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Mucociliary transport as a link between chronic rhinosinusitis and trace element dysbalance

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ABSTRACT

Chronis rhinosinusitis is considered as a widespread public health issue with a prevalence of 10%. The disease significantly reduces quality of life and increases the risk of cardiovascular diseases as well as certain forms of cancer. Alteration of mucociliary clearance frequently observed in the patients and plays a significant role in disease pathogenesis. Certain studies have demonstrated that patients with chronic rhinosinusitis are characterized by significant reduction of essential trace elements and toxic metal overload. However, the particular mechanisms of the role of trace element dysbalance in chronic rhinosinusitis are unclear. We hypothesize that exposure to toxic trace elements (arsenic, nickel, cadmium) damages ciliary mucosal epithelium thus affecting mucociliary transport. In turn, altered mucociliary transport results in reduced removal of the inhaled metal-containing particles from nasal mucosa leading to their absorption and further aggravation of toxicity. Essential trace elements (zinc, selenium) play a significant role in regulation of mucociliary transport and immunity, thus their deficiency (either dietary or due to antagonism with toxic metals) may be associated with impaired functions and increased toxic metal toxicity. Therefore, a vicious circle involving metal accumulation and toxicity, essential element deficiency, impairment of mucociliary transport and metal particle removal, resulting in further accumulation of metals and aggravation of toxic effects is formed. The present hypothesis is supported by the findings on the impact of trace elements especially zinc and arsenic on mucociliary clearance, the role of mucociliary transport in heavy metal particles elimination from the airways, trace element dysbalance in chronic rhinosinusitis, as well as toxic and essential metal antagonism. The data from hypothesis testing and its verification may be used for development of therapeutic approach for management of chronic rhinosinusitis. Particularly, the use of essential elements (zinc, selenium) may reduce toxic metal toxicity thus destroying the vicious circle of heavy metal exposure, toxicity, alteration of mucociliary clearance, and aggravation of chronic rhinosinusitis. Essential element supplementation may be considered as a tool for management of chronic refractory rhinosinusitis. In addition, analysis of essential and toxic trace element status may provide an additional diagnostic approach to risk assessment of chronic rhinosinusitis in highly polluted environments.

Introduction

Chronic rhinosinusitis is a group of different of disorders characterized by mucosal inflammation in the nose and paranasal sinuses of at least 12 weeks' duration [1]. Chronis sinusitis is considered as a widespread public health issue. A study in seven Chinese cities demonstrated that the prevalence of chronic rhinosinusitis varies from 4.8% to 9.7% with an average prevalence of 8% [2]. The results of GA^{2}LEN demonstrated that the overall prevalence of CRS may achieve as much as 10.9% [3]. In turn, the prevalence of CRS in the USA population was estimated to be 12.5% [4]. It is notable that the prevalence of chronic rhinosinusitis exceeds that for any chronic

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inflammatory condition in patients under 45 y.o. [5]. It also accounts for 7.1% of all adult outpatient antibiotic prescriptions [6].

Medico-social impact of chronic rhinosinusitis

Certain studies have demonstrated the impact of chronic rhinosinusitis on quality of life [7] with otologic/facial pain and sleep-related symptoms being the key drivers [8]. At the same time, women with chronic sinusitis had significantly lower quality of life than men [9].

Analysis of comorbidity profile of chronic rhinosinusitis revealed higher the association with asthma, chronic pulmonary disease, obesity, weight loss, as well as migraines [10]. Particularly, a strong association between chronic rhinosinusitis and asthma (OR: 3.47; 95% CI: 3.20–3.76) has been revealed [11]. Chronic rhinosinusitis is also known to increase the risk of cardiovascular diseases. Particularly, patients with chronic sinusitis have 34% higher risk of ischemic but not hemorrhagic stroke [12]. In addition, the risk of myocardial infarction in patients with chronic rhinosinusitis was 70% and 48% higher before and after adjustment for cardiovascular risk factors in a 6-year follow-up period [13]. Pediatric chronic rhinosinusitis is characterized by additional adverse health effects [14].

Due to the high prevalence, as well as the effects on healthy and quality of life the costs of rhinosinusitis are rather high. It has been demonstrated that annual productivity cost associated with chronic rhinosinusitis is $10,077 per patient [15].Taken together with outpatient visits, pharmacy fills, urgent visits, hospital days, the total costs of chronic rhinosinusitis in the USA was considered to be $4.3 billion in 1994 [16]. In a more recent study direct healthcare costs accounted for $8.6 billion [6]. Both direct and indirect costs of chronic rhinosinusitis were estimated to be $22 billion in 2014 [17]. Even higher values exceeding $60 billion were calculated for 2011 based on the data from US Medical Expenditure Panel Survey [18].

Taking into account a high medico-social impact of chronic rhinosinusitis, intensive studies aimed at assessment of novel pathogenetic mechanisms and potential targets are highly required.

Mucociliary transport in chronic rhinosinusitis pathophysiology

Mucociliary clearance provides the first-line defense mechanism of innate immunity consisting of mucous layer, airway surface liquid layer, and ciliary epithelia. Mucus produced by goblet cells of the mucosa is required for binding of the airborne pathogens. Permanent beating of cilia moves the xenobiotic-containing mucus to the pharynx where it is either expectorated or swallowed [19]. Normal functioning of the mucociliary clearance requires high frequency, coordinated, and directional ciliary beating (metachronal waves), as well as proper airway surface liquid and mucus secretion [20]. Ciliary beat frequency was shown to be the key determinant of mucociliary transport efficiency [21].

Chronic rhinosinusitis is associated with ciliary dysfunction due to a variety of factors including environmental, mechanical, infectious, or inflammatory stimuli [22]. It has been demonstrated that in patients with chronic rhinosinusitis exogenously applied adenosine triphosphate did not result in a significant ciliary beat frequency, whereas a significant 50–70% increase was observed in healthy examinees [23]. Abnormalities of ciliary ultrastructure including pathology of axoneme membrane, compound cilia, and impaired ciliary orientation were shown to be associated with reduced ciliary beat frequency (8.5 Hz vs 11.75 Hz, $p < 0.05$) in experimental chronic rhinosinusitis [24]. Similar findings were obtained during examination of patients with severe chronic rhinosinusitis. Particularly, 28% of patients had no cilia, although foci of normal ciliated epithelium were observed only in 19% of all examinees. Ultrastructural defects of ciliated epithelia included compound cilia and microtubule and dynein arm defects associated with a reduction of differentiated epithelial cells [25]. Proinflammatory signals produced in chronic rhinosinusitis including IFN-γ, IL-13, and IL-17 significantly reduced ciliary beat frequency and mucociliary differentiation of nasal epithelial cells as assessed by β-tubulin IV being a specific cilia marker [26].

Mucociliary clearance is also dependent on mucus properties. Increased mucin (MUC5AC) production in chronic rhinosinusitis due to IL-5 [27], IL-13 [28], and IL-19 [29] may result in excessive mucus production also resulting in decreased mucociliary clearance [19]. Correspondingly, an in-depth proteomic analysis demonstrated upregualtion of Mucin 5AC and 5B genes in chronic sinusitis with nasal polyps as compared to the controls [30].

As a result, alteration of mucociliary clearance results in reduced evacuation of the airborne pathogens and/or pollutants thus resulting in their persistence and sinonasal inflammation through a variety of mechanisms [31–33]. Therefore, improvement of mucociliary clearance is beneficial in chronic rhinosinusitis patients with impaired munociliary transport [32].

Trace element status of chronic rhinosinusitis patients

A number of studies has demonstrated the role association between trace element metabolism and nasal pathology in general and chronic sinusitis in particular. Examination of 24 children with chronic rhinosinusitis demonstrated a significant decrease in serum levels of zinc and copper as well as vitamin E and C deficiency [34]. Another study demonstrated a significant reduction in circulating copper levels in 43 chronic rhinosinusitis patients [35]. Our recent data demonstrate a significant elevation of hair arsenic and beryllium [36] as well as platinum, gallium, thallium, and zirconium [37] levels in children with chronic rhinosinusitis. These data generally corroborate the observed association between occupational metal exposure and chronic rhinitis and sinusitis [38,39].

Hypothesis

Exposure to toxic trace elements (arsenic, nickel, cadmium) damages ciliary mucosal epithelium thus affecting mucociliary transport. In turn, altered mucociliary transport results in reduced removal of the inhaled metal-containing particles from nasal mucosa leading to their absorption and further aggravation of toxicity. Essential trace elements (zinc, selenium) play a significant role in regulation of mucociliary transport and immunity, thus their deficiency (either dietary or due to antagonism with toxic metals) may be associated with impaired functions and increased toxic metal toxicity. Therefore, a vicious circle involving metal accumulation and toxicity, essential element deficiency, impairment of mucociliary transport and metal particle removal, resulting in further accumulation of metals and aggravation of toxic effects is formed (Fig. 1).

