An Evolutionary Medicine Approach to Understanding Factors That Contribute to Chronic Obstructive Pulmonary Disease

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Key Words

Biological evolution · Chronic obstructive pulmonary disease · Disease susceptibility · Evolutionary medicine · Reproduction

Abstract

Although many studies have been published on the causes and mechanisms of chronic obstructive pulmonary disease (COPD), the reason for the existence of COPD and the reasons why COPD develops in humans have hardly been studied. Evolutionary medical approaches are required to explain not only the proximate factors, such as the causes and mechanisms of a disease, but the ultimate (evolutionary) factors as well, such as why the disease is present and why the disease develops in humans. According to the concepts of evolutionary medicine, disease susceptibility is acquired as a result of natural selection during the evolutionary process of traits linked to the genes involved in disease susceptibility. In this paper, we discuss the following six reasons why COPD develops in humans based on current evolutionary medical theories: (1) evolutionary constraints; (2) mismatch between environmental changes and evolution; (3) co-evolution with pathogenic microorganisms; (4) life history trade-off; (5) defenses and their costs, and (6) reproductive success at the expense of health. Our perspective pursues evolution-

ary answers to the fundamental question, 'Why are humans susceptible to this common disease, COPD, despite their long evolutionary history?' We believe that the perspectives offered by evolutionary medicine are essential for researchers to better understand the significance of their work.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a common disease that causes 2.9 million deaths annually worldwide, and it is ranked as the third leading cause of death of humans [1]. In COPD, inhalation of cigarette smoke and air pollutants induces chronic inflammation of the lungs, and excessive oxidants and proteases cause the destruction of the alveoli (pulmonary emphysema) and fibrosis of the peripheral airways, leading to airflow obstruction (Global Initiative for Chronic Obstructive Lung Disease) [2]. While cigarette smoking is the most common risk factor for COPD, biomass smoke, occupational exposures and genetic risk factors, such as α_1 -antitrypsin deficiency, are also important [2]. While a number of studies have been conducted on the pathogenesis of COPD, examining factors such as cigarette smoking, biomass smoke exposure, genetic factors and inflam-

Fig. 1. Comparison between the avian uni-directional respiratory system (a) and the human bidirectional respiratory system (b). Reproduced with permission from West et al. [18].

mation, the reasons why COPD exists and the reason why it develops in humans have hardly been studied. Even though humans are supposed to have obtained a delicate structure and excellent function of the lung throughout the course of a long evolutionary process, many modern human beings develop COPD. Why does the common disease, COPD, develop in humans despite their evolution over a long course in history? According to a recent report, the heritability of COPD is as high as 37% [3]; why have humans acquired this genetic predisposition?

There are proximate and ultimate factors in the etiology of disease. Approaches based on experiments and investigations are required to elucidate underlying proximate mechanisms that lead to the development of a disease. On the other hand, evolutionary (Darwinian) medical approaches are required to explain the ultimate, or evolutionary, causes such as why a disease is present and why a disease develops in humans [4–16]. Evolution is not a goal-oriented phenomenon. According to the concepts of evolutionary medicine, diseases are present because of natural selection during the evolutionary process of traits that lead to genetic susceptibility to these diseases. For example, various alleles responsible for genetic predispositions to diseases may have become fixed in populations by the process of natural selection, while being transmitted through generations. Recently, Nesse et al. [5–9], pioneers of evolutionary medicine, have proposed that there are six evolutionary reasons for the acquisition of disease susceptibility traits: (1) evolutionary constraints; (2) mismatch

between environmental changes and evolution; (3) co-evolution with pathogenic microorganisms; (4) life history trade-off; (5) defenses and their costs, and (6) reproductive success at the expense of health. In this paper, we have focused on smoking-induced COPD, because cigarette smoking is the best studied risk factor for COPD. We attempt to explain why humans are susceptible to COPD from the standpoint of evolutionary medicine.

Evolutionary Constraints on Selection

There is a constraint on the evolution of organisms in that the inadequacies of organogenesis cannot be corrected by going back to earlier stages of phylogeny. For example, the eyeballs of vertebrates have the disadvantage that the sites of entry of the blood vessels and nerves into the retina are blind spots and are susceptible to retinal detachment; however, organogenesis is path dependent, which means the eyeball cannot evolve into a form that does not contain any blind spots by going back through the evolutionary path to cephalopods [10].

A structural inadequacy of the human respiratory system is that it is bidirectional, in that the lung has both gas exchange and ventilatory functions; therefore, both inspired and expired air pass through the same space (fig. 1). As a result, particulate matter from cigarette smoke tends to become deposited in the bronchioles and alveoli, where airflow velocity is reduced [17, 18]. On the other hand,

Fig. 2. Biological state index (Ibs) values over the past 15,000 years of human evolution (adapted from Ruhli and Henneberg [27]). The index value is a probability that an average person will be able to fully participate in reproduction of the next generation. The lower index values, the greater the opportunity for natural selection. d_x = A fraction of dying people of age x ; S_x = reproductive value of a person of age x (for example, $S_{65} = 0$, while $S_{15} = 1$). This figure illustrates that in the Stone Age there was a very significant opportunity for the process of natural selection because of high levels of differential mortality that allowed less than half of the individuals born to pass on their genes to the next generation, eliminating the other half [27].

the avian lung has a unidirectional respiratory system in which the air leaving the air sacs (ventilation area) flows continuously in a unidirectional manner through the parabronchi (ventilation area). Therefore, the airflow velocity is not reduced and particulates are not easily deposited [17, 18]. Furthermore, human alveoli have the disadvantage that they, unlike the avian parabronchi, repeatedly expand and contract, which makes them vulnerable to mechanical injury and ventilation-perfusion ratio inequality [18]. However, humans cannot correct these structural inadequacies by going back on the phylogenetic tree to the stage of birds in order to acquire a unidirectional respiratory system.

One of the biochemical inadequacies of the human lung is that elastin fibers do not regenerate; therefore, the elasticity of the emphysematous lung cannot be restored [19–21]. While the durability of human lung elastin is as long as the lifetime of individuals [22], elastin fibers in the adult lung cannot regenerate, because of the reduced ability of the lung to produce tropoelastin or to coacervate/cross-link [19, 20, 23]. The assumed evolutionary reason behind this is that the selection pressure to acquire regeneration competence is weak, because of the long durability of the elastin fibers. Alternatively, it could be assumed that elastin has acquired long durability in its evolution to avoid the enormous costs of regeneration of the complex fiber structure. Similarly, the eye lens crystalline, another long-life protein, has been reported to have long durability, but limited capacity for regeneration, resulting in increased susceptibility of the elderly to developing cataracts [24, 25].

Another constraint on selection is that the genes responsible for diseases in the elderly are less susceptible to

natural selection. This has been explained as being due to the small number of elderly individuals in earlier times, and the fact that even if the carriers of the genes responsible for diseases in the elderly survived to old age, they would have already left offspring (i.e. the genes would have been transmitted to their offspring before the diseases had a chance to manifest) [26] (see the Life History Trade-Off section below). The force of selection is stronger during the reproductive period than in the postreproductive period. If COPD was a disease of the young, it might not exist today. This can be explained as follows. It has been argued that exposure to biomass smoke is a risk factor for COPD, particularly in young individuals and women [2]. If the young individuals in the Stone Age had inhaled biomass smoke from fires and developed COPD in their early life, genetic predispositions to COPD would have been under strong negative selection pressure (fig. 2) [27]. Exertional dyspnea would have caused a decrease in physical activity, reducing the ability to survive circumstances, such as hunting and wars, thereby reducing the chances of reproduction.

Thus, the first reason why COPD develops in humans is considered to be the inability to correct the basic design of the lung or to eliminate genetic predispositions to diseases of the elderly, because of evolutionary constraints.

Mismatch with Modern Environments

Through natural selection, organisms have acquired resistance and tolerance to toxic substances that are present in the natural world, but it takes time for humans to

adapt themselves to environmental changes, because of the long generation time. For example, the distribution of the gene conferring tolerance to cow's milk (lactase persistence) has been under strong positive selection pressure. Nevertheless, it is speculated that it took 5,000–10,000 years before the prevalence of cow's milk resistance alleles increased to 99% in a population [12, 28].

Humans have continuously used fire since they evolved into *Homo sapiens* approximately 150,000 years ago, and they are supposed to have gradually adapted themselves to biomass smoke particulates. However, it has been only 500 years since smoking, which is associated with the production of a large amount of particulates (15–40 mg/cigarette) [29], became prevalent worldwide, with world cigarette consumption increasing by a factor of 1,000 in the last 100 years from a few billion per year in 1900 to present values of approximately 5.5 trillion worldwide [30]. The number of human generation changes is approximately 20 over a period of 500 years, and even if humans had an allele conferring resistance to cigarette smoke, the 500-year time period is not sufficient to fix the allele in a population.

Dependence on drugs such as nicotine is a state in which the incentive mechanisms of 'liking' and 'wanting' are hijacked by external drugs in the brain [31]. Susceptibility to nicotine dependence depends on the rate of metabolism of nicotine. For example, carriers of CYP2A6 alleles with a high rate of nicotine metabolism are more susceptible to nicotine dependence than carriers of alleles with a low rate of nicotine metabolism (CYP2A6*9, CYP2A6*12, CYP2A6*2 and CYP2A6:4) [32]. However, for the same reasons mentioned earlier, it will still take a long time before the distribution of CYP2A6 alleles in a population change so much that it reduces nicotine dependence.

Many of the genetic predispositions to COPD are considered to be conferred by alleles that originally had neutral effects, but came to have deleterious effects, because of modern environmental changes. Another presumed reason why COPD develops in humans is that humans have had no time to acquire resistance to cigarette toxicity and dependency throughout natural selection, because of the long generation time. Other examples of modern environmental changes that may influence development and progression of COPD include occupational exposures, such as organic and inorganic dusts, chemical agents and fumes, as well as diet and poverty [2]. These environmental changes, as well as cigarette and biomass smoke exposures, may affect gene expression patterns through epigenetic changes, including altered

DNA methylation, decreased levels of histone deacetylases and reduced microRNAs levels. Thus, a second potential evolutionary reason for the development of COPD in humans is a mismatch between evolution and environmental factors.

Co-Evolution of the Immune System and Microorganisms

Host-microorganism interactions are neutral, antagonistic or synergistic. The immune system is considered to have co-evolved with microorganisms. More specifically, evolution has been driven by repeated competition insofar as if a microorganism acquired a countermeasure against the immune response of a host, the host would acquire a more advanced immune response to overcome the countermeasure [33–35]. Animals with a long lifespan, such as humans, are exposed to repeated invasions by the same microorganisms, and these animals are considered to have highly developed adaptive immunity in the airways and intestinal mucosae, which are the areas most exposed to microorganismal invasion; these animals quickly cope with the invasion, as the microorganisms are recognized by the immune memory function [34, 35].

In COPD, the immune responses to cigarette smoke particulates, particularly adaptive immune responses, are enhanced [36]. In other words, inflammation in COPD is a state in which the sophisticated immune system that has developed as a countermeasure against microorganisms is activated by cigarette smoke. Actually, the same cells (macrophages, neutrophils and lymphocytes) and signaling molecules (pattern recognition receptors, inflammasomes, interleukin-1 and nuclear factor- κ B, for example) are activated in inflammatory responses to particulates and microorganisms [36–38]. In animal experiments, there are actually commonalities and interactions between airway inflammation caused by cigarette smoke and that caused by microorganismal invasion. For example, it has been reported that airway inflammation induced by viral pathogen-associated molecular pattern stimulation is similar to that in COPD [39], and that cigarette smoke exacerbates airway inflammation induced by viral pathogen-associated molecular patterns [40]. In addition, it has been reported that latent adenoviral infection exacerbates airway inflammation and emphysematous lesions caused by cigarette smoke [41], and that simultaneous exposure to cigarette smoke and bacteria results in the formation of lesions similar to those in COPD

