss of cells in the alveolar walls and, consequently, in emphysema; and the release of increased amounts of inflammatory cytokines by senescent cells, resulting in enhanced inflammation [15].

Deregulated nutrient sensing. The IGF-1/AKT/mTOR axis

(involved in nutrient sensing) can contribute to the pathogenesis of emphysema since lung overexpression of the mTOR suppressor Rtp801 promotes lung inflammation and apoptosis of alveolar epithelial cells, suppresses autophagy and counteracts activation of forkhead box "O" (FOXO) transcription factors, which are central regulators of metabolism, stress resistance, cell cycle progression and programmed cell death [70,71].

Altered intercellular communication. Altered intercellular communication (e.g. changes in the innate as well as adaptive immune responses) is well-established in COPD [72].

Extracellular matrix (ECM) dysregulation. Dysregulated protease/anti-protease balance contributes to the loss of alveolar *septae* and emphysema formation [73,74]. Dysregulated matrix metalloproteases (MMP) also contribute to COPD [73,74].

Dysregulated autophagy. Animal models with partial autophagy deficiency have shown reduced emphysema [75], and an enhance resistance to mucociliary disruption [76] suggesting that the degradation of bronchial cilia due to autophagy (*ciliophagy*) may contribute to COPD. Besides, stimulation of autophagy increases neutrophil death resulting in release of harmful amount of elastase in the lung [77].

Age-dependent chronic inflammation (Inflammaging). It results from a variety of stimuli that induces aberrant activation of the innate immune system with age [78]. These stimuli include oxidative stress, abnormal senescent immune cells, accumulation of DAMPs from senescent cells and decreased autophagy, all of them present in the lungs of smokers, thus with the potential to lead to COPD [79,80].

Dysbiosis. Repeated insults such as respiratory infections, cigarette smoke, and particulate matter exposure alter the lung microbiome composition [81]. Airway bacterial infections during early childhood alters lung growth [82–84]. Dysbiosis can cause chronic airway inflammation [85] and contribute to lung damage and impaired lung function [86].

5. Exercise and lung regeneration in COPD

Contrary to what is generally believed, *de novo* lung tissue formation can occur in the adult lung, both in experimental animals (e.g., after refeeding following alveolar septal apoptosis induced by prolonged calorie restriction) [87] and in humans (e.g., after surgical lung volume reduction) [88]. In fact, the adult lung contains numerous progenitor/stem cell populations, including basal cells, bronchioalveolar stem cells (BASCs), distal airway stem cells (DASCs), and type II pneumocytes, although it is also generally thought that, in patients with COPD, these cells are "exhausted" [25]. Yet, when removed from their extracellular milieu, they are capable of *de novo* lung tissue formation, indicating that they remain viable but likely in a state of hibernation in clinical COPD [89,90]. The latter, in turn, appears related to cellular senescence of many components of the pulmonary mesenchyme, including fibroblasts, pericytes, and endothelial cell lineages, which are needed for ECM deposition and organization, angiogenesis, and ultimately *de novo* lung tissue formation, due to the chronic inflammatory *milieu* in the airways and pulmonary parenchyma that characterizes COPD, as well to the loss of mechanical strain on these cells caused by ECM remodeling, since the mesenchyme is remarkably mechanosensitive [25]. Recent studies have identified mesenchymal senescence in lung tissue of COPD patients and suggest that maladaptive angiogenesis is an early critical event in the development and progression of the disease [91,92]. This maladaptive angiogenesis would then result in a progressive reduction in microvascular density, followed by progressive alveolar destruction and the development of emphysema [91].

Regular exercise can theoretically influence several of these mechanisms and, by doing so, contribute to lung regeneration in COPD, including an anti-inflammatory effects of exercise on low grade systemic inflammation [26,93], the lung mechanical strain during exercise, and exercise-induced hypoxemia, which can potentially improve mesenchymal senescence [25]. Available evidence of the potential pro-regenerative effects of exercise in COPD is lacking but potential future studies in humans need to consider the duration and nature of the training intervention, since alveologenesis is a slow process in humans that probably occurs over the course of months to years [25]. Such studies may facilitate the development of treatments that specifically target the structural and functional regeneration of the pulmonary vasculature [25].

