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House Dust Mite Exposure: Can It Be A Severe COVID-19 Prevention?

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ABSTRACT

Background: In the midst of the ongoing COVID-19 pandemic, many studies are looking for treatmentto suppress viral replication and prevention through vaccination. However, to this day thenumber of incidences and deaths due to COVID-19 is still increasing.
Objective: The purpose of this article is to review theoretically the alleged increase in eosinophils in house dust mite exposure can prevent the severity of COVID-19 symptoms.
Methods: This article was compiled through a literature search in reputable international journals by the time 2020-2021.
Result: The severity of symptoms that arise due to COVID-19 infection is one of them caused by eosinophenia.On the other hand, the host immune response to house dust mite exposure can increase the number of eosinophils through stimulation of IL-6, IL-8, GM-CSF, IL-5 and IL-33. These eosinophils will then express TLR-7 on the cell surface which makes them able to recognize SARS-CoV-2. Stimulation of this eosinophil receptor triggers the production of cytokines, degranulation, superoxide, and nitric oxide (NO) through NO synthase which has a direct antiviral effect. EDN and ECP of human eosinophils can decrease viralinfectivity through a ribonuclease-dependent mechanism. Eosinophils are capable of producing extracellular traps composed of eosinophilic granule proteins bound to mitochondrial DNA in response to viral infection in vitro, especially in an oxidative lungtissue environment. Eosinophils also rapidly mobilize granules of Th1 cytokines, including IL-12 and IFN-γ which are important for antiviral immune responses.
Conclusion: Although available data are still limited, there are indications that eosinophils have a protective effect during SARS-CoV-2 infection. Therefore, biological agents such as exposure to house dust mites targeting eosinophils may be useful to help clarify the role of eosinophils in their antiviral response.

Introduction

The rapid spread of COVID-19 poses a serious threat to public health. This prompted researchers to explore the pathogenic characteristics of the SARS-CoV-2 virus in order to develop effective drugs. (Seyed et al, 2020) However, to this day the incidence and death rates due to COVID-19 are still increasing. From 224 countries around the world, there are more than 220 million confirmed positive COVID-19 patients with more than 4

million of them dying. (Jee Y et al, 2020) In Indonesia, there are more than 4 million COVID-19 sufferers with 136,000 deaths. (Van Empel et al, 2020)

There are several predictors of the severity of COVID-19 symptoms, including age >55 years, multiple comorbidities, hypoxia, biomarkers of organ dysfunction, and laboratory test abnormalities, including a decrease in the eosinophil count below the normal range (<0.02x109/L). (Gallo et al, 2021) The response of eosinophils during COVID-19 infection has been reviewed previously. (Lindsley et al, 2020) So far, the role of eosinophils in the mucosal immune response of the respiratory tract has often been focused on their adverse effects which are considered to have potent proinflammatory functions. In fact, research shows that eosinophils have a molecular device that allows them to recognize and respond to respiratory viruses. (Flores et al, 2019)

Questions from several reviews have led to the extent to which the role of eosinophils is suggested for the prevention of severe COVID-19. For example, will patients with eosinophilia-related diseases be immune to COVID-19? Do patients with eosinophilia have typical COVID-19 disease manifestations? This question is considered relevant because eosinophilia has been reported in patients with acute impairment of respiratory function during SARS-CoV-2 infection. (Zhang et al, 2020) Do eosinophils have an impact on lung pathology induced during COVID-19? Indeed, pulmonary pathology associated with eosinophils is known to occur following certain viral infections, such as respiratory syncytial virus (RSV). (Lindsley et al, 2020)

On the other hand, the host immune response to exposure to house dust mites can increase the number of eosinophils through stimulation of proinflammatory cytokines. (Abu et al, 2020) The purpose of this article is to review theoretically the alleged increase in eosinophils in house dust mite exposure can prevent the severity of COVID-19 symptoms.