[42]. Furthermore, it has been elucidated that CXCL13 is involved in lymphoid follicle formation in the airways of COPD patients as well as in response to viral infections [43, 44]. Also, genome-wide association studies have pointed out that many genes encoding anti-infectious mediators, such as β -defensin, chemokines and tumor necrosis factor- α , promote the development of COPD [45, 46].

As described above, there are many commonalities and interactions between immune responses to cigarette smoke and those to invasion by microorganisms. Therefore, the third presumed evolutionary reason for the development of COPD in humans is that the immune system, which developed through co-evolution with microorganisms, responds strongly to cigarette smoke.

Life History Trade-Off

Genetic traits that are beneficial to the growth and health of the young are subject to positive natural selection to increase reproductive success, even if they are detrimental to the health and survival of the elderly [47, 48]. In evolutionary medicine, this understanding, known as antagonistic pleiotropy theory, is explained as follows: 'Fitness accrues via reproductive success summed across all stages of an individual's life history, and reproductive events in early life contribute more to fitness than do those late in life' [16]. An extended postreproductive life span should evolve when postreproductive individuals can make significant contributions to the fitness of their children and grandchildren [49]. Antagonistic pleiotropic genes that have been naturally selected by such a trade-off between early- and later-life fitness are considered to cause various monogenic and polygenic diseases, a phenomenon known as life history trade-off [50]. Examples of well-known antagonistic pleiotropic genes are the allele for sickle cell anemia (Hb-S), which increases the resistance to malaria infection, and alleles of the cystic fibrosis gene, which enhance fertility and resistance to tuberculosis and cholera infections. The nature of these alleles is considered to have led to the fixation of the heterozygous alleles that do not cause diseases in certain populations (heterozygote advantage) [5, 9, 51–54]. Here, we would like to provide three examples of life history trade-offs by antagonistic pleiotropic traits to explain why COPD develops in humans.

First, COPD patients have genetic mutations that confer susceptibility to inflammation [46]. These mutant genes conferring susceptibility to inflammation are con-

sidered to have been distributed across populations in past ages, when the prevalence of infections was the greatest threat to life, because they increased early-life fitness by enhancing the ability to defend against infections, thereby increasing reproductive success [55]. At the present time, it is considered that if carriers of these mutant genes conferring susceptibility to inflammation experience exposure to smoke, intense inflammation will occur in the lung, increasing the risk of development of COPD in later life [55].

Second, antitrypsin deficiency caused by S- and Z-allele variants causes juvenile COPD, and it is considered that variant α_1 -antitrypsin polymers formed by conformational changes increase the inflammatory response, and are thereby advantageous for defense against infections [56]. Furthermore, in antitrypsin deficiency, tissue protease activity is increased, which is considered to be advantageous for the removal of microorganisms and sperm penetration through the zona pellucida of the ovum at fertilization [57, 58]. It is considered that antitrypsin deficiency alleles were selected at a certain frequency in populations for early-life fitness because of these properties of infection defense and fertilization promotion [56–58].

Third, cellular changes, such as apoptosis and cellular senescence, are involved in the development of COPD [59, 60]. These cellular changes are thought to act to prevent carcinogenesis in early life when cell proliferation is active, while inhibiting cell regeneration and promoting the development of diseases of the elderly, such as COPD, in later life [61–63].

Thus, the fourth presumed reason why COPD develops in humans is that gene and cell traits that have been naturally selected to increase early-life fitness have antagonistic (negative) effects in later life.