Hypothesis validation

Trace element metabolism in chronic rhinosinusitis and nasal pathology

Certain studies demonstrated alteration of trace element metabolism in chronic rhinosinusitis. Particularly, the latter was shown to be associated by impaired Zn metabolism characterized by down-regulation of metallothionein and zinc influx transporter genes [40], whereas Zn efflux transporter gene was found to be up-regulated. Moreover, these changes were associated with altered zonula occludens 1 (ZO-1) protein expression [40]. Zinc levels were found to be significantly elevated in nasal exudates from women with both acute and chronic rhinosinusitis [41]. Certain studies have demonstrated the interaction between trace element metabolism and nasal polyposis, being tightly associated with chronic rhinosinusitis [42]. Particularly, nasal polyp tissue was characterized by reduced levels of selenium, zinc, copper, and lead as compared to the healthy tissue obtained from donors [43]. Depression of Se and Zn levels in nasal polyp tissue was also associated

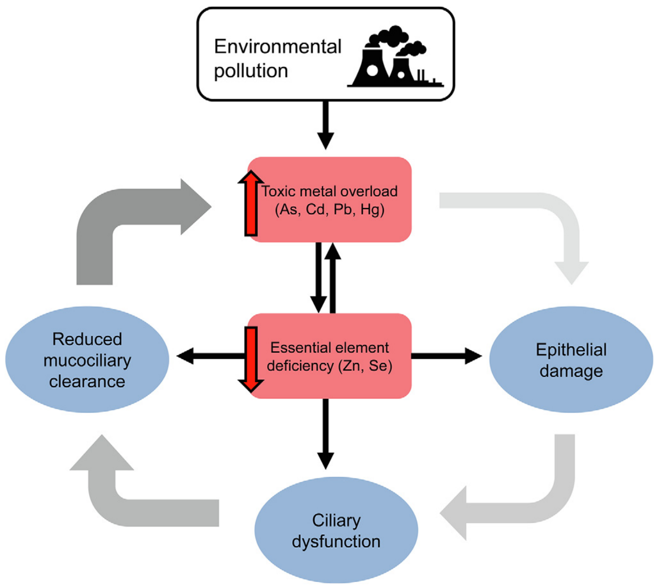

Fig. 1. The proposed mechanism of the role of toxic and essential trace element antagonism in modulation of mucociliary clearance and chronic rhinosinusitis pathogenesis. Toxic trace element exposure results in inflammation, oxidative stress, and alteration of mucociliary clearance. Impairment of essential trace element metabolism (especially zinc) known to play a significant role in ciliary functioning also contributes to reduced mucociliary clearance. The latter in turn results in reduced elimination of toxic metals from the airways thus forming a vicious circle including toxic metal exposure, essential trace element deficiency, inflammation, impaired mucociliary clearance and further accumulation of heavy metals and metalloids. Dietary insufficiency of essential elements may also increase susceptibility to accumulation of toxic metals and chronic rhinosinusitis risk.

with impaired antioxidant enzyme activity [44]. Gene expression profiling also demonstrated a significant down-regulation of zinc alpha2-glycoprotein expression in polyp tissue in chronic rhinosinusitis [45]. At the same time, Khlifi et al. [46] demonstrated a marked accumulation of cadmium, chromium, nickel, and arsenic levels in nasal polyp tissue [46]. Moreover, the authors have also revealed a reliable elevation of blood As concentration in nasal polyp patients, being 75% higher (2.1 μg/l vs 1.2 μg/l) as compared to the control values [47].

Allergic rhinitis is interrelated with pathogenesis of chronic rhinitis [48]. Several studies have been performed to reveal the potential association between trace elements and allergic rhinitis. Examination of 22 patients with allergic rhinitis in comparison to allergic and non-allergic asthmatics, as well as controls demonstrated reduced copper but not zinc levels in blood plasma, being associated with decreased Cu, Zn-SOD activity [49]. At the same time, another study revealed reduced serum levels of Mg and Sr, whereas the concentration of Zn, Cu, Fe, Ca, and Mn remained unaltered [50]. The results from Osaka Maternal and Child Health Study also demonstrated an inverse association between calcium, magnesium, and phosphorus, but not zinc intake and allergic rhinitis in pregnant women [51].

Therefore, although being sometimes contradictory the existing data definitely indicate a significant interrelation between trace element metabolism and nasal pathology, although the mechanisms are generally unclear.

The impact of trace elements on mucociliary transport

Toxic trace elements

The ability of airborne pollutants to impair mucociliary clearance was first reviewed in a detailed study by Wolff [52]. Further it has been demonstrated that chronic exposure to a mixture of pollutants in Southwest Metropolitan Mexico City resulted in a significant decrease in ciliated cells in nasal mucosa biopsies. Moreover, the most significant alterations in ciliary epithelia were associated with p53 expression [53]. At ultrastructural level these changes were associated with absence of central microtubules, supernumerary central and peripheral tubules, as well as ciliary microtubular discontinuities [54]. Inhalation of a mixture of pollutants released from biomass burning also affected nasal mucociliary clearance [55]. Experimental studies also demonstrated a complex negative effect of pollutant exposure on ciliary epithelia [56–58]. Therefore, the existing studies demonstrate the effect of atmospheric pollution and airborne pollutant exposure on mucociliary clearance. At the same time, a particular role of heavy metals and metalloids in alteration of mucociliary transport is insufficiently studied, although first indications appeared more than 40 years ago [59].

Adverse effects on mucociliary transport and upper airway epithelia was demonstrated for arsenic (As). Particularly, in has been demonstrated that in utero As exposure significantly affected expression of genes in the lung involved in mucus production, innate immunity, as well as lung morphogenesis in C57BL/6 mice [60]. The mechanisms of As-induced impairment of innate immunity and damage repair in airway epithelial cell may also include alteration of ATP-Dependent Ca^{2+} Signaling [61,62]. As exposure was shown to induce ubiquitin-dependent degradation of cystic fibrosis transmembrane conductance regulator (CFTR) playing a significant role in mucociliary clearance [63]. In addition, Cd exposure was shown to disrupt tight junction integrity [64] that is also essential for proper mucociliary clearance [65]. Therefore, it has been proposed that the increased susceptibility to infections in response to in utero and early life As exposure may be associated with impaired mucociliary clearance and other toxic effects of arsenic on airway epithelia [66].

The effect of cadmium on ciliary activity was largely demonstrated in trachea organ cultures [67]. Particularly, exposure to 10 μM Cd acetate resulted in a complete impairment of ciliary activity within 5 h. It is also notable that this effect was prevented by sodium selenite treatment [68]. A later study by the authors demonstrated that Cd has the most significant adverse effect on ciliary apparatus of trachea as compared to other toxic metals (Hg, Pb) [69]. Alteration of mucociliary clearance in response to Cd treatment being characterized by decreased cilia beat frequency and aberrant mucin production was demonstrated in an in vitro human airway tissue model [70]. Cd-induced induction of mucin expression [71] may also contribute to decreased mucociliary clearance [72]. Cadmium-containing tobacco smoke was also shown to reduce the rate of nasal mucociliary clearance as assessed by saccharin transit time [73].

It has been also demonstrated that platinum and palladium exposure has a significant negative effect on ciliary epithelia of the upper airways [74]. Particularly, platinum chloride exposure was shown to decrease cilia beat frequency in a dose-dependent manner due to impaired ciliary structure [75].

Data on the usefulness of *N*-acetylcysteine, a heavy metal antagonist [76], in treatment of chronic rhinosinusitis and improvement of ciliary function [77] also indirectly supports the potential effect of heavy metal removal in chronic sinusitis.

Essential trace elements

The role of essential trace elements in the functioning of mucociliary barrier may be mediated via their antioxidant and anti-inflammatory functions as well as specific functions of metalloproteins.

The most significant data were accumulated for the role of zinc in mucociliary clearance [78] that is at least partially confirmed by an observation of localization of Zn largely in ciliary basal bodies of airway epithelia [79]. Particularly, zinc plays a significant role in the functioning of the upper airway epithelia as evidenced by high rate of ZnT4 expression [80]. It has been demonstrated that Zn treatment significantly improves mucociliary clearance and increases in ciliary beat frequency (22.4 ± 4.33 Hz vs basal 5.99 ± 3.16 Hz) through Ca^{2+} dependent mechanisms and P2X receptor activation [81]. At the same time, Zn chelation resulted in a significant 25% decrease in ciliary beat frequency in nasal and bronchial epithelia [80]. The latter may be associated with Zn-mediated protection of tubulin sulfhydryl groups [80] and reduced proapoptotic signaling [79]. It has been demonstrated that Zn as well as ascorbate and N-acetylcysteine reduce oxidative stress in nasal mucosa tissue cultures [82]. Antioxidant function of zinc was shown to be tightly associated with protection of ciliary microtubules from oxidative stress as well as regulation of apoptosis in ciliary epithelia through procaspase-3 [83].

Although selenium deficiency did not impair mucociliary differentiation and epithelial cell morphology, it was associated with increased mucus production and increased Muc5AC mRNA levels having a negative effect on mucociliary clearance [84]. These data correspond to the observed effects of selenium irrigation including reduced mucosal edema, microvascular permeability, as well as LPS-induced Muc5ac expression [85].

Role of mucociliary transport in inhaled metal particle elimination

Mucociliary clearance is a mechanism of innate immunity aimed at removal inhaled xenobiotics from the airways [18]. In parallel with elimination of bacterial pathogens [86] it is also required for removal of environmental pollutants including metals [87]. Particularly, the role of mucociliary clearance in metal elimination was demonstrated for nickel [87], cadmium [88], lead [89], and arsenic [90]. Although once being removed from the airways the metals are swallowed into gastrointestinal tract and may be absorbed, the bioavailability of metals in gastrointestinal tract is much less than that in lungs. Particularly, only 5% of Cd is absorbed from gastrointestinal tract, whereas its absorption from alveoli may achieve 100% [91]. In turn, gastrointestinal absorption of nickel varies from 1 to 10% [92]. Alteration of mucociliary transport mechanism results in increased absorption of metal-containing particles in lungs and higher risk of toxicity [93].

Chemical and functional antagonism between essential and toxic elements

Multiple studies have demonstrated the interaction between essential and toxic trace elements. Particularly, the most significant antagonism was observed between essential zinc and selenium and toxic mercury, arsenic, cadmium, and lead.

The interplay between zinc and arsenic is of particular interest in view of the existing data on the role of these elements in regulation of mucociliary clearance. Particularly, Zn was shown to prevent teratogenic effects of prenatal As exposure [94] that may be associated with modulation of As-induced DNA damage mechanisms [95], oxidative stress [96,97], metallothionein synthesis [98], and inflammatory response [99]. Zinc and arsenic differentially affect NF-kB thus having an opposite effect on inflammation [100]. At least a part of the effects mediating antagonism between zinc and toxic metal(loid)s may be associated with binding of metal ions to zinc finger proteins [101]. Particularly, As was shown to bind zinc finger proteins with different zinc binding motifs [102], e.g. DNA repair protein poly(ADP-ribose) polymerase-1 (PARP-1) [103].

The interaction between mercury and selenium is the one of the most studied between all trace elements. It has been demonstrated that the affinity of mercury to selenol groups (–SeH) is higher than that for sulfhydryl groups [104]. Mercury and selenium interact in vivo with a formation of various compounds including $(MeHg)_2Se$, MeHg-selenol compounds, HgSe, $(HgSe)_n$-SelP [105]. Such interaction decreases Se bioavailability for selenoprotein synthesis, although being a mechanism of mercury detoxication [106]. Se-Hg antagonism also involves modulation of redox environment and inflammation [107].

Se is also known as a potent antagonist of arsenic. Particularly, selenium may counteract As toxicity through direct interaction with the formation of As-Se compound ($[(GS_3)_2AsSe]^-$) that is readily excreted [108]. In turn, As exposure was shown to affect selenoprotein expression resulting in oxidative stress and endoplasmic reticulum stress [109,110]. In turn, selenium status has a significant impact on arsenic methylation capacity and the resulting toxicity outcomes [111]. At the same time, under certain conditions including high Se concentration it can increase As toxicity [112].

Molecular antagonism between cadmium and zinc is largely based on physicochemical properties of the metals resulting in displacement of Zn^{2+} from active sites of the enzymes by Cd^{2+} ions [113,114], as well as modulation of ZIP Zn transporters [115]. In addition, Cd and Zn may mutually affect their handling in the organism through modulation of metallothionein synthesis [116]. Interactive effects of Cd and Zn were shown to have a significant impact on oxidative stress, inflammation, apoptosis, DNA repair [117–119].

Certain studies demonstrated the antagonistic effect of lead and selenium [120–122] and zinc [123–125]. Interaction of lead ions with zinc finger proteins [126] and selenoproteins [127] may also underlie Se-Pb and Zn-Pb interactions.

Perspectives

The data from hypothesis testing and its verification may be used for development of therapeutic approach for management of chronic rhinosinusitis. Particularly, the use of essential elements (zinc, selenium) may reduce toxic metal toxicity thus destroying the vicious circle of heavy metal exposure, toxicity, alteration of mucociliary clearance, and aggravation of chronic rhinosinusitis. Supplementation with Zn or Se can be considered in regions or individuals with deficiency, also as a tool for management of refractory rhinosinusitis. Trace element supplementation may be also used in addition to antibiotic and corticosteroid treatment to reduce the number of adverse effects and increase efficiency of therapeutic management of chronic rhinosinusitis. In addition, analysis of essential and toxic trace element status may provide an additional diagnostic approach to risk assessment of chronic rhinosinusitis in highly polluted environments.

Conflict of interest

The authors declare no conflict of interest.

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