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Pathophysiological aspects of exposure to dampness-associated indoor mould and mycotoxins: A mini-overview

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ABSTRACT

Indoor mould growth presents a potential health risk. The aim of this writing is to provide an overview on the pathophysiological aspects of exposure to dampness-associated indoor mould and mycotoxins. The paper briefly deals with the host's defence against mould invasion; mechanisms by which moulds can override the host's defence mechanisms; potential adverse health effects posed by moulds, as well as symptoms and disorders associated with exposure to indoor moulds, including respiratory disorders, and non-respiratory disorders. References to recent in-depth reviews on specific aspects of the subject are provided. The prominent role of the inflammatory response, both as a defence mechanism against mould invasion and as the basis for mould-associated pathology is pointed out.

1. Introduction

Moulds are filamentous fungi. Their spores may germinate into multicellular filamentous structures (hyphae), which can grow further into complex networks known as mycelia. Depending on the species, the strain and environmental conditions, moulds can produce products such as mycotoxins and proteases (Holme et al., 2020). Damp surfaces and high levels of relative humidity provide conditions favourable for the indoor growth of mould. Exposure to such damp-associated indoor mould particles and metabolites may contribute substantially to the burden of respiratory disease (World Health Organization, 2009).

A variety of different mould genera and species have been reported in mould infested buildings. According to the Nationaenter for Environmental Health (NCEH) of the Centers for Disease Control and Prevention (NCEH, 2022), the most common indoor mould genera are Cladosporium, Penicillium, and Aspergillus (Centers for Disease Control and prevention (CDC), 2022). Species commonly reported for damp indoor environments include *Penicillium chrysogenum, Aspergillus versicolor, Stachybotrys chartarum,* and *Aspergillus fumigatus* (Holme et al., 2020). However, the potential range is much wider, for instance, 18 different mould species were recently reported when 51 samples of building material samples from naturally mould-infested buildings (24 households) in the north-west of Germany were examined. Moulds of the genera Penicillium and Aspergillus were omnipresent (Lindemann et al., 2022).

Mycotoxins are secondary metabolites, frequently produced by moulds in water-damaged indoor environments. The potential diversity of mycotoxins in indoor environments is illustrated in the results of the north-west Germany study previously referred to (Lindemann et al., 2022). In the study, 38 secondary metabolites derived from indoor mould genera like *Aspergillus, Fusarium, Penicillium,* and *Stachybotrys* were tested for, and 16 different mycotoxins detected. Many of the mycotoxins known to affect the health of humans are products of the genera *Aspergillus, Fusarium, Penicillium,* Trichoderma and Stachybotrys (United States Environmental Protection Agency, 2013). Mycotoxins from water-damaged indoor environments with reported relevance to health include, but are not limited to, metabolites such as ochratoxins, gliotoxins, aflatoxins, sterigmatocystin, and the trichothecenes (e.g., T2 toxin, deoxynivalenol, and the macrocyclic trichothecenes, satratoxin and verrucarin) (Hope et al., 2013; Wu et al., 2022).

Figures given for exposure to indoor dampness, and dampness-associated indoor mould, vary, depending on factors such as the quality of housing, housing maintenance, occupant lifestyle, occupant density, climate, the season in which the survey is carried out, as well as the way in which the survey is performed. As far back as 2009 the World Health Organization (WHO, 2009), estimated that 10%–50% of home environments in Europe, North America, Australia, India and Japan, are damp. Three years later a meta-analysis, taking into account regional and climatic differences, as well as differences in study design, methodology and definitions, in houses from 31 European countries, reported weighted prevalence estimates of 12.1% for dampness, 10.3% for

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mould, 10.0% for water damage, and 16.5% for combinations of two or more indicators (Haverinen-Shaughnessy, 2012). By 2020 in a review on mould growth in energy efficient buildings, it was estimated that the proportion of buildings damaged by mould is 45% in Europe, 40% in the USA, 30% in Canada and 50% in Australia (Brambilla and Sangiorgio, 2020). According to a review by Coulburn and Miller (2022), of what is described as relatively recent prevalence studies, dampness and indoor mould occur in up to 21% of European homes, up to 27% of homes in Northern Europe, up to 47% of American homes, in 12–78% of New Zealand homes and between 12 50% in China.

Thus far the majority of epidemiological reports on the prevalence of dampness and dampness-associated mould infestations are based on questionnaires, walk-through observations, expert inspections, or observational assessment methods such as the Dampness and mould Assessment Tool developed by the National Institute for Occupational Safety and Health (Park et al., 2022). However, recently, where practical and financial considerations permitted, high throughput sequencing studies further expanded the scope by allowing for identification and quantifying of, not only visible, but also nonvisible mould growth in water-damaged buildings (Sun et al., 2022; Sylvain et al., 2019).

The aim of this writing is to provide a brief overview on the pathophysiological aspects of exposure to dampness-associated indoor mould and mycotoxins. Aspects of the pathophysiology dealt with include the host's defence against mould invasion; mechanisms by which moulds can override the host's defence mechanisms; the adverse health effects of moulds and mould-derived particles, including symptoms and disorders associated with exposure to indoor moulds.

2. Methods

Scientific databases were searched, including Embase, PubMed, MEDLINE, APA PsychInfo, Academic Search Complete, Scopus, TOC Premier, and CINAHL. Access to the majority of the databases was obtained through EBSCOhost. Searches were also performed by hand and links obtained from cross references. In addition, separate searches were run on the involvement of inflammation [Search terms (moulds or molds) and (inflammation or inflammatory or inflammation response)], and on potential neurological and/or neuropsychiatric effects of mould exposure [Search terms (moulds or molds) and (brain or neuro or neural)]. Published dates were from 2011. Interface - EBSCOhost research databases included Academic Search Complete; APA PsycArticles; APA PsycInfo; CINAHL and MEDLINE.

3. Host defence against mould invasion

The first line of defence against invading moulds are the skin and the mucosal barriers, including the associated physiological microbiotica and secreted antimicrobial substances such as β-defensins, cathelicidins, surfactant proteins, lysozyme, lactoferrin, and mucins (Żelechowska et al., 2021). With airborne dampness-associated mould exposure, tight junctions and trapping of particles by mucus and removal by the muco-ciliary escalator are important. The innate immune response associated with mould exposure starts with recognition of mould particles and products by pattern recognition receptors (PRRs). In general, PRRs are said to detect structures on pathogens, known as pathogen-associated molecular patterns (PAMPs), and structures associated with damage caused by pathogens, known as damage associated molecular patterns (DAMPS). Pattern recognition receptors, expressed on innate immune cells and respiratory epithelial cells, recognize and react with these components on the surface of mould particles and secretory products to stimulate innate immune activities such as recruitment of innate immune cells; phagocytosis; production of reactive oxygen species; production and release of pro-inflammatory cytokines and other inflammatory mediators, including inflammasomes, a family of proteins involved in the induction of inflammation (Bartemes and Kita, 2018; Drummond et al., 2014). Relevant to activation of the pro-inflammatory response are those PRRs involved in stimulation of pro-inflammatory antifungal immunity including TLR-2 (involved in increases of pro-inflammatory cytokines); Dectin-1 (involved in stimulating NF-κB signalling, inflammasome activation, phagocytosis and production of reactive oxygen species); Dectin-2 (involved in increasing pro-inflammatory cytokines); Mincle (involved in pro-inflammatory cytokine increases and stimulation of Th17); the mannose receptor (involved in pro-inflammatory cytokine increases), complement receptor 3 (stimulation of Th17) and DC-SIGN (involved in increases in pro-inflammatory cytokines) (Burgess et al., 2022; Drummond et al., 2014). Innate immune responses following upon the pattern recognition process not only play a major role in innate antifungal immunity, but also help initiate and shape the adaptive antifungal immunity, including Th1-, Th2-, and Th17-type $CD4^+$ T cell activity (Bartemes and Kita, 2018). The reader is referred to the paper by Bartemes and Kita (2018) for a review on innate and adaptive immune responses to airway fungi.

Despite some controversial issues regarding immunity against moulds found in damp indoor conditions (Rudert and Portnoy, 2017), it is generally accepted that the inflammatory response forms an essential part of both the innate and adaptive defence systems, that several indoor mould species can elicit strong inflammatory reactions, but when uncontrolled, these defence mechanisms form the basis for a large part of the immunopathology associated with mould exposure (Bartemes and Kita, 2018; Vincent et al., 2017).

4. Mechanisms by which moulds can override the host's defence mechanisms

Mould particles and especially mycotoxins, can modulate the innate and adaptive immune systems of the host in various ways. Mycotoxins can, for instance, compromise the structural integrity of mucosal and other barriers; eliminate favourable microbiotica, suppress macrophage phagocytosis and NO production; suppress neutrophil activation, chemotactic activity and oxidative burst; and inhibit the synthesis and release of reactive oxygen species, chemokines and pro-inflammatory cytokines (Brown et al., 2021). Under conditions of dysregulated or immunocompromised immunity, mycotoxins have similarly been shown to impair barrier functions of organs such as the respiratory system and the blood brain barrier by, for instance, causing epithelial cell death, compromising the integrity of tight junctions, cytoskeletal remodelling, suppression of ciliary function; restricting the activity of microbiotica; and by suppression of immune functions such as inflammatory processes meant to protect the host from mould invasion (Kraft et al., 2021). Various mould species and mycotoxins are implicated in immune suppression, for example, results from a 2022 study on the potential risk of damp building microbiota, including Aspergillus species, showed immune-suppression through secretion of mycophenolic acid, a potential immunosuppressant (Vaali et al., 2022). Suppression of the inflammatory response, *per se,* has been shown for the *Aspergillus* mycotoxins aflatoxin B1 and gliotoxin (Bossou et al., 2017), and for alternariol, a secondary metabolite formed by *Alternaria alternata* (Kollarova et al., 2018). The latter appears to suppress the lipopolysaccharide-induced inflammation in THP-1 derived macrophages through targeting of the NF-κB signalling (Kollarova et al., 2018).

In addition to modulation of the innate and adaptive immune systems by mould particles and mycotoxins, mechanisms exist that protect mould particles from elimination by the host defence. Over and above the immune suppression mentioned in previous paragraphs, protection is accomplished by directing the immune response in the direction of an anti-inflammatory process, by shielding stimulatory MAMPs from detection by PRRs, and by mould particles avoiding phagocytosis through entering host cells (Żelechowska et al., 2021).

5. Adverse health effects of moulds and mould-derived particles

Exposure to indoor damp-associated mould fragments, spores and mycotoxins can lead to infections, toxicity, allergies and inflammation (World Health Organization, 2009). Indications are that moulds, such as Penicillium and Aspergillus, not only form part of the body's natural microbiome, but could also serve as sources of infection (Bartemes and Kita, 2018). In fact, colonization by Aspergillus could become a continuous source of allergens, leading to unremitting immune activation and chronic airway inflammation (Bartemes and Kita, 2018).

Much of the pathology associated with indoor mould exposure can be linked to inflammatory processes. While inflammation is primarily intended as a major part of the body's defence, it may, if chronic or uncontrolled, present as immunopathology, especially in the pre-sensitised and immunocompromised. Respiratory symptoms and disorders of the inflammatory response against mould particles and metabolites range from non-specific symptoms such as stuffy nose, wheezing, and fever, to chronic, disabling conditions such as severe asthma (Centers for Disease Control and Prevention (CDC), 2022; Valtonen, 2017; World Health Organization, 2009). Inflammatory processes such as the secretion of proinflammatory cytokines and other inflammatory mediators are also implicated in the effects of mycotoxins in neuropsychiatric and other non-respiratory disorders and symptoms (Ratnaseelan et al., 2018).

The toxicological mechanisms of mycotoxins have best been studied in research related to the food and feeding industries (Awuchi et al., 2022), but much of the information also applies to mycotoxins derived from dampness-associated indoor moulds. Toxicity of mycotoxins include mechanisms such as the inhibition of protein and DNA synthesis, DNA and RNA damage and DNA and RNA mutations, inhibition of mitochondrial function, an increase in antimitochondrial antibodies, as well as cellular effects ranging from membrane dysfunction to cell cycle arrest and apoptosis. The effects of these cellular and subcellular deviations vary from skin to multi-organ involvement, impacting on well-being, growth, immunity and even on the human genome (Awuchi et al., 2022; Campbell and Weinstock, 2022; Lieberman and Curtis, 2020; Hope et al., 2013).