Costs of Defense Responses and Tolerance

Inflammation does not only offer the benefit of defending the host against microorganisms, but it also entails the cost of collateral tissue damage by reactive oxygen species (ROS) and the risk of the systemic inflammatory response syndrome, chronic inflammatory diseases and autoimmune diseases [64]. The cost-benefit balance of inflammation is adjusted in organisms at a level that is optimal for the individuals' survival according to the environment [35, 65] (fig. 3a). In past human history, the prevalence of infections has been a major threat to life, and high-cost (but high-benefit) inflammatory traits are

Fig. 3. The cost-benefit (**a**) and resistance-tolerance (**b**) relationships in the defense responses. **a** The cost-benefit balance of inflammation in organisms is set to be optimal for the individuals' survival, according to the environment. In humans, the prevalence of infections has been a threat to life, and high-cost but high-benefit inflammatory traits (**a**) have been naturally selected so that microorganisms can be effectively removed. **a** = High-cost and high-benefit inflammation; **b** = low-cost and low-benefit inflammation. **b** There is a trade-off relationship between resistance and tolerance. Organs with low resistance to microorganisms (for example, the large intestine) have high tolerance (**c**); on the other hand, organs with high resistance to microorganisms (for example, the lower respiratory tract) have low tolerance (**d**).

considered to have been naturally selected so that microorganisms could be effectively counteracted. However, in modern industrialized countries, false inflammatory triggers such as high-salt/high-fat dietary habits and smoking, instead of infections, are increasing. These false inflammatory triggers cause low-intensity chronic inflammation, and this is considered to induce the immunopathology of arteriosclerosis, COPD and other conditions, because high-cost inflammatory traits are maintained [66].

The costs of inflammation depend on the balance between resistance (the ability to remove microorganisms and injurious agents) and tolerance (the ability to reduce the harmful effects of microorganisms and injurious agents without removing them). There is an evolutionary trade-off relationship between resistance and tolerance [33, 67, 68] (fig. 3b). For example, in the large intestine, which has low resistance, many microorganisms (10^{10} microorganisms, consisting of more than 100 species of commensals per gram of feces) live symbiotically, but tissue injury does not occur because of the developed tolerance. However, it is known that severe inflammation and Crohn's disease occur in the large intestine when mutations in the nucleotide-oligomerization domain 2 lead to reduced tolerance [69, 70]. On the other hand, the lower respiratory tract has developed resistance to maintain

aseptic conditions. In contrast to the large intestine, tolerance is set low as a trade-off for the developed resistance [67, 71]. Therefore, if the resistance fails for some reason and bacteria colonize the lower respiratory tract, chronic airway lesions, such as bronchiectasis, may develop easily because of the low tolerance. A reduction in immunological tolerance and oxidative stress tolerance is involved in the development of COPD [72, 73]. Tolerance set low to give priority to resistance in the evolution of the lower respiratory tract as an evolutionary trade-off relationship between resistance and tolerance is considered to be a reason behind the susceptibility of humans to COPD.

In tissues with low tolerance, ROS produced by inflammatory cells can easily cause collateral tissue damage [74]. For example, oxidative stress tolerance through the Keap1-NF-E2-related factor 2 (NRF2) pathway, whose components include glutathione synthetase and hemoxygenase-1, requires preconditioning by mild oxidative stress [75, 76]; the system cannot cope with acute lung injury that is associated with sudden exposure to a large amount of ROS. Activation of oxidative stress tolerance is not constitutive but inducible, probably for the following reasons. First, energy cost (consumption of free energy) is needed to constitutively activate the antioxidant system. Second, physiological levels of ROS are needed as signaling factors to maintain normal cellular activity [77]. For example, it has been pointed out that excessive 'antioxidative stress' is cytotoxic [78], and that constitutive NRF2 activation is carcinogenic [79]. Third, preconditioning for oxidative stress tolerance may occur frequently in the lung, because the lung is exposed to injurious agents from the respiratory tract and blood on a daily basis. For example, in healthy smokers, antioxidant enzymes and glutathione-dependent detoxification systems are upregulated by NRF2 activation [73]. However, it is considered that in COPD patients, such adaptation does not take place, allowing damage to occur as a result of ROS [73].