6. Putting it all together: GETomics, aging, exercise and COPD

GETomics proposes that health and disease are the end-result of many dynamic, complex and cumulative gene-environment interactions occurring since conception to death [10]. A clinically relevant consequence of this GETomic approach in respiratory medicine is the realization that, in the general population, there is a range lung function trajectories through the lifetime (i.e., a trajectome) characterized by different developmental and aging phases (Fig. 3) [4,8]. Both phases allow for some individual plasticity, catch-up and/or growth failure during lung development [94] and different rates of lung function decline at older ages [9], in general trajectories below the normal range are associated with a higher prevalence and earlier incidence of multi-morbidity and premature death [95], whereas those above the normal range are associated with healthier ageing, fewer cardiovascular and respiratory events, as well as with a survival benefit [96,97].

Aging is inevitable. However, different people age differently (better or worse). This indicates that there are genetic, epigenetic and environmental factors that, as reviewed above, contribute to healthy or unhealthy ageing. From a GETomics perspective, it is of note that there are pleiotropic genes with opposite effects at different ages; while being beneficial at early stages, these genes are detrimental at a later age [57]. They include p53 and mammalian target of rapamycin (mTOR) pathway and some key developmental signaling pathways, such as Wnt signaling [57]. Interestingly, aberrant activity of the latter pathways has been demonstrated in COPD patients, particularly in those with emphysema [98].

Regular exercise has pleiotropic effects in many hallmarks of aging and health [29,30] (Figs. 1 and 2). As reviewed above, this may occur not only in healthy subjects but also in COPD patients. Interestingly, in keeping with the GETomics paradigm [10], evidence is stronger in younger individuals. It makes entire sense that to prevent aging you have to be young! Besides, it has been suggested (albeit not yet proven) that maladaptive angiogenesis is an early (the time axis again!) critical event in the development and progression of COPD [91,92] and that regular exercise may have pro-regenerative effects in the lungs of these patients [25]. Importantly, in real life practice COPD does not exist in isolation since it is almost invariable accompanied by multimorbidity [99]. Ageing is also a key factor in the development of multimorbidity and, while waiting for the appropriate evidence, in the context of

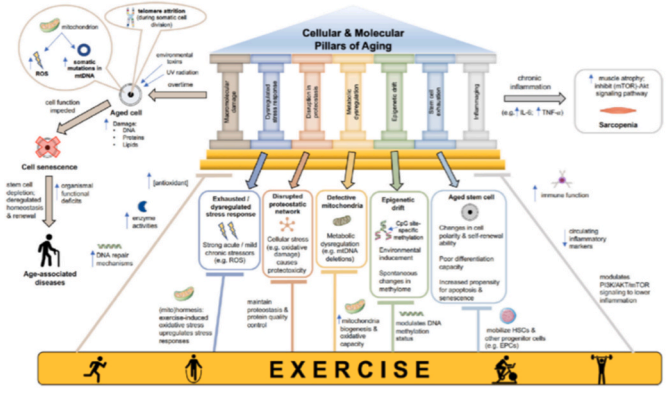

Fig. 2. Potential effects of exercise in seven pillars of aging. For further information, see text. Reproduced with permission from Ref. [21].

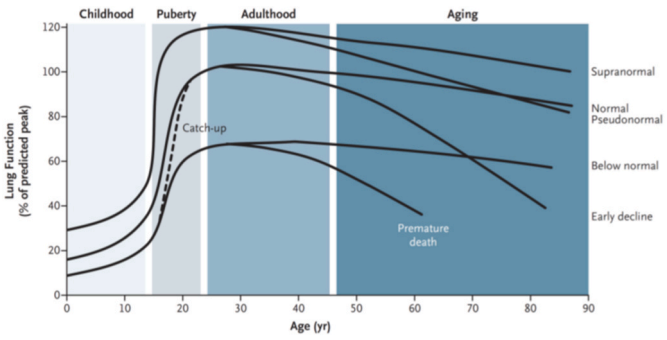

Fig. 3. Different lung function trajectories through life (i.e., the trajectome). For further information, see text. Reproduced with permission from Ref. [4].

GETomics, exercise can very well have pleiotropic effects not only on COPD but also on the frequently accompanying multimorbid diseases, thus contributing to improve the health status and prognosis of these patients [16,100,101].

The recently released 2023 report by the Global Initiative for Chronic Obstructive Lung Disease (www.goldcopd.org) acknowledges that COPD is a complex disease that can have roots early in life and can occur in young individuals, thus opening new windows of opportunity for the prevention and early diagnosis and treatment of the disease. From the above discussion, regular exercise may be an excellent therapeutic recommendation not only to rehabilitate patients with advanced disease (as prescribed currently) but to prevent disease progression in younger ones (in coupling with avoidance of major risk factors (such as tobacco smoking) and appropriate pharmacological treatment if needed).

Declaration of competing interest

There is no conflict of interest.

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