6. Symptoms and disorders associated with exposure to indoor mould

Individuals living or working in moisture-damaged buildings may experience any of a range of non-specific symptoms, such as nasal stuffiness, a runny nose, irritation of the throat, or red, itchy, or watery eyes. The symptoms are generally mild, reversible, and related to irritation of the mucosal membranes.However, exposure to indoor mould contamination has also been associated with an increased risk of developing and/or exacerbating allergic and non-allergic diseases. Sufficient epidemiological evidence exists to show that the occupants of damp, mouldy housing and public buildings are at increased risk for a number of respiratory disorders. In addition, exposure to dampness-associated indoor mould particles and mycotoxins are implicated in several non-respiratory illnesses, especially neurological and neuropsychiatric disorders (World Health Organization, 2009).

6.1. Respiratory symptoms and disorders associated with exposure to indoor mould

In humans, an association between asthma and fungal exposure/sensitization, in particular Alternaria and Aspergillus, is recognized in various countries (Bartemes and Kita, 2018). As early as 2002 the outcome of a multicentre epidemiological survey (cross sectional study from European Community Respiratory Health Survey), involving 30 centres and 1 132 asthmatic adults between 20 and 40 years of age, were published in the BMJ (Zureik et al., 2002). Results showed sensitisation to moulds to be a powerful risk factor for severe asthma in adults. In 2009 the World Health Organization issued guidelines on indoor air quality in which it stated that sufficient epidemiological evidence is available from studies conducted in different countries and under different climatic conditions to show that the occupants of damp or mouldy buildings are at increased risk of respiratory symptoms, respiratory infections and exacerbation of asthma (World Health Organization, 2009). Since then, multiple studies reported a causal association between moulds such as *Alternaria* and *Aspergillus* in the development and/or exacerbation, not only of asthma, but also rhinitis. In 2013, the existence of a causal relationship between indoor dampness-associated mould and the risk of different types of rhinitis was confirmed by a systematic review and meta-analysis of 31 studies (Jaakkola et al., 2013). A more recent overview (Caillaud et al., 2018), covered systematic reviews, meta-analyses, case-control studies, panel and longitudinal epidemiological studies, published from 2006 to 2017, on the associations between indoor mould exposure with asthma and rhinitis, respectively. The conclusions, based on the results of more than 50 000 individuals, were that sufficient evidence support the existence of a causal relationship between mould exposure and the development and/or exacerbation of asthma in children. In adults the association with asthma was found to reach significance with exposure in the workplace. Strong evidence was found for an association between mould exposure and allergic rhinitis (Caillaud et al., 2018). An association between respiratory morbidity and mould exposure in children was recently (2022) also reported from China. In a cross-sectional survey of 4691 school-age children in the Chinese cities Lanzhou and Wuhan, household mould exposure was found to be significantly associated with increased risks for asthma and allergic rhinitis (Li et al., 2022).

In the study by Li et al. (2022), younger children appeared to be more affected. The question thus arises whether sensitisation is age-dependant and whether exposure during infancy can be a risk factor for respiratory morbidity at a later age. Indications from data on 3 293 children derived from the BAMSE cohort were that exposure during infancy could increase the risk for asthma, rhinitis, and elevated IgE levels up to 16 years of age, especially the risk of persistent asthma during adolescence (Thacher et al., 2017). In agreement with that, Tischer et al. (2021) found the exposure of infants to moisture damage and mould to correlate with increased FeNO levels, a reflection of lung inflammation, by the age of 6 years. However, in 2018 the same authors reported that early life exposure does not appear to increase subclinical systemic inflammation by 6 years of age (Karvonen et al., 2018). It is obvious that further studies on early life pre-sensitisation are needed, including studies that differentiate between clinical and subclinical observations (Mustonen et al., 2016).

Airway pathology in patients with asthma and mould sensitisation have been described. Airway inflammation with goblet cell hyperplasia, excess mucus secretion, and impaired airway clearance with subsequent structural changes such as subepithelial fibrosis and smooth muscle hypertrophy is reported as features (Namvar et al., 2022).

The reported prevalence of associations between respiratory symptoms and exposure varies and is relatively inconsistent. For instance, the reported adjusted odds ratio (OR) between exposure and symptoms such as wheezing vary between 2.04 (CI: 0.67–6.18) for minor moisture (Tischer et al., 2022); 3.68 (CI: 1.04–13.05) for major damage with visible mould (Tischer et al., 2022); and. 6.05 (CI: 1.19–30.7) when mould odour was present (Holst et al., 2020). For asthma, ORs values such as 3.52 (CI: 1.01–12.7) for household moisture damage (Holst et al., 2020); 1.3 for moisture and mould (Wang et al., 2022); and 1.32 – 1.73 for mould/ spots/ odour (Sio and Chew, 2021), are reported.

6.2. Non-respiratory symptoms and disorders associated with exposure to indoor mould

While a multitude of studies have been performed on the link between dampness-associated indoor mould exposure and respiratory morbidity, a degree of ambiguity exists about the association with some of the non-respiratory disorders. In fact, there are those who unequivo-

cally deny the existence of such causal associations (Chang and Gershwin, 2019). However, in general, evidence is growing that exposure to indoor moulds and mycotoxins has the potential to impact negatively on the nervous systems of vulnerable adults and children, with deleterious neurological and neuropsychiatric effects (Empting, 2009; Ladd et al., 2021; Ratnaseelan et al., 2018). Based on clinical observations and research, moulds are implicated in a number of non-respiratory disorders such as Alzheimer's disease (Arce-López et al., 2021; Bredesen, 2016); Parkinson's disease (Arce-López et al., 2021; Pisa et al., 2020); Menier's disease (Frejo et al., 2018); myalgic encephalomyelitis/chronic fatigue syndrome (Wu et al., 2022); multiple sclerosis (Purzycki and Shain, 2010); sporadic amyotrophic lateral sclerosis (French et al., 2019); autism spectrum disorders (De Santis et al., 2019; Tuuminen and Rinne, 2017); autoimmune conditions (Tuuminen and Rinne, 2017); as well as local and focal pain syndrome complexes (Empting, 2009). Although more studies are required for indisputable proof of a causal association between indoor mould exposure and some of the neurological and neuropsychiatric disorders, it would do to remember the prominence of the inflammatory response in mould-associated pathophysiology, coupled to the fact that inflammation, particularly neuroinflammation, is implicated in a host of neurological and psychiatric disorders (Miller, 2020; Ratnaseelan et al., 2018; Skaper et al., 2018). The interested reader is referred to Skaper et al. (2018) who reviewed mechanisms by which inflammation can contribute to peripheral and central nervous system pathogenesis, including neuropathic pain, fibromyalgia, Alzheimer disease, Parkinson disease, multiple sclerosis, motor neuron disease and the autism spectrum disorder. Results from a number of studies also suggest an association between mycotoxins and the risk of cancer, however, meta-analysis of 16 studies (4 907 participants) could not support the relationship in humans (Ekwomadu et al., 2022).

While not trying to negate the existence of causal associations between indoor mould exposure and certain non-respiratory disorders, some observations could, at least partially, be epiphenomenological and related to the effects of other, co-existing, allergenic microorganisms, unhealthy living conditions, or unconnected pathology.

7. Conclusions

Several mechanisms contribute to the defence against invasion by mould and mycotoxins, including innate and adaptive immune processes. The inflammatory response forms an essential part of both the innate and adaptive defence systems. In contrast, uncontrolled inflammatory reactions form the basis for a large part of the immunopathology associated with mould exposure. This applies particularly to the symptoms and disorders associated with the respiratory system. A degree of ambiguity exists about the causal associations reported between indoor mould exposure and some of the neurological and neuropsychiatric disorders. However, inflammation has long been implicated in neurological and neuropsychiatric disorders. It is thus reasonable to propose that inflammatory activity may also form the basis for the mould exposure-associated neurological and neuropsychiatric disorders.

Statement of novelty

The inflammatory response, as defence against mould invasion and as the basis for mould-associated pathology is described. While the role of the inflammatory response in the respiratory pathophysiology is evident, we may be the first to point out that inflammatory activity may also form the basis for mould exposure-associated neurological and neuropsychiatric disorders.

The pathophysiology of dampness-associated indoor moulds is dealt with in an up-to-date, yet condensed manner which, we hope, renders it reader-friendly to those who are interested, yet not prepared to go to an inordinate amount of trouble for a broad understanding of current knowledge on the subject.

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Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Supplementary materials

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