Increased Eosinophils in House Dust Mite Exposure

Der p 1 is a cysteine protease as the main allergen of house dust mites. In addition to being an antigen, Der p1 can also activate protease-sensitive receptors (PARs) and TLR4 or trigger cell injury in epithelial cells. This activates the NLRP3 inflamasome and secretes cytokines and chemokines that recruit myeloid cells including dendritic cells, eosinophils, and ILC2. (Abu et al, 2020)

Activation of pattern-recognition receptors (PRRs) in the epithelium by allergens or via contaminant pathogen-associated molecular patterns (PAMPs) represents one of the core steps in Th2-mediated sensitization that will result in the release of proinflammatory cytokines and chemokines, thereby amplifying the entry of eosinophils, Th2 cells, basophils, dendritic cells, and other inflammatory cells. (Proud et al, 2011) Furthermore, the released cytokines activate innate immune cells such as eosinophils, mast cells, group 2 innate lymphoid cells (ILC2), and basophils to maintain the inflammation mediated Th2.(Spits et al, 2012)

A study conducted by Cunningham et al. showed that exposure to activated papain can increase IgE and IgG1 antibody responses thereby triggering eosinophilia, IL-4, IL-5, and IL-10 in broncho alveolar

lavage (BAL) from mice. (Cunningham et al, 2012)

House dust mite allergen-mediated activation of PARs will trigger the release of pro-Th2 cytokines and chemokines including IL-6, GM-CSF, and IL-8 in cultured airway epithelial cells. These cytokines and chemokines trigger extravasation and accumulation of eosinophils, neutrophils, and basophils. (Kauffman et al, 2006) In addition, lipopolysaccharides (LPS) from bacteria that contaminate house dust mites can also trigger Th2 responses and eosinophilic inflammation when Th1 responses and neutrophilic inflammation occur. (Eisenbarth et al, 2002)

Der p2 sensitization induces Th2-mediated inflammation through airway eosinophilia, lymphocytosis, mucus metaplasia, and elevated plasma IgE concentrations in mice (Trompette et al, 2009)

Recent studies have shown that the NLRP3 complex modulates house dust mite-induced inflammation by controlling the influx of eosinophils, Th2 cytokines and chemokines in the mouse airway. Therefore, NLRP3 mice trigger an increase in airway inflammation in response to HDM which is associated with infiltration of immune cells, especially eosinophils, Th2 cytokines and chemokines in their airways. This study demonstrated that mice lacking caspase-1 due to house dust mite exposure trigger eosinophilia and increased cytokines IL-25, TSLP, and IL-33. (Madouri et al, 2015) Decreased inflammation is associated with less leukocyte infiltration into the lung, especially eosinophils. (Zaslona et al, 2020)

The relevance of the C-lectin receptor to house dust mite-mediated allergy is reinforced by evidence that dectin-1 is important for the development of eosinophil and neutrophil influx into the lung, as well as attracting Th2 cytokines. (Barrett et al, 2011) Stimulation of dectin-1 or mannose receptors by chitin will mediate polarization. Th1, Th2, and Th17 thus recruiting basophils and eosinophils. (Lee et al, 2011)

Eosinophil Response in COVID-19

Human eosinophils express several Toll-like receptors (TLRs), including TLR3, TLR7, and TLR9 which can detect virus-associated molecular patterns.(Mansson et al, 2010) TLR7 enables eosinophils to recognize single-stranded RNA viruses such as coronaviruses and stimulation of these receptors in human eosinophils trigger the production of eosinophil cytokines, degranulation, generation of nitric oxide (NO) and superoxide, and prolong cellular resistance.(Nagase et al, 2003)) Eosinophil cationic protein (ECP/RNAse3) and eosinophil- derived neurotoxin (EDN/RNAse2) from human eosinophils reduce viral infectivity via a ribonuclease-dependent mechanism.(Domachowske et al, 1998) Both human and mouse eosinophils produce NO via an inducible NO synthase, which has direct antiviral effects against several viruses.(Drake et al, 2016) Eosinophils are capable of producing extracellular traps composed of eosinophilic granule proteins bound to genomic DNA and mitochondria. In addition, mouse eosinophils can release this DNA trap in response to viral infection in vitro, (Silveira et al, 2019) particularly in an oxidative lung tissue environment. (Yousefi et al, 2018) Eosinophils can also rapidly mobilize newly formed granules of Th1 cytokines, including IFN-gamma and IL-

12, which is important for antiviral immune responses.(Davoine et al, 2014) In the mouse model, pulmonary eosinophils upregulate CD86 and MHC-1 in response to viral infection, both of which can directly interact with CD8 T cells and promote T cell recruitment. Virus-specific CD8 into the lungs to enhance antiviral immunity. (Samarasinghe et al, 2017) Activated mouse and human eosinophils also express MHC-II molecules and costimulatory molecules, and can function as antigen-presenting cells for viral antigens, leading to T cell activation, and cytokine secretion.(Del Pozo et al, 1992)

IL-5 transgenic mice that constitutively overproduce IL-5 and possess eosinophils have accelerated viral clearance during infection. In contrast, mice genetically engineered to be eosinophil-deficient had lower viral clearance than controls. (Phipps et al, 2007) Adoptive transfer of eosinophils from Aspergillus fumigatus antigen-sensitized mice into the respiratory tract of virus-infected mice decreased virus titers and increased CD8 T cells. (Samarasinghe et al, 2017) Interestingly, human subjects with asthma who were treated with the antieosinophil drug mepolizumab (an anti-IL-5 humanized mAb) or placebo and consecutively exposed to the virus showed that patients treated with mepolizumab results in a significant increase in viral titers in the upper respiratory tract. This supports the antiviral role of eosinophils. (Sabogal et al, 2019) The growth of biologic agents targeting eosinophils may be useful to clarify the role of eosinophils having different antiviral roles. Although preclinical studies have demonstrated the antiviral activity of eosinophils, their clinical relevance in the immune response to different respiratory viruses requires further investigation. (Lindsley et al, 2020)

Influenza, RSV, and rhinovirus are common triggers of virus-induced asthma exacerbations, while coronaviruses are less likely to trigger acute asthma exacerbations. (Edwards et al, 2017) Asthma has been identified as not a major risk factor for the severity of SARS-CoV-1 infection. (Yin et al, 2018) In line with SARS-CoV-2, the study by Zhang et al(2020) reported that none of the 140 patients hospitalized positive for COVID-19 in China had asthma or atopic comorbid disease. Another recent review of 548 patients treated for COVID-19 in hospitals in Wuhan only reported an asthma prevalence of 0.9%, i.e. only 5 cases, which is lower than the prevalence of asthma in the adult population in Wuhan (6.4%). Leukocytosis, with an elevated absolute neutrophil count, is associated with severe COVID-19 manifestations. (Li X, 2020)

Interestingly, Zhang et al reported that more than half of patients with COVID-19 (53%) had eosinophilia (defined as an absolute eosinophil count < 0.02 x 109 cells/liter) at the time of admission. (Zhang et al, 2020) So did Du et al (2020). who reviewed the medical records of 85 fatal COVID-19 cases and noted that 81% of patients had an absolute eosinophil count below the normal range at the time of hospital admission. Lymphopenia is also a common finding in COVID-19 patients and blood eosinophil counts are positively correlated with lymphocyte counts in both severe and mild cases.(Zhang et al, 2020) Liu et al(2020) also noted the incidence of eosinophilia at the start of a cohort study of patients treated with lopinavir. Eosinophil levels improved in all patients shortly before being discharged. This suggests that

the resolution of eosinophenia can be an indicator of improved clinical status. The pathophysiology for eosinophilia in COVID-19 remains unclear, but appears to be multifactorial, involving inhibition of eosinophil egress from the bone marrow, blockade eosinophilopoiesis, decrease expression of chemokine receptors or adhesion factors, (Hassani et al, 2020) and/or induce eosinophil apoptosis directly via the release of type 1 IFNs during acute infection. (Butterfield et al, 2007)

No increase in eosinophils in lung tissue was observed from samples of patients with COVID-19 in the early stages of the disease (37) or on postmortem analysis (Barton et al, 2020). Although current data are limited, there is little indication that eosinophils have a protective role during SARS-CoV-2 infection. However, eosinphenia may act as a prognostic indicator for severe COVID-19. (Lindsley et al, 2020)

Conclusion

Although available data are still limited, there are indications that eosinophils have a protective effect during SARS-CoV-2 infection. Therefore, biological agents such as exposure to house dust mites targeting eosinophils may be useful to help clarify the role of eosinophils in their antiviral response.

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