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Is intrinsic aerobic exercise capacity a determinant of COPD susceptibility?

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ABSTRACT

Chronic obstructive pulmonary disease is a leading cause of morbidity and mortality, which is most commonly associated with smoking or exposure to environmental pollutants. Unfortunately, there is an inadequate understanding of the molecular and physiological determinants governing one's susceptibility for developing COPD. Here, we describe a novel hypothesis: *Individuals with intrinsically low aerobic exercise capacity are more likely to develop COPD after exposure to key risk factors*. The hypothesis is based on observations that aerobic exercise capacity is tightly associated with mortality across many complex diseases. The premise is supported by recent studies demonstrating that smokers who exercise regularly are less likely to develop or be hospitalized for COPD. Herein, we describe the evolutionary and molecular basis for this hypothesis and how it is a natural extension of previous theories explaining COPD susceptibility.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a syndrome characterized by airflow limitation that is progressive and largely irreversible. In the vast majority of patients, the airflow obstruction is due to structural changes to the distal airways, resulting from smoking heavily for many years. In the smaller airways, the injury leads to airway wall inflammation, subepithelial fibrosis, and inflammatory mucus exudates (aspirated down from the central airways) occluding the lumen of the bronchioles [1]. Further, destruction of the alveoli (i.e. emphysema) also leads to an increased incidence of dynamic small airways collapse because the alveolar walls provide structural support to the airways to maintain small airway patency. How smoking induces these changes is not entirely clear. Dogma suggests that the free radicals in the smoke and those generated by inflammatory cells injure the lung tissue and cause these pathologies; however, direct clinical evidence to substantiate these theories are still lacking.

As with other complex diseases, it is important to note that not all individuals exposed to risk factors associated with COPD (i.e. cigarette smoke) develop the disease. In fact, only about 25% of the smoking population are said to be susceptible [2]. The mechanisms underlying COPD susceptibility have been poorly defined and non-specific, generally attributed to a gene-by-environment interaction. Unfortunately, little clarity has been born out of the genome-wide association studies that have now been completed in several COPD patient cohorts [3]. Many of the single nucleotide polymorphisms (SNPs) that have been identified in these studies occur in genes associated with inflammation or the response to free radical stress; nevertheless, these associative studies have not, as yet, made any impact on treatment paradigms for these patients.

Studies approaching the problem from the preclinical side have fared no better. For over 20 years, several groups have now used animal models of smoking-induced lung injury to assess the efficacy of candidate mechanisms. To date, no therapy that has shown efficacy in these models has yet made a ***substantial*** impact on the therapeutic options available to patients. The failure to identify new treatments may be due, in part, to the departure from using classical, integrative physiological approaches to interrogate disease mechanisms. Instead, the primary tactic for investigating disease mechanisms has been to grossly overexpress or completely delete the expression of specific molecular targets to implicate these

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single entities as causative factors instigating the onset of complex, heterogeneous diseases. While these techniques are valuable tools, we and others have argued that complex diseases are not likely to stem from the interaction between a mutation in a single gene and an environmental trigger; rather these diseases are the result of the combined expression of allelic variants in several genes whose functions are sensitive to a given environment [4–6]. As such, new paradigms are now warranted to identify therapies to impact diseases, such as COPD. Replacing the practice of molecular modification of single genes with approaches that concentrate on defining and modeling physiological traits that are commonly observed in disease-susceptible populations are required to determine whether these polygenic traits play a causative role in disease pathogenesis.

2. Exercise capacity, metabolism, and COPD—are they linked?

Aerobic exercise capacity is a complex trait that has been shown to be the most powerful predictor of mortality across several disease indications [7]. Whether the reduced exercise capacity is a cause or consequence of these conditions is still an open question; however, more recently several lines of evidence indicate that reduced aerobic fitness is a key risk factor associated with several diseases [8–11].

Consistent with these observations, physical activity has been shown to play a protective role in the pathogenesis of COPD. Analyzing data from the Copenhagen City Heart Study, Garcia-Aymerich and colleagues have shown that the risk of being admitted to hospital and mortality are reduced in COPD patients that exhibit some degree of physical activity [12]. Further, moderate to high levels of regular physical activity can reduce the risk of developing COPD amongst active smokers (odds ratio = 0.77; $p = 0.027$) [13]. In fact, the data indicated that physical activity improved lung functioning in a dose-dependent fashion, improving FVC by 2.6 and 4.8 ml/year in the moderate and high level activity groups, respectively, relative to low activity group (p-for-trend < 0.0001) [13]. Most preclinical studies have also demonstrated that exercise training provides protection against lung injury induced by cigarette smoke exposure in different mouse strains (Table 1). Exercise training has been shown to attenuate smoking-induced airway inflammation, oxidative damage, matrix remodeling, lung pathologies, and changes to airway mechanics.

While these data indicate that an interaction between exercise capacity and smoking can influence susceptibility to developing COPD, it is unclear as to why. It has been proposed by many that exercise can reduce inflammation and oxidative stress. Timmerman and colleagues have recently shown that exercise attenuates the activation of leukocytes and specifically the so-called pro-inflammatory (CD14+CD16+) monocyte that is associated with a number of chronic diseases [19,20]. Further, regular exercise elevates the expression of antioxidant molecules and enzymes [21,22]. Several molecular pathways that are activated by exercise have been shown to control the transcription of inflammatory and antioxidant genes [14,17,23].

Exercise also regulates pathways involved in oxygen metabolism that are central to maintaining cellular homoeostasis. While exercise increases the expression and activity of these pathways, smoke can disrupt these processes. Using gene set enrichment analysis we have previously shown that the expression of metabolic gene sets are significantly affected by smoke exposure in rats [24]. Similarly, Pierrou and colleagues reported that the most significant expression differences in airway epithelium between asymptomatic smokers and COPD patients were gene sets involved in oxygen metabolism and detoxification, which suggest these pathways may play a role in disease pathogenesis [25]. Not only can smoke affect the expression of metabolic pathways, it can also directly disturb the metabolic machinery within cells. For example, cigarette smoke contains an abundance of ultrafine particles, which

Table 1
The effect of exercise training in preclinical models for COPD-related inflammation and pathologies.

	Stimuli	Method to increase aerobic capacity	Model	Outcome	Ref
Models of COPD-associated disease	Cigarette smoke (CS)	Moderate intensity exercise on a treadmill for 60 min, 5 days/week for 24 weeks	Male C57BL/6 mice	Exercise reduced the effect of CS on: • Pulmonary elastance and mean linear intercept • BAL ROS & lung tissue 8-isoprostane expression No effect of exercise on CS-induced: • Alveolar wall remodeling (increase in % collagen fibers) • Increase in BAL macrophages	14
	Diesel exhaust particles (DEP)	Moderate intensity exercise on a treadmill for 60 min, 5 days/week for 5 weeks	Male BALB/c mice	Exercise reduced the effect of DEP on: • Exhaled NO • ROS • Pro-inflammatory cytokines levels in BALF, serum, and expression in parenchyma; BALF neutrophils and lymphocytes • Parenchymal neutrophils and collagen density	15
	LPS	Low intensity swimming for 60 min, 5 days/week for 6 weeks	Male BALB/c mice	Exercise reduced the effect of LPS on: • Exhaled NO • BALF and parenchymal neutrophils No effect of exercise on LPS-induced: • Remodeling (volume proportion of elastic fibers) • Impaired lung mechanics (lung tissue resistance)	16
	Cigarette smoke	Swimming for 30 min, 2 times/day, 5 days/week for 8 weeks.	Male C57BL/6 mice	Exercise reduced the effect of CS on: • Alveolar enlargement and septa destruction, • Macrophage and neutrophil infiltrate • Remodeling (volume density of elastic fibers) • Oxidative stress parameters (anion superoxide production) No effect of exercise on CS-induced: • Collagen content (hydroxyproline) • Oxidative damage by lipid peroxidation	17
	Papain	Exercise on a treadmill for 10–35 min, 6 days/week for 9 weeks.	Male Wistar rats	Exercise increased papain-induced airspace enlargement	18

BAL: bronchoalveolar lavage; LPS: lipopolysaccharide; ROS: reactive oxygen species.