Annals of Global Health
VOL. 82, NO. 1, 2016
ISSN 2214-9996
http://dx.doi.org/10.1016/j.aogh.2016.01.007

STATE-OF-THE-ART REVIEW

The Impact of Early-Life Exposure to Air-borne Environmental Insults on the Function of the Airway Epithelium in Asthma

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Abstract

The airway epithelium is both a physical barrier protecting the airways from environmental insults and a significant component of the innate immune response. There is growing evidence that exposure of the airway epithelium to environmental insults in early life may lead to permanent changes in structure and function that underlie the development of asthma. Here we review the current published evidence concerning the link between asthma and epithelial damage within the airways and identify gaps in knowledge for future studies.

KEY WORDS asthma, allergens, air pollution, virus, epithelium, early life, airway remodeling, immunity

INTRODUCTION

Asthma has a complex etiology and has been viewed conventionally as being caused by a dysregulated adaptive immune response[1] for which individuals are genetically predisposed. However, in more recent years the contribution of both the airway epithelium and the innate immune response to the development of asthma in early life has been considered. The airway epithelium is the interface between the internal environment of the lungs and the inhaled environment. It not only provides a physiological barrier critical in directly protecting the airways from environmental insults, but also is an intrinsic part of the innate immune response to respiratory challenges. Airway epithelial cells (AECs) are capable of producing a wide range of cytokines and chemokines that activate immune cells. The response of the airway epithelium to environmental insults has a lasting effect on respiratory health and plays a critical role in the early-life establishment of chronic respiratory disease. Recurrent or severe exposure to environmental insults during the first years of life may induce lifelong changes to the structure and function of the airway epithelium. Moreover, a growing body of evidence links epithelial damage with the development of asthma in early life.[2,3]

The *exposome* is a term recently used to encompass all of the environmental insults humans are exposed to during the first years of life.[2] For the respiratory system, these include pathogens, allergens, and pollutants. However, chronic respiratory illnesses are not only the result of early-life exposures. Genetic factors also influence the effect of the exposome on the development of respiratory disease.[3]

In this review, we consider the evidence that the early life exposome has an effect on the structure

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and long-term function of the airway epithelium. We discuss the main mechanisms by which these environmental insults induce long-term dysregulation of the structure and function of the airway epithelium. We focus on in vitro research that has been carried out using cultured primary AECs of bronchial or nasal origin. However, studies using transformed cell lines, primarily BEAS-2B and 16HBE14o cells, will be discussed. Immortalized human lung alveolar cells, A549s, have traditionally been the predominant cell line used, however, they of limited relevance being derived from a carcinoma. Most studies using primary AECs have used submerged monolayer cultures, which are composed of epithelial cells in basal morphology. In recent years, air-liquid interface (ALI) cultures have been used as they mimic a physiological airway and therefore allow the investigation of barrier function and repair. Mouse and monkey models have been included in this review where they have been used directly to investigate epithelial cell responses.

THE AIRWAY EPITHELIUM IN EARLY LIFE

The airway epithelium is the first line of defense against environmental insults. When functioning normally, it forms a physical barrier of stratified ciliated epithelial cells, mucus-secreting goblet cells, and surfactant-secreting clara cells. The formation of tight junctions at the apical surface of the columnar cells and other adhesion mechanisms along the basal surface ensure an impermeable barrier. Tight junctions are formed by interacting adhesion proteins such as ZO 1-3, occludin, claudins 1-5, E-cadherin, and β-catenin[4,5] in addition to extracellular matrix (ECM) interactions.[6] However, this essential barrier between the external environment and the lung is not fully formed at birth. Infant lung alveolarization is not complete until 2 to 4 years of age. During this time, the airway epithelium is vulnerable to environmental challenges that can alter genetic and epigenetic determinants of lung function, induce airway remodeling, and reduce the long-term capacity of the airways to repair.[7]

In addition to perinatal physiological lung development, the immune system is also developing in the neonate.[7] The lack of a functional adaptive immune response makes infants highly susceptible to infections and dependent on the innate immune response. As such, the residing immune cells of the airway epithelium and epithelial cells themselves are a vital part of the innate immune response to environmental insults of the airways and long-term reprogramming of these cells may mediate lifelong chronic disease.[1]

VIRUSES

There is a long-standing debate concerning the link between viral infections in early life and the inception of asthma. However, growing experimental and clinical evidence shows that early-life exposure to severe and repeated viral infections causes episodic airway inflammation, which leads to a cycle of tissue damage, repair, and remodeling. Over time, this may lead to persistent pathological changes in the epithelium.[7,8] The principal viruses that cause early life wheeze are human rhinoviruses (HRVs), respiratory syncytial virus (RSV), and human metapneumovirus (hMPV).[9] For pediatric cohorts, research concerning the effect of viral infection on the airway epithelium has been focused mainly on HRV and RSV, whereas the long-term effect of early-life infections by hMPV is largely unknown.

Several cohort studies[10-13] consisting of infants hospitalized for respiratory infections during their first year of life have identified a significantly increased risk for asthma at 5 years of age. In particular, RSV bronchiolitis in early life has been linked to the development of wheeze and asthma, with cohort studies demonstrating that up to 50% of children who experience severe RSV bronchiolitis in infancy develop asthma.[13-17] The strongest evidence that RSV-induced wheeze and bronchiolitis predispose infants to the later development of asthma comes from clinical trials of anti-RSV treatments. A nonrandomized trial in which late-preterm infants were prophylactively administered anti-RSV antibodies demonstrated a 68% to 80% reduction in the risk for recurrent wheeze, thus demonstrating a causative link between RSV and early-life wheeze.[18] Furthermore, a randomized control trial with 429 preterm infants found that prophylactively administered anti-RSV antibodies reduced the duration of wheezing by 61% during the first year of life.[19] The causative mechanisms that underlie the link between RSV and asthma are not entirely clear. It is believed that early-life RSV infections may elevate susceptibility to repeat viral infections via the dysregulation of immunologic pathways, long-term epithelial damage, and airway remodeling. A strong association also exists between HRV infections and lower respiratory illness in children, with infants hospitalized for HRV-induced wheeze having increased