From smoking to COPD – current approaches

De la fumat la BPOC – abordări curente

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Abstract

Chronic obstructive pulmonary disease (COPD) remains a leading cause of death all over the world. Even though it is the most intensely studied disease induced by cigarette smoking there are still incomplete researches concerning its pathophysiology and treatment. So far it has been determined the deleterious effects of the secreted molecules diversity and some feasible therapies for their diminution. According to current studies more relevance gains the possible autoimmune origin of COPD and the epigenetic modifications. The idea of autoimmunity in smoking induced COPD began to be speculated with the discovery of autoantibodies in patient's serum, but there are some studies who consider antibody complexes that reside in the lung tissue as more relevant for future research. By developing the autoimmune aspect of COPD it will become possible to select more precise treatment strategies. The importance of epigenetic changes in this field might be appreciated starting with the fact of an existing connection between epigenetic modifications induced by maternal smoking and latter COPD development. This explains the tendency toward different drugs capable of restoring these transformations such as deacetylation agents expected also to prevent steroid resistance. Nevertheless smoking cessation remains as the indispensable approach for COPD treatment and prevention.

Keywords: ***COPD, smoking, epigenetic changes***

Rezumat

Bronhopneumopatia cronică obstructivă (BPOC) rămane una dintre cauzele majore de mortalitate din întreaga lume. În pofida faptului că este cea mai studiată maladie indusă de fumat, încă nu sunt date concludente în privința aspectelor fiziopatologice și a tratamentului, chiar dacă au fost determinate efectele dăunătoare ale diversității de molecule implicate și au fost propuse câteva terapii fezabile pentru diminuarea secreției acestora. Studiile actuale se axează preponderent pe originea autoimună a BPOC și pe modificările epigenetice. Ideea de autoimunitate în BPOC indus de fumat a prins contur odată cu identificarea autoanticorpilor în serul pacientului, pe când unele studii consideră complexele de anticorpi localizate în plămâni mai importante pentru viitoarele cercetări. Investigarea aspectelor autoimune ale BPOC va permite selectarea unor strategii de tratament mai concrete. Pregnanța modificărilor epigenetice din acest domeniu poate fi apreciată pornind de la existența unei conexiuni dintre modificările epigenetice induse de fumatul matern și dezvoltarea ulterioară a BPOC. Aceasta explică tendința savanților pentru medicamentele capabile să restabilească aceste transformări precum agenții de deacetilare, care posibil că previn și rezistența către steroizi. Totuși stoparea fumatului rămâne a fi abordarea indispensabilă pentru tratamentul și prevenția BPOC.

Cuvinte-cheie: ***BPOC, fumat, modificari epigenetice.***

Introduction .

Chronic obstructive pulmonary disease (COPD) represents one of the leading causes of death worldwide. According to World Health Organization (WHO), COPD retains the III, IV and V places in upper-middle , lower-middle and high income countries respectively and by 2020 will attain the third place all over the world. Nonetheless there is still inconsistent research about its pathophysiological mechanisms and treatment. This leads to irreversible alterations not only in patient's lungs but also has systemic consequences. On long term COPD might lead not only to higher aortic pulse-wave velocity, lower bone mineral density, appendicular skeletal muscle mass index and shorter telomere length[(1)], but also to poorer health related quality of life specifically for current smokers, as well as to mildly impaired productivity and to greater costs[(2)] and what is even more dangerous to lung cancer - squamous cell carcinoma[(3)] or another multiple severe comorbidities.

An important point is also the fact that COPD is still poorly diagnosed and consequently treated. Amidst the explanations there is the unawareness of the smokers that COPD is a potential threat for their health and this disregard varies among different populations[(4)].

There is an indisputable connection between COPD and smoking since approximately 40% of those who developed the disease are smokers or ex-smokers[(5)]. In a recent study there was even found a correlation between the time to the first cigarette and the risk of developing COPD: current smokers with reduced time to first cigarette after waking are more prone for COPD development compared to those with prolonged one[(6)]. There is mounting evidence for higher nicotine dependence between smokers with COPD than amidst smokers without this condition[(5)]. Some studies scored this dependence using Fagerström Test for Nicotine Dependence and it was also determined that for every point of this test there is a raise of 11 % of the probability to develop COPD[(7)]. Unfortunately the risk of developing COPD is very high not only for current cigarette smokers, but even for those exposed to maternal smoking in the early childhood[(8)].

This paper is a brief review of particular aspects related to the link between cigarette smoking and COPD.

Impact of smoking on pathogenesis of COPD

Smoking has deleterious actions, especially on lungs, through varied mechanisms. According to common views the major ones are: inflammation, oxidative stress and the increase of protease activity, the last two maintaining and incrementing the first one. Smoking's detrimental effects on lung include mucous glands hyperplasia, inflammatory infiltrate and the obstruction of the airways, especially the smallest ones (in COPD airways with a diameter less than 2 mm are the dominant site of obstruction), number of vibratile cilia's reduction, alveolar destruction, metaplasia and reduction of small arteries diameter[9]. Oxidative stress determines lung components lesion such as epithelium, airways and alveoli, and also leads toward the increase of proteases that degrade lung's matrix[3,10,11].

Speaking about the inflammatory process induced by cigarette smoking that will further degenerate into COPD there has been studied the role of various cells like: macrophages, neutrophils, different subsets of T and B lymphocytes and dendritic cells[3]. Hoetzenecker et al provided data concerning the role of CD4+ cells in maintaining the inflammatory alteration in COPD patients by displaying a proliferative response toward elastin and collagen exquisitely of lung origin[12]. Another study concluded that CD(+)(8)T-lymphocytes infiltration is responsible for pulmonary inflammation that later degenerates into COPD[13].

It was settled that the direction toward a pro-inflammatory versus anti-inflammatory response in COPD patients is established by specific shifts in the equilibrium of Th17/Treg cells[14]. Probably dioxins contained in smoke, which exhibit the function of ligands for the aryl hydrocarbon receptor might be implied in this shift since this receptor has controlling effects on Treg/Th17 balance[15]. In addition to the previously presented studies, there is evidence of consistent increase of IL-17A in severe to very severe COPD (GOLD III/IV) in both smokers and non-smokers[16]. Along with an increase in IL-17 there is a raise in an extensive variety of other molecules such as: TNF-alpha, IL-1beta, granulocyte-macrophage colony-stimulating factor (GM-CSF), transforming growth factor (TGF)-beta1, MCP-1, LTB4, IL-8 elaborated by pulmonary epithelium[17,18] chemotactic chemokines like CXCL9, CXCL10, and CXCL11 secreted by macrophages[19]; also proteolytic enzymes MMP-2, MMP-9, MMP-12, and cathepsins[20].

The release of these molecules activates a complex reaction cascade that urges lung matrix's degeneration and leads toward COPD. Likewise there has been discovered that smokers with COPD develop fragmentation of the reticular basement membrane in lungs, a feature that potentially exposes them to greater extension of the inflammation process[21]. That defines the relevance of therapies directed toward reducing the production of all these molecules that do not only initiate but also preserve smoke induced inflammation in lungs. According to a novel study carried on mice, IL-8 production might be diminished by AMP-activated protein kinase[22]. By suppressing cytokine production not only the inflammation diminishes but also the regenerative process can be initiated there. Among other novel treatments implicated in epithelial regeneration is azithromycin - capable of reversing vascular endothelial growth factor (VEGF) aberrant expression mostly induced by smoking and it also inhibits the production of reactive oxygen species[23]. This drug also has the role of suppressing CD8+ T cell granzyme B in COPD patients[24].

An innovative facet in COPD pathophysiology induced by cigarette smoking is CC16 (a marker of lung epithelial injury produced by Clara cells) that are found in a diminished proportion in COPD might exhibit a regenerative action towards airway epithelium[25].

An earlier research paper showed that chronic exposure to cigarette smoke causes waste of CD28 and the up-regulation of NK cell receptor expression on T cells[26]. Similar to this one, comes another study that identified a decrease of CD4+ and CD8+ T cells during acute exacerbations of COPD[27]. There are also articles that contradict the previous hypothesis, stating that, there is an augmentation of CD8+T-cells in the lungs of COPD patients that are also current smokers[28,29] as well as an increment in the percentage of CD8+CD45RA+ T-lymphocytes, that possess greater destruction potential for lung tissue as long as they have accomplished the final maturation-activation state[30].

A possible autoimmune origin of smoking induced COPD

During the last years the idea of the autoimmune component in COPD is intensively speculated. That is why Faner et al tried to match Witebsky postulates (criteria for autoimmune diseases) in order to consider a disease of autoimmune origin and accomplished their goal by grabbing direct, indirect and circumstantial evidence from a considerable number of studies. Also, they presumed that dendritic cells are partially activated in healthy subjects lungs by autoimmune antigens not by DAMPs that explains the induced tolerance to them comparative to COPD patients where these cells maturation is thorough by autoimmune agents and DAMPs[31].

Among the studies debating the autoimmune origin of COPD one found out that CD8/CD28(null) T cells produce co-stimulatory molecules that might wield a role in the autoimmune responses in COPD[32]. Another evidence supporting the autoimmune nature of COPD could be considered its association with 18 autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, psoriasis and other diseases[33]. Also there are various papers debating the presence of ubiquitous autoantigens and subsequently autoantibodies that also serve as an evidence for the autoimmune component of COPD. Come some papers which operate with COPD patients and identify various types of antibodies like: antiendothelial cell antibodies[35], also autoantibodies to thyroid-specific antigens, thyroid peroxidase (TPO), thyroglobulin, carbonyl modified self-protein, etc.[36]. What is intriguing about antibodies against carbonyl modified self-protein is that they have a tendency

toward IgG1 profile and their titer inversely correlates with the severity of COPD. At least this was established in a single study and needs further confirmation. Another study hypothesis that by determining the antibodies profile it might be possible to ascertain the status and phenotype of the disease[37]. A different view is projected in an investigation where they suppose that future studies need to be directed toward antibody complexes that reside in the lung tissue comparatively to circulating ones because they did not identify any difference between COPD and control subjects after adjusting anti-elastin antibody levels[38].

Amidst other mechanisms involved in autoimmunity is incriminated the peroxynitrite radical which is generated in large amount in the lower airways of COPD patients and it might potentially induce the elaboration of neo-autoantigens[3]. In consonance with previous research that spotted a modification in the CD4 phenotype concretely in lungs, owing to smoking exposure[39] the disclosure of a peculiar Th17 cell subset and precisely of the T cells that display chemokine receptor CCR6 could gain its place in the autoimmunity origin of COPD[40].

Epigenetics changes determined by smoking in COPD

Taking into consideration the fact that only a proportion of 40% of smokers will develop COPD, emerges the idea that there have to be additional factors implied in the pathogenesis of the disease. A common element of COPD's formation is the genetic predisposition. A substantial genetic contributor is the nicotinic acetylcholine receptor gene cluster CHRNA5-A3-B4 that acts by modifying smoking behavior. This explains why some smokers who have rs16969968, risk allele in CHRNA5, smoke more than others and they have a greater risk to develop advance COPD[41]. Also a high risk for developing COPD exists in patients with the rs1051730 allele in CHRNA determining them to attain airway obstruction and destruction of lung parenchyma[42].