Thus, the fifth presumed reason for the development of COPD in humans is that the lower respiratory tract is susceptible to inflammatory side effects as a result of evolutionary selection of a high cost of inflammation and a low tolerance in the respiratory tract.

Reproductive Success at the Expense of Health

Higher reproductive success early in life may come at the expense of disease and mortality. For example, in humans, higher testosterone and estrogen levels cause high-

er fertility, but also higher susceptibility to prostate and breast cancer [80]. In addition, women who reach menarche at a younger age and those with BRCA mutations have higher levels of fertility, but are also more susceptible to breast cancer [81, 82]. Similarly, men with shorter CAG repeats in the androgenic receptor gene have higher sperm viability and higher fertility [83], but they are more susceptible to prostate cancer [49, 84]. These are good examples that explain the trade-offs between early fertility and later survival by reproduction-enhancing pathogenic traits.

It can be pointed out that reproduction-enhancing pathogenic traits may also be involved in the susceptibility to COPD. For example, some chemicals in cigarette smoke are bioactivated into toxic compounds by cytochrome P₄₅₀ (CYP) enzymes in the lung, and estrogen is known to activate CYP1A1 and CYP1B1, enhancing the toxicity of cigarette smoke [85–88]. Furthermore, it has been reported that estrogen stimulates the production of mucin (MUC5B) in airway epithelial cells, thereby increasing sputum production [89]. These estrogen actions are considered to increase women's susceptibility to COPD [85, 86]. In addition, it has been reported that β -defensin, which promotes the development of COPD [45, 90–92], facilitates sperm maturation and fertilization, thereby increasing fertility [93].

Thus, the sixth presumed reason for the development of COPD in humans involves the evolutionary costs of reproduction.

Limitations of the Evolutionary Approach to Explain the Development of COPD

The evolutionary medical approach, as described, is useful for explaining not the pathogenesis (i.e. the causes and mechanisms of COPD), but the ultimate reason why the disease occurs at all in humans. However, this approach also has its limitations. First, evolutionary medicine is not directly useful in the diagnosis and treatment of COPD. However, the concepts presented when exploring the tenets of evolutionary medicine provide information that can lead to a clearer understanding of the etiology and pathogenesis of COPD; this perspective is also necessary for researchers to better understand the significance of their work. Second, it is difficult to scientifically prove the validity of the core principles constituting the framework of evolutionary medicine. For example, it is practically impossible to experimentally prove or observe the effects of natural selection and the trade-offs

Fig. 4. Etiopathogenetic mechanism of COPD involving evolutionary factors.

between early and later life in mammals, which have long lifespans. However, the questions asked in evolutionary medicine are the 'why' questions (for example, why diseases exist in the first place). It is difficult to scientifically prove the correctness of the answers to questions of this nature, unlike the questions about causes and mechanisms. Third, an evolutionary medical explanation for the occurrence of COPD, as described in this paper, represents one of the few opportunities for applying evolutionary principles to explain the development of COPD, as many other examples can be given. For example, it would be necessary to consider not only natural selection, but also genetic variations due to founder ef-

fects, genetic drift and migration to explain the distribution of genetic predispositions and susceptibility traits to COPD.

Conclusion

In summary, there are at least six possible evolutionary reasons for the development of COPD in humans. The evolutionary explanations described in this paper (evolutionary constraints, mismatch between environmental changes and genes, co-evolution of pathogenic microorganisms and the immune response, trade-offs between early and later life, high cost of inflammation and low tolerance in the respiratory tract and reproductive success at the expense of health) provide new insights into the understanding of why COPD develops in humans,

why many COPD patients are elderly, and why some subpopulations are more susceptible to COPD (fig. 4). In order to obtain a clearer understanding of the etiology of COPD, it is not only necessary to elucidate any proximate factors, such as the causes and mechanisms, but also to consider the ultimate factors involved in the development of COPD.

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