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REVIEW

Epigenetic Targets for Therapeutic Approaches in COPD and Asthma. Nutrigenomics – Possible or Illusive

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Oxidative stress generated by cigarette smoking, environmental pollution, or other noxious particles leads to epigenetic changes in the cells of the respiratory tract. They reflect cell adaptation in response to chronic exposure to external factors. Although there is no change in the genetic code, epigenetic changes may be heritable and translated from one generation to another, accumulating abnormalities and rendering cells into entirely different phenotype, causing disease. DNA methylation, post-translation histone modification, ubiquitination, sumoylation and miRNA transcriptional regulation are the major processes that are responsible for the epigenetic control of gene expression. All of them are reversible. They can be regulated by targeting specific enzymes/proteins involved in the process in order to mitigate inflammation. Chronic respiratory diseases have epigenetic signatures that affect gene expression in the lung. Targeting them provides the development of novel diagnostic and therapeutic approaches in respiratory medicine. Nutrigenomics reveals the beneficial effect of natural phytochemicals, affecting key steps in the signaling pathways of chronic respiratory diseases.

INTRODUCTION

EPIGENETIC VIEWPOINT OF CHRONIC RESPIRATORY DISEASES

Chronic obstructive pulmonary disease (COPD) and asthma are the most prevalent respiratory diseases, characterized by low grade persistent inflammation. Each of them is presented by a distinctive profile of cells, cytokines and pathomorphological changes triggered by inflammatory signaling pathways. It is now assumed that oxidants generated from inhaled noxious agents (cigarette smoke, environmental pollution, allergens) lead to oxidant-antioxidant imbalance, thus provoking oxidative stress. Both asthmatic and COPD lung specimens demonstrate elevated oxidation and a lack of adaptive antioxidant protection. The oxidative milieu stimulates transcription factors [nuclear factor-kappa-B, (NF-κB), activator protein-1 (AP-1)] via several redox-sensitive kinases. Once activated, transcription factors reach the nucleus and induce transcription of pro-inflammatory genes. The modification of transcription factors (acetylation or phosphorylation) is of paramount importance, but is never enough to activate transcription.[1] In eukaryotic cells, DNA is present in the form of chromatin. Chromatin structure is critical for the access of the transcription factors. DNA may be tightly coiled around core histones (H2A, H2B, H3, and H4) forming the nucleosome. In this state (heterochromatin), it is inaccessible for binding, which inhibits gene expression - gene silencing. If uncoiled, DNA stretches into a linear structure and is reached by the transcription factors - gene expression ensues. The regulation of coiling/uncoiling is performed by histone post-translational modification.[2] Transcription may also be regulated by circulating miRNAs.[3]

Molecular targets for epigenetic therapeutic interventions in chronic respiratory diseases.

The modification of chromatin structure is a result of complex epigenetic changes of DNA organization, that are reversible and may be targeted, by the manipulation of various enzymes, responsible for these processes. Unraveling the key epigenetic changes that are important for the chronic inflammatory process in COPD and asthma will provide a step forward in their treatment strategy.

DNA methylation as a therapeutic target

Methylation usually happens at sites where cytosine bases are paired by guanine (CpG -islands). The process is catalyzed by DNA methyl-transferase (DNMT). In COPD and asthma, both hypermethylation and hypomethylation of DNA have been reported.[4-6] Only some of them, however, correlate with functionally important differences in gene expression. In asthma, DNMT activity limits asthma severity. Acute inhibition of DNMT activity with 5-azacytidine (non-selective inhibitor of DNA methyl-transferases) reduces airway hyper-reactivity and inflammation. In COPD, PI3K/Akt and antioxidant NFE2-related factor-2 (Nrf2) pathways have been identified as differently regulated. Both are assumed as treatment targets for COPD.[7,8] In COPD CpG-hypermethylation destroys protective, and promotes pathogenic pathways. Hypomethylation of the HDAC6 promoter, however, leads to its elevation and epithelial dysfunction.[9] The effectiveness of the experimental modification of DNMT in COPD and asthma are currently elusive and not applicable into clinical practice.[10]

Histone acetyl-transferases and histone deacetylases as therapeutic targets

Histone acetyl-transferases (HATs) are enzymes binding an acetyl group to the N-terminal domains of lysine residues in histones. Non-histone proteins, including transcription factors, are also targets of HAT. The effect of acetylation depends on the domain, being modified. There are also proteins that share HAT activity - CBP and p300. In asthmatic airways HAT activity is elevated. Similar are the data, regarding CBP/p300 and p300/CBP-associated factor (PCAF). In comparison to asthmatics, lung biopsy specimens from COPD patients showed no significant change in HAT activity.[11]

Histone deacetylases (HDACs) catalyze the removal of the acetyl group from lysine residues of histone and non-histone proteins leading to transcriptional repression. By now, 18 different HDACs have been identified. HDACs are divided into four classes: I (HDAC1, -2, -3, and -8), II (HDAC4, -5, -6, -7, -9, and -10), III (Sirt1, -2, -3, -4, -5, -6, and -7) and IV (HDAC11). In lung inflammatory diseases sirtuin 1 (SIRT1) and HDAC2 are most extensively studied.

Smokers and COPD patients' macrophages have decreased HDAC2, if compared to healthy non-smokers. In the lung tissue of COPD patients, low levels and reduced activity of HDAC2 are detected. In asthmatic lung HDAC activity in peripheral blood monocytes progressively diminishes from mild, through intermittent and severe asthma.[12,13] Decreased HDAC2 activity leads to imbalance and allows acetylation of histone and non-histone proteins. Cigarette smoke/oxidants usually mediate phosphorylation and ubiquitin-proteasome-dependent degradation of HDAC2. In addition to oxidative stress, some viral proteins may also change HAT/HDAC activity. It has been detected that adenoviral infection increases the expression of inflammatory genes. This is mediated via adenoviral E1A protein, which interacts with HAT-containing co-activators.[14] COPD patients are assumed to be carriers of latent adenoviral infection, which may be a mechanism for amplification of COPD inflammation.[15,16] Adenoviral infection may as well induce a significant reduction in HDAC activity in the lungs of ovalbumin-sensitized animals.[17] Persistence of adenoviral infection is also implicated in steroid-resistance in children with asthma.[18] Other viruses may also impair the action of HDAC2 and induce steroid resistance.

The role of HDAC in steroid insensitivity in COPD and asthma patients - clinical implications

Corticosteroids recruit HDAC2 to switch off pro-inflammatory genes. HDAC2 reduced activity coincides with corticosteroid insensitivity. The low levels of HDAC2 leads to acetylation and degradation of nuclear factor erythroid-related factor 2 (Nrf2) - a regulator of antioxidant defense. SIRT1 is a class III HDAC. In comparison to non-smokers, COPD patients and smokers have decreased nuclear SIRT1 levels in the lungs. Cigarette smoke, airway pollution, oxidants or aldehydes lead to SIRT1 degradation and decreased enzymatic activity.[19] SIRT1 deficiency stimulates the acetylation of RelA/p65 subunit of NF-κB and allows the elevation of the autophagy of lung cells in COPD patients. In contrast, to the other HDAC (SIRT2, SIRT3, SIRT6, and SIRT7)

sirtuin-1 is also significantly reduced in severe asthma.[20] Experimental models where inhibitor of sirtuin-1 (sirtinol) is applied describe a significant elevation of IL-4, whereas no change in IFN-gamma levels are detected. It is established that sirtuin inhibition facilitates GATA-3 phosphorylation and IL-4 synthesis. The application of sirutin-1 in severe asthma leads to a substantial decrease in IL-4 levels without any change in IFN-gamma. Thus, sirtuin-1 is essential in maintaining the Th-balance and in preventing cellular differentiation toward Th2 phenotype.[20]

Ubiquitination

Ubiquitination is a post-translational modification that generally directs proteins for degradation by the proteasome or by lysosomes.[21] It has been implicated in many cellular processes, including transcriptional regulation, DNA repair, regulation of protein-protein interactions and association with ubiquitin-binding scaffolds. Though, in COPD, ubiquitination is responsible for both alveolar cell death and endothelial apoptosis[22,23] there is no therapeutic approach targeting it. In contrast to this, the inhibition of ubiquitination has been reported as beneficial in preventing muscle atrophy in COPD[24]. Ubiquitination in asthma has been responsible for the abnormal Th2 maturation and Th2 cytokine secretion in both eosinophilic and non-eosinophilic inflammation.[25-27] To date, no experimental data have been reported regarding this mechanism.

Sumoylation

Small Ubiquitin-like Modifier (or SUMO) proteins are a family of small proteins that are covalently attached to and detached from other proteins in cells to modify their function. SUMO-ylation is a post-translational modification involved in various cellular processes, such as nuclear-cytosolic transport, transcriptional regulation, apoptosis, protein stability.[28] Though sumoylation has recently been implicated in COPD-associated pulmonary hypertension and abnormal macrophage differentiation, no research has been performed.[29,30]

MICRO-RNAs AS THERAPEUTIC TARGETS

MiRNA and glucocorticosteroids

MicroRNAs (miRNAs) are non-coding RNAs that regulate mRNA stability and/or translation. They consist of up to 20-30 nucleotides and are highly conserved among species. MiRNA play an important role in a variety of biological processes ranging from embryonic developmental patterning to stress responses and epigenetic inheritance.[31] MicroRNAs bind to target sites in the 3' UTR of mRNAs. They may cause post-transcriptional repression or decay of mRNAs. MiRNA expression is not altered in response to corticosteroid (budesonide) treatment.[32] Some microRNAs (e.g., microRNA-18 and microRNA-124a) downregulate glucocorticoid receptor levels.[33] Li et al. prove that IFN-gamma and LPS synergistically increase the expression of miR-9 in macrophages and lung tissue. Authors show that miR-9 regulates glucocorticosteroid receptor signaling and steroid-resistant airway hyper-responsiveness. They establish that miR-9 is a mediator in IFN-gamma/LPS–induced inhibition of dexamethasone activity in macrophages. MiR-9 reduces and attenuates the activity of protein phosphatase-2, which abrogates dexamethasone nuclear translocation.[34] Similar is the data by Kim et al., who also share their experience with the role of miRNA in steroid sensitivity. Kim et al. define a novel miR-21/PI3K/HDAC2 axis in a previously unrecognized severe steroid insensitive asthma. They prove that chlamydia and haemophilus influenzae infection augment the Th1/Th17 activation of neutrophilic inflammation in experimental allergic airway disease. Influenza and respiratory syncitial virus trigger Th17 immune reaction. Under both conditions miRNA-21 levels increase, PTEN activity reduces, which facilitates PI3K-phosphorylation state. As a result HDAC2 is acetylated and therefore inactive.[35]

Antagomirs and miRNA mimics

There are two therapeutic approaches based on miRNA modulation - miRNA antagonists and miRNA mimics. MiRNA antagonists treat diseases that arise from miRNA gain of function. Small interfering RNA (siRNA) oligonucleotides, complementary to the endogenous miRNA, are applied. They bind to the target miRNAs, preventing them from being processed by the RISC complex.[36] In contrast, miRNA mimics are duplex oligonucleotides composed of a guide and a passenger strand. They restore loss of miRNA function and are applied for replacement therapy. The guide strand contains the same sequence as the endogenous miRNA. The passenger strand is complementary to the mature miRNA. These miRNAs are processed via similar pathways as the endogenous miRNA of interest.[36] Efficient and stable delivery of siRNA/miRNA is required. Several delivery systems have been developed to provide administration, stability, and intracellular

uptake.[37-40] The major obstacles for the success of miRNA-based therapy are that it should be biostable, tissue specific, without off-target effects; it should possess good transmembrane penetrance and high intracellular concentration.

MiRNA antagonists and mimics have been applied in experiments, providing effective results. Most of the studies are performed in non – COPD lung disease models. After intravenous administration of a neutral lipid emulsion that contained the let-7 mimics a successful inhibition of tumor growth in a mouse model of lung cancer is observed.[41] A synthetic miR-34a mimic in another mouse model of lung cancer prevents lung tumor growth and suppresses known cancer-promoting genes.[42] The suppression of miR-155 in a mouse model of eosinophilic inflammation led to an attenuated T-helper cell (Th2) response.[43] These data show the potential of bringing miRNA studies in COPD from experimental animal models to clinical trials. Experimental data in asthma depicted inhibitors of miR-106a, miR-126, miR-145, miR-221.[44-48] Inhibition of miR106a in a mouse model of asthma reduced Th2-cytokine production, airway hyperreactivity, mucin content, and subepithelial collagen deposition. Inhibition of miR-106 reduced airway inflammation, hyper-responsiveness, and mucus hypersecretion.[45] Inhibition of miR-145 alleviated eosinophilic inflammation, mucus hyper-secretion, Th2 differentiation and airway hyper-reactivity.[44] Inhibition of miR-221 also reduced airway inflammation in a mouse model.[49] MiR-25, miR-133a, and miR-146a/b are also promising targets for asthma therapy.[10] They regulate contractile proteins and inflammatory proteins, RhoA and immune signaling respectively. MiR-25 is responsible for the regulation of contractile, proliferative and inflammatory phenotype through negative regulation of Kruppel like factor-4.[46] MiR-25 is down-regulated after exposure to allergen. Transgenic smooth-muscle targeted deposition of miR-25 in mice alleviates lung function.[47] MiR-133a was also down-regulated, resulting in increased expression of RhoA. Transfection of human bronchial smooth muscle cells with a miR-133a antagonist upregulated RhoA, suggesting endogenous miR-133a normally restrains RhoA expression.[50] In contrast to miR-25 and miR-133a, which are downregulated, miR-146a and miR-146b are upregulated after sensitization.[51,52] MiR-146a/b inhibits IL-1 receptor-mediated signaling and the expression of HuR (RNA-binding protein that stabilizes pro-inflammatory transcripts).[53-56] Upregulation of miR146a/b in the ovalbumin mouse model may be a response to blunt airway inflammation. A mir-146a mimic reduced expression of HuR, which was associated with downregulation of COX-2 and IL1-β expression.[52] Therefore, upregulation of miR-146a expression should antagonize allergic airway inflammation. Even though there are multiple reports of successful local delivery into lung, miRNA therapy is currently ineffective and challenging. The lung anatomy, the presence of mucous plugs and the existence of small airway obstruction hinder adequate administration and bioavailabilty.[10]

NUTRIGENOMICS

Some natural products – beta-carotene, vitamin C, curcumin, resveratrol, anacardic acid, catechins and garcinol may change epigenetic structure, which is known as nutriepigenomics. Dietary intake of polyphenols such as quercetin, naringenin, and hesperetin reduces the risk of asthma.[57] Consumption of green tea and apples, and other food items containing flavonols and polyphenols improves pulmonary function, reduces cough and breathlessness in COPD.[58] These studies indicate that natural products may be of importance in chronic respiratory diseases.

Beta-carotene

The earliest research of natural compounds, capable of targeting certain signaling pathways, are those of beta-carotene, astaxantin, lycopene, vitamin C. It has been established that they can inhibit NF-κB-activity and block the expression of pro-inflammatory genes. Beta-carotene acts as a powerful antioxidant in oxidative stress and lipid peroxidation. Bai et al. have performed an experimental research with macrophage cell lines and have proved that beta-carotene may inhibit the expression of pro-inflammatory genes by inhibition of NF-κB activation.[59] It suppresses the expression of iNOS, TNF-alpha, IL-1beta, and COX-2 and the production of NO and PGE2 in LPS-stimulated macrophages. Under such conditions beta-carotene blocks iNOS promoter and NF-κB-activation and reduces the accumulation of intracellular ROS level.[59] There are a lot of studies, dedicated to both asthma and COPD, that evaluate the relationship between beta-carotene and oxidative stress status. Some of them are even more convincing, presenting data about an association with the rate of lung function decline, quality of life and overall mortality. Ochs-Balcom et al. establish a correlation between oxidative stress state, evaluated by thiobarbituric acid reactive substances and serum

beta-carotene, vitamin C and lycopene levels in 218 patients with COPD. They also prove that the latter are positively associated with FEV1, FVC.[60] Similar is the data reported by Guenengo et al. They have followed up the rate of lung function decline in 523 patients with a certain genotype of heme oxygenase -1, that lead to low levels of this anti-oxidant enzyme. They claim that for a period of 8 years the rate of FEV1 decline is steeper in carriers with low beta-carotene levels than in non-carriers. Among subjects with high-to-normal beta-carotene levels neither high, nor normal beta-carotenes are associated with the rate of lung function decline.[61] Tsiligianni et al. have made a review, regarding the role of various vitamins (vitamin C, D, E, A, beta- and alpha-carotene). They claim that all of them are associated with the alleviation of the symptoms and health state, as well as FEV1. No data, however proves that antioxidant supplementation may reduce the rate of exacerbations, lung function decline or COPD mortality.[62] Hu et al. disclaim this. They have used data from the Third National Health and Nutrition Examination Survey comprising a sample, representative of the US population in 1988-1994 (n = 18,162 subjects aged > or =17 years), and have explored the individual and joint effects of vitamin C, vitamin E, beta-carotene, and selenium intake. Both dietary assessment and serum biomarkers of antioxidant status were analyzed. Each of the dietary and serum antioxidant nutrients seems to be significantly associated with FEV1. If analyzed simultaneously (dietary and serum variables), independent associations are observed for most nutrients. Serum beta-carotene is less positively associated with FEV1 in smokers, than in non-smokers. The authors claim that higher levels of antioxidant nutrients are associated with better lung function.[63] Walda et al. studied the dietary intake of fruit in middle-aged men from three European countries. They have followed up 2917 patients for 20 years and state that there is no association between beta-carotene and vitamin C levels lung function status. Fruit intake, as well as vitamin E levels seem to be protective, regarding mortality.[64] The authors, however, do not confirm the data, as they have no objective measurement of serum antioxidant levels.

The role of beta-carotene in asthma is not as convincing as in COPD. It seems that in childhood asthma the low levels of beta-carotene are not associated with lung inflammation.[65] Similar is the data, presented by Ricconi et al.[66] Fabian et al. compared a total of 35 asthmatic children and 21 healthy controls and have found that plasma levels of vitamins A and E, co-enzyme Q10 but not beta-carotene are positively associated with the oxidative state (measured by malon-dialdehyde level), as well as, with fractionated exhaled nitric oxide (FeNO). In contrast to this, Guo et al. state that the antioxidant supplementation (beta-carotene, vitamins C and E) for a month in adult asthmatics improves dysregulated oxidant and anti-oxidant status, inflammation and immune responses (hs-CRP, and CD19 and CD4/CD8 lymphocyte ratio, IgE levels), pulmonary function, and health-related quality of life in patients with mild to moderate allergic asthma.[67] Also, their asthma control and health-related quality-of-life scores have increased significantly. Wood et al. also detect an association between reduced circulating antioxidant defenses and airway hyper-responsiveness, poor asthma control and severe disease pattern. Whole-blood carotenoids (beta-carotene, lycopene, alpha-carotene, beta-cryptoxanthin, lutein/zeaxanthin) and tocopherols (alpha-, delta-, gamma-tocopherol) have been measured by high performance liquid chromatography in 41 stable asthmatics. Antioxidant potential has also been determined. Asthmatic subjects with airway hyper-responsiveness (AHR) had reduced levels of beta-carotene and alpha-tocopherol, compared with those without AHR. Subjects with uncontrolled asthma had low antioxidant potential, compared to those with controlled or partly controlled asthma. Subjects with severe persistent clinical asthma pattern have reduced levels of alpha-tocopherol, compared to those with a mild to moderate asthma pattern. Authors conclude that asthmatic subjects with AHR, uncontrolled asthma and a severe asthma pattern have impaired antioxidant defences.[68]

Lycopene

Lycopene attenuates the maturation of murine bone-marrow-derived dendritic cells. Dendritic cells (DC) are the most potent antigen-presenting cells. Their most important function is to initiate the immune response by presenting antigens to naive T lymphocytes. Kim et al. prove that lycopene down-regulates the expression of co-stimulatory molecules and major histocompatibility complex type II molecules.[69] They detect that lycopene-treated DC secrete low levels of interleukin-12, and do not stimulate T-cell proliferation. Kim et al. also show that lycopene treated dendritic cells are unable to induce a normal cell mediated immune response.[69]

In the PLAVA study, Riccioni et al. state that

plasma lycopene levels are lower in asthmatics.[70] Serum lycopene concentration has been significantly lower in asthmatic subjects than in healthy control subjects. Similar is the data, regarding serum vitamin A concentrations. Serum vitamin E and beta-carotene have not been different in the two groups. Hazelwood et al. have studied the effect of supplementation with lycopene in a mouse model of airway disease. They prove that it reduces eosinophilic infiltrates in blood, lung tissue and broncho-alveolar lavage fluid, as well as the mucus-secreting cell numbers in the airways. The release of Th2-associated cytokines IL-4 and IL-5 is also reduced.[71] This data is confirmed by Lee et al. They have described that administration of lycopene results in a significant inhibition of the infiltration of inflammatory immunocytes into the bronchoalveolar lavage, and attenuated the expression of eosinophil peroxidase. Lycopene reduces the increased levels of GATA-3 mRNA level and IL-4 expression in ovalbumin-challenged mice, but increases IFN-gamma expression.[72] Lycopene rich treatment may also influence non-eosinophilic inflammation. Wood et al. show that 10-day low antioxidant diet in asthmatics led to lower plasma carotenoid concentrations, worse Asthma Control Score; FEV%(1) and %FVC decrease, and higher percentage of sputum neutrophils. Twenty-one day treatment with both tomato juice and extract has led to reduced airway neutrophil influx and reduced sputum neutrophil elastase activity.[73] Data is confirmed by the fact that lycopene attenuates inflammation induced by rhinoviral infection , as well as lipopolysaccharide-stimulated inflammation in airway epithelial cells.[74] It suppresses the release of IL-6 and IFN-gamma, following exposure to lipopolysaccharide.

Vitamin C

Carcamo et al. have investigated the effect of vitamin C on GM-CSF–mediated responses.[75] The authors show that vitamin C modulates GM-CSF signaling responses. The application of vitamin C in cell lines inhibits the production of ROS, induced by GM-CSF, thus decreasing intracellular levels of ROS. Therefore, vitamin C indirectly regulates host defense cells and controls inflammatory responses. Being an antioxidant, ascorbic acid (AA) becomes oxidized to dehydroascorbic acid (DHA). Carcamo et al. have discovered that DHA, but not AA, directly inhibits IkappaB-alpha kinase beta (IKKbeta) and IKKalpha enzymatic activity in vitro, which leads to NF-κB inhibition. Authors prove that if cells are loaded with AA and induced to generate DHA by oxidative stress, NF-κB activation is inhibited. They depict a dual molecular action of vitamin C in signal transduction. AA quenches ROS intermediates involved in the activation NF-κB and is oxidized to DHA, which directly inhibits IKK-beta and IKK-alpha enzymatic activity.[76] Several large studies (Lowensohn et al., McEvoy et al.) prove that vitamin C supplementation prevent the effects of tobacco-smoke exposure on infant lung function and respiratory health during pregnancy.[77,78] Shorey-Kendrick et al. also demonstrate convincing data, regarding the beneficial effect of vitamin C supplementation. They describe that vitamin C prevents offspring DNA-methylation changes, associated with maternal smoking in pregnancy.[79] In adult asthmatics vitamin C role is largely debated. Some authors see no effect of vitamin C supplementation,[80] while others describe that vitamin C is important in alleviating exercise-induced asthma.[81] Himlah et al. have made a review analyzing the effect of vitamin C in asthma. They summarize that the beneficial effects of vitamin C are mostly demonstrated in enhanced oxidative stress conditions like in respiratory infections or exercise induced asthma.[82]