Some studies hypothesized that there might be a central mechanism that exerts adjustments in the transcription of the airway basal cell genes affected by cigarette smoking which potentially can lead to COPD. The discovery of this mechanism could help in identifying a way to restore the molecular phenotype of smoker's airway basal cells[43]. But certainly first-rate solution for COPD prevention is smoking cessation[44]. Also, there is important evidence supporting smoking cessation as one of the best solutions for COPD patients because it leads to a lower level of bronchial epithelial remodeling but only after a prolonged period as it was stated in a study published more than 3.5 years[45].

There prevail even tighter connections between epigenetic modifications provoked by smoking that could potentially lead to COPD[41]. The idea of epigenetic changes implicated in COPD pathogenesis came after there was established that those single-nucleotide polymorphisms distinguished through genome-wide association studies connected with COPD cannot reveal the frequency of the disease manifestation[10]. Explained differently, there is an exceeding number of COPD patients that lack risk alleles, contributing to this disease pathology, so, there has to be another factor contributing to the development of this disease.

According to recent studies the most frequent epigenetic modifications entangled with COPD development are: DNA methylation, histone acetylation and deacetylation, phosphorylation and ubiquitination[46]. Epigenetic alterations are not only incriminated in inflammation but also in cellular senescence and steroid resistance. For example diminution of the HDAC2 (histone deacetylase) leads not only to inflammatory response but also to steroid resistance and senescence in lung[47]. So it can be admitted that a cause of glucocorticosteroid treatment's inefficacy in COPD might be histone deacetylase. What is even more curious is the idea of other epigenetic modifications in COPD's therapy resistance , that is why by overcoming these changes it will be possible to improve patients outcome. Modifications in the activity of histone deacetylase and DNA-methylation patterns could be induced even to fetus by its exposure to maternal smoking during pregnancy[8]. Maternal smoking during pregnancy is also associated with transformations in DNA methylation of CpG dinucleotides of distinct gene regions. The DNA methylation status is linked not only with the existence of COPD and other lung disorders but conjointly to their severity[48].

Furthermore, some studies suggests that epigenetic changes are incriminated for disturbing the balance between pathogenic and commensal pathogens determining the exhibition of neo-epitopes[41]. These neo-epitopes serve for autoantibody elaboration and sustain lung inflammation. Even more strikingly remains the fact that cigarette smoking promotes epigenetic changes in different cells. For example, an intriguing paper about the prevalence of down-regulation of multiple microRNAs (miRNAs) precisely in lung macrophages hypothesizes that it might serve as a predominant manager of the disease-promoting macrophage phenotype[49].

It is very important to add that these epigenetic changes can reverse after smoking cessation. Toward the probable time of reverse most of the researchers agree on long period of smoking cessation while a quite novel study found that there is possible to observe specific loci methylation modifications towards non-smoking status within 12 weeks of smoking arrest[50,5]

Conclusions

Current research regarding the association between cigarette smoking and COPD revealed a broad area of unknown aspects that require further investigations. Alongside confirming some of the existing theories there were determined new associations. To be more precise the evidences about the autoimmune origin of COPD gained more ground and the relevance of epigenetic changes in COPD pathogenesis.

Discouraged by the fact that autoimmunity represents a black box full of surprises, identifying an autoimmune origin in COPD induced by smoking might serve not only as a starting point for new research but also

strengthens the relevance of smoking cessation in such patients. By establishing tighter connections among smoking and the autoimmune origin of COPD similar to well defined autoimmune diseases there will be achievable to direct COPD's therapy toward different classes of medicine.

Along with these come the discoveries concerning epigenetics modifications induced by smoking, more importantly being the fact that they can be induced even by maternal smoking predisposing the child to future lung pathology. Studies in regard to histone deacetylation that induced steroid resistance in COPD patients direct research toward novel strategy therapies able to overcome such epigenetic changes.

In what concerns the available approaches toward smokers with COPD, the vital step in defeating the disease and preventing other noxious effects of cigarette smoking, remains smoking cessation. ■

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