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Review: Asthma and Viruses: A Toxic Relationship

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Abstract

Since time immemorial, human beings have had a relationship with viruses, especially respiratory ones. It is suggested that in certain cases these can stimulate the development of the innate immune system at an early age, but in the presence of susceptible hosts they may contribute to the development of asthma and its exacerbations.

In this review we will assess the mechanism by which viruses infect us, how our immune system acts, and our knowledge to date of the intervention of viruses as a cause of asthma and its exacerbations.

Introduction

About viruses

Viruses are strands of genetic material RNA or DNA, many are encapsulated with glycoprotein sheaths (called capsids), others protect this genetic material with an envelope derived from the cell they infect, and some surround their capsid with a cell membrane. They cannot reproduce by themselves, so they need to use a host cell to replicate the genetic material. DNA viruses need to enter the nucleus of the cell for replication, as DNA is more stable, DNA viruses do not change or mutate much, unlike RNA viruses that can replicate directly in the cell cytoplasm, as they are more unstable, they suffer more mutations.

These mutations lead to antigenic changes in the viruses that can occur when by a genetic recombination or regrouping of two or more different viruses that infect the same host cell, they combine their genetic material in that way or when a virus mutates in the human host and that mutated virus initiates several cycles of transmission between humans. In both cases this antigenic change creates a new subtype of the virus for which we have no existing antibodies and identification of these subtypes is necessary for the creation of new vaccines.

An example is the need to identify annually the antigenic changes of *Influenza A* that can infect many species such as humans, birds, pigs, dogs, horses, unlike *Influenza B* and *C* that have little or no recombination capacity.

How our immune system reacts to respiratory viruses

When infected by a virus, the body's innate and acquired immune system is set in motion to eradicate it. Innate immunity inhibits infection through Interferon Type 1 and the death of NK-lymphocyte-infected cells. Adaptive immunity is mediated by antibodies produced by B lymphocytes, which block the binding and entry of the virus into host cells, by CD4 T lymphocytes that assist macrophages in eliminating ingested molecules, and by CD8 T lymphocytes that destroy infected cells. The host can acquire immunity to the virus following the antigen response (acquired immunity), or by passing on antibodies or cells from an immunized person (passive immunity) [1,2]. Although it is believed that most responses to viruses are neutrophilic in nature, eosinophils may promote an antiviral response against respiratory viruses, which is different in the case of patients with asthma where it may cause an inflammatory hyper-response leading to host damage.

In healthy hosts and homeostatic conditions, eosinophils assist in modulating local and systemic immune and inflammatory responses. The cytokines IL-3, GM-CSF and especially IL-5, are critical for the stimulation, differentiation and maturation of eosinophils in the bone marrow. Once eosinophils are mature, IL-5 controls their exit from the marrow into the circulation, migrating into the tissues by controlling several cytokines, some more specific to eosinophils, such as eotaxin. Eosinophils are normally found in significant numbers in the bone marrow, thymus, digestive tract (except the esophagus), uterus, and mammary gland, in healthy subjects. When eosinophils are activated, instead of completely releasing their granules, they have the ability to release this content in a measured and staged manner. Among these granules is EDN (Eosinophil-Derived Neurotoxin) which has antiviral activity.

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Eosinophils can respond to pro-inflammatory cytokines released by T cells and other inflammatory cells and communicate with other eosinophils, as well as with lymphocyte-type cells and dendritic cells. Eosinophils release preformed cytokines, such as IL-4 and IL-13, as well as interferons, which impact both Th1 and Th2 responses. Eosinophils may also promote immune responses by stimulating B-lymphocytes to produce specific IgM. Eosinophils have also been shown to have bidirectional communication with resident macrophages and mast cells. They have a number of homeostatic receptors and produce several substances that may serve to amplify the immune response, but also to decrease inflammation. In several studies it was observed that rhinovirus infection promotes the secretion of several cytokines such as IL-6, IL-8, IL-11 and IL-16 by epithelial cells. IL-6 and IL-8 are known to be pro-inflammatory cytokines and IL-8 is also a potent neutrophil chemotherapeutic factor. IL-11 may have a direct action on bronchial hyperresponsiveness and IL-16 is a potent lymphocyte chemotherapeutic, macrophage and eosinophil activator and appears to be a very important mediator in the pathogenesis of asthma and inflammation secondary to rhinovirus infection. Rhinovirus infection also promotes the secretion of RANTES, a chemotactic active chemokine for eosinophils, monocytes and T-lymphocytes.

In the case of patients with Type 2 asthma this immune and inflammatory response to viral exposure would be amplified. Elevated levels of ECPs (Eosinophilic Cationic Proteins) and EDNs (Eosinophil Derived Neurotoxin) have been observed in asthmatics, and higher levels of ECPs and EDNs have been found during asthma exacerbation compared to healthy patients and those with stable asthma. This would suggest that airway inflammation as a consequence of asthma exacerbation is characterized not only by an increase in the number of eosinophils, but also by an increase in the degranulation of eosinophils in the airways [3-8].

Viruses as a cause of asthma

The big dilemma is whether viral infections in early childhood can increase the risk of developing asthma or whether viruses are a trigger for asthma in an airway previously altered both immunologically and pathophysiologically by prior genetic conditions.

While no clear causal relationship was found between Respiratory Syncytial Virus (RSV) and Asthma, a study of over 95,000 children found that the time of birth relative to the peak of the winter virus (particularly RSV) independently predicted the development of asthma, with the highest risk estimated for those born 121 days before peak [9]. In two studies, the administration of anti-RSV immunoglobulin (palivizumab) to children at high risk of chronic airway disease improved lung function and reduced evidence of asthma and atopy, suggesting that prevention of RSV infection has long-term effects relevant to avoiding the development of asthma [10,11]. But since a large majority of children are infected with RSV before the age of one, there are other associated factors that should contribute to the development of asthma. There are several studies indicating the role of the Human Rhinovirus (HRV), this infects mostly children under 1 year and asymptomatic children, and its severity may depend on host predisposing factors or viral strains plus pathogens. In the Perth Cohort, rhinovirus was the most common pathogen associated with respiratory infection in the first year of life, followed by RSV.

Another virus associated with increased wheezing in childhood is the Human Bocavirus (HBV), a new parvovirus that often causes co-infections, as well as it's parainfluenza, *influenza A* and *human metapneumovirus* [12-21]. Two hypotheses were put forward:
1) The consequent hypothesis, states that viruses persist or affect the immature respiratory and immune system of the newborn, leading to bronchial hyperreactivity and long-term sequelae, and 2) the common causal hypothesis, is that genetically susceptible infants either already have a decline in lung function prior to viral infection or both. Both hypotheses are likely to coexist [22,23].

A reduced expression of IFN-γ was observed in infants with severe RSV disease during the period of infection and this persisted, diminished in those children who developed asthma later, and an increase in IL-10 was also observed in the convalescence phase of children with RSV bronchiolitis and its levels were higher in those with recurrent wheezing. Decreased levels of IFN-γ would produce a failure of apoptosis and increased viral replication in the tissues of asthmatics, which would explain why asthmatic subjects are more susceptible to viral infections. By administering IFN-γ after infection, chronic airway dysfunction was reduced, suggesting that factors that increase innate immunity might prevent the development of asthma or its exacerbations [24-26]. Genetic variants were found with polymorphisms associated with severe bronchiolitis and in those children with greater risk of developing asthma in the face of viral infections [27-29]. IL-13 appears to be important in inducing a state of airway hyperreactivity after infection, while prior exposure of the airway to an allergen increases virus-induced airway hyperreactivity [30-34].

TH1/TH2 deregulation would be a consequence of abnormal development of the innate immune system [35]. Children with reduced levels of lung function in childhood appear to be at increased risk of chronic lower respiratory tract sequelae following viral infections and congenital airway tone dysregulation may also exist [36,37].

Studies in mice were able to determine that if infection occurs at an earlier age, and in a genetically susceptible host, the likelihood of developing asthma is greater. What is not clear is whether this alteration of innate immunity would be favored by previous alterations of the host or the infectious process being coadjacent to this situation. In this sense, recent studies place us in the dilemma of the so-called hygiene hypothesis, in which it is proposed that early exposure to endotoxins, including viruses, could act as a protective mechanism in the balance and adequate development of innate immunity to prevent the future development of atopias and/or asthma. In an agricultural environment, increased exposure to high levels of endotoxin has been associated with lower allergy rates and high numbers of interferon-conducting cells in the blood [38-42].

This theory leads us to believe that early prenatal and early postnatal exposure to pathogens and allergens may provide a protective effect against the development of allergy. The role of adequate development of the respiratory microbiome and its interrelationship with the intestinal microbiome, influenced by the factors described above would contribute to the good development of the innate immune system and the prevention or risk of developing atopic diseases and asthma [43].

Asthma is a heterogeneous condition due to a deregulation of the body's immune and airway responses, produced by different specific and non-specific exposures that occur mostly in early life in individuals who have a certain genetic predisposition.

Viruses as a cause of asthma exacerbation

Three peaks of seasonal asthma exacerbations have been observed.

The first was in the autumn, exacerbations were predominant in children, where rhinovirus is the predominant pathogen. A second peak was in mid-winter, where an increase in over-50s was observed, mostly caused by Influenza and a third peak was in late spring, season related to higher environmental level of pollens and high humidity. It is therefore considered that between 80% and 85% of asthma exacerbations in children and almost 50% in adults are caused by viruses [44,45].

The exacerbations, especially those of viral cause are more related to a neutrophilic inflammation, except in children who present predominance of eosinophilic inflammation. In an asthmatic subject, when the bronchial epithelial cells are infected by a virus, they are damaged. This makes the bronchial epithelium more susceptible to environmental irritants that can lead to an increase in mast cell histamine and increased bronchoscopy. On the other hand, a greater alteration of the immune system with the release of mediators, cytokines, chemokines and growth factors can generate an increase in cellular recruitment of eosinophils, neutrophils and mast cells. The predominance of one of these will depend on the mediators released, for example: The release of cytokines, such as IL4, IL5, IL13, and chemokines with CCL5/RANTES, CCL11/Eotaxin, will result in increased recruitment of eosinophils.

The release of mediators such as *CXCL8*/IL-8 will increase recruitment of neutrophils. These cells in turn release mediators that can cause airway hypersensitivity, bronchoconstriction, and inflammation that lead to the symptom's characteristic of asthma exacerbation [46,47]. Like other respiratory viruses, SARS COV2 increases exacerbations in the asthmatic patient, but these patients have not been reported to have higher mortality from this virus compared to the general population [48].

Conclusion

Viruses and asthma have had a toxic relationship since their inception. In genetically susceptible individuals, whether or not associated with certain environmental or individual exposures such as the microbiome, they may cause the development of asthma. In asthmatic individuals, they can trigger inflammatory cascades due to immune imbalances, with viral infection being one of the main causes of asthma exacerbations.

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