Resveratrol

Phytoalexin or resveratrol is a component of grapes, wine, soy and peanuts. It possesses antiageing, anti-inflammatory, anticancer and neuroprotective effects. Its biological action is mediated by Sirtuin-1 – SIRT1; resveratrol increases its levels.[83] Resveratrol binds to SIRT1 and deacetylates RelA/p65 subunit of NF-κB.[84] This inhibits the transcription of pro-inflammatory genes. SIRT1 deficiency abolishes the anti-inflammatory effect of resveratrol, which means that is a necessary precondition.[85] By means of this reaction resveratrol has been reported to neutralized the inflammatory effect induced by cigarette exposure. Bound to SIRT1 resveratrol induces the association between SIRT1 and p300. This inhibits NF-κB acetylation and nuclear translocation.[86] Resveratrol activates Nrf2 and exhibits itself radical scavenging effects.[87] Activating SIRT1, resveratrol reduces MMP-9 and lung autophagy. Resveratrol mitigates the release of inflammatory cytokines and MMP-9.[88] Its anti-inflammatory effects are suggested as more potent than corticosteroids.[89] The poor clinical application is explained by low bioavalibility, because of extensive metabolism in the intestine and liver, despite of good resorption -

75%. Variable approaches are suggested to facilitate its clinical application.

Curcumin

Diferuloylmethane - curcumin is a component of Curcuma longa, which is known as turmeric and Indian saffron. Curcumin has a pleiotropic role and is capable of interacting with numerous molecular targets - transcription factors, cytokines, protein kinases, and other enzymes involved in epigenetic regulation. It is suggested that curcumin shifts the histone acetylation/deacetylation balance and thus exhibits its anti-inflammatory activities. It is a specific p300/CBP-HAT inhibitor, and has no effect, regarding methyltransferase activities.[90] It is assumed that curcumin envelopes not only the active site of p300/CBP, but also other domains, thus changing its conformation.[90] It effectively represses the acetylation of non-histone proteins. Curcumin inhibits acetylation (inhibiting p300/CBP) and simultaneously activates deacetylation HDAC2.[91] This abrogates NF-κB-DNA binding and prevents inflammation. The activation of HDAC2 is supported in experiments with monocytes.[93] Having in mind that corticosteroids act by means of HDAC2 recruitment and that cigarette-smoke down-regulates its expression it seems that curcumin-mediated HDAC2 restoration is of paramount importance for their therapeutical effects.[92] The epigenetic effects of curcumin are exhibited by regulation of microRNA expression.[93] Curcumin has anti-inflammatory actions by directly inhibiting IKK, which is responsible for the degradation of the inhibitory protein κB.[94] Thus, NF-κB activation cannot be released from the complex. So, curcumin blocks the inflammatory effects of NF-κB, by inhibiting its release, acetylation, DNA-binding and transcription initiation.

Similarly to resveratrol, curcumin exhibits potent anti-oxidant activity. It scavenges the free radicals and activates Nrf2-mediated expression of anti-oxidant genes, such as heme oxygenase-1, glutathione peroxidase, modulatory subunit of glutamyl-cysteine ligase, and NAD(P)H quinone oxido-reductase 1.[95] Few clinical studies have shown that oral intake of curcumin has anti-inflammatory effects. It is safe at the dose of 12 g/day. Its low bioavailability is the major disadvantage for the use of curcumin as a therapeutic drug. Its hydrophobic nature, leads to poor absorption. Curcumin has also rapid metabolism and rapid systemic clearance, contributing to low plasma and tissue levels.

Catechins

Catechins are the major component of the green tea extract. There are several isomers of catechins - catechin, catechin gallate, gallocatechin, gallocatechin gallate, epicatechin, epicatechin gallate, epigallocatechin, and epigallocatechin gallate (EGCG). EGCG is the most effective. It is a specific inhibitor of HAT. Its anti-inflammatory effect is mediated by the inhibition of p300-mediated acetylation of NF-κB.[96] It also inhibits the binding of p300 to the pro-inflammatory gene promoter of NF-κB.[97] EGCG has poor oral bioavailability due to limited absorption. Its dietary intake improves lung function (as measured by FEV1) and reduces chronic cough, breathlessness, and sputum in COPD.[59]

Garcinol

Garcinol is derived from kokum (Garcinia indica) fruit. It is a non-specific inhibitor of CBP/p300 and HATs. Garcinol inhibits acetyl-transferase activity by binding with histones and acetyl-Co-A binding sites of HAT.[98] The anti-inflammatory activity of garcinol is mediated by the disruption of interaction between HAT and NF-κB.[99] It down-regulates gene expression by repressing chromatin transcription.

Anacardic acid

Anacardic acid is derived from cashew nuts. It inhibits CBP/p300 and HAT activity. Anacardic acid interferes with NF-κB pathway by preventing acetylation and NF-κB activation.[100] Knock-down of p300 HAT-abrogated the anti-inflammatory effect of anacardic acid.[101]

CONCLUSIONS

Epigenetic mechanisms are of key importance for mediating cellular responses under various stress conditions. The respiratory system is constantly under various stressors - chemical irritants and air pollutants. There is emerging evidence that epigenetic changes (DNA-methylation, post-translational histone modification and aberrant expression of miRNA) are of paramount importance in respiratory medicine. They all contribute to the pathogenesis of pulmonary diseases. It is plausible to apply activators or inhibitors to the enzymes that catalyze methylation or acetylation. The therapeutic interest, regarding miRNA is even larger. miRNA mimicry or antagomirs are novel therapeutic tools, successfully applied not only in respiratory medicine. While all these therapeutic approaches are in experimental

phase, and seem illusive, accumulating data, regarding the effects of natural compounds, unveils the possible role of nutrigenomics in clinical practice.

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Эпигенетические „мишени“ для терапевтических подходов при ХОБЛ и астме. Нутригеномика - возможна или иллюзорна

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Оксидативный стресс, вызванный курением, загрязнением окружающей среды или другими вредными частицами, вызывает эпигенетические изменения в клетках дыхательных путей. Они отражают клеточную адаптацию в ответ на хроническое воздействие внешних факторов. Хотя в генетическом коде нет изменений, эпигенетические изменения могут быть унаследованными и передаваться из поколения в поколение, накапливая аномалии и превращая клетки в совершенно другой фенотип, вызывая тем самым заболевание. Метилирование ДНК, посттрансляционная модификация гистонов, убиквитинирование, сумоилирование и транскрипционная регуляция микроРНК являются основными процессами эпигенетического контроля экспрессии генов. Все они обратимы. Они могут регулироваться путём нацеливания на конкретные ферменты / белки, участвующие в процессе, для уменьшения воспаления. Хронические респираторные заболевания имеют эпигенетические признаки, которые влияют на экспрессию генов в лёгких. Их исследование привело бы к разработке новых диагностических и терапевтических подходов в респираторной медицине. Нутригеномика выявляет полезные эффекты природных фитохимических веществ, тем самым влияя на ключевые этапы сигнальных путей хронического заболевания лёгких.