Fetal Eosinophils Get on the Nerves of Airways

Early Origins of Bronchoconstriction

A complex interaction between genes and environmental factors underpins the development of asthma in early life, with a history of maternal asthma consistently identified as one of the strongest predictors. In this issue of the *Journal*, Lebold and colleagues (pp. 493–502) elegantly demonstrate a critical role of maternal IL-5 crossing the placenta in inducing fetal eosinophilia by interbreeding wild-type, IL-5 transgenic and eosinophil-deficient mice (1). Fetal eosinophilia increased airway sensory innervation and reflex bronchoconstriction in the offspring. Importantly, increased epithelial nerve density observed in wild-type offspring born to IL-5 transgenic female mice also potentiated airway hyperreactivity (AHR) and inflammation in response to house dust mite exposure in later life. This exaggerated AHR was not due to enhanced smooth muscle contractility but rather was a consequence of vagal reflex-mediated bronchoconstriction, probably mediated by the sensory tachykinin substance P.

The mechanisms underpinning the role of eosinophils in the pathogenesis of exaggerated AHR and bronchoconstriction are complex. Mice genetically defective in developing blood and lung eosinophilia, for instance, because of deficiencies in IL-5 and eotaxin or direct depletion of eosinophilic cells, show ameliorated AHR and inflammation in response to allergen exposure (2, 3). This is associated with an intrinsic defect in allergen-specific type 2 (T2) cytokine production in the absence of eosinophils, likely due to their function in antigen presentation, costimulation, and release of soluble proinflammatory factors (4, 5). The results from Lebold and colleagues suggest that eosinophils affect airway inflammation by also increasing nerve density, as offspring born to IL-5 transgenic female mice displayed more airway inflammation after house dust mite exposure (1). This may involve expression of neurotrophins and release of eotaxin and substance P from neurons, rather than increased cytokine production by T helper 2 and T2 innate lymphoid cells. However, further investigation is warranted to substantiate this hypothesis.

T2 cytokines promote eosinophilopoiesis and eosinophilia and induce tissue expression of eosinophil-attracting chemokines. In response to eotaxin release by neurons, eosinophils colocalize with airway nerves and release major basic protein that can block inhibitory M2 muscarinic receptors on parasympathetic nerves (6). Loss of M2 receptor signaling potentiates nerve-mediated bronchoconstriction (7). Furthermore, increased airway sensory innervation and structural remodeling of airway epithelial sensory nerves is observed in eosinophilic airway inflammation. This correlated with a lack of bronchodilator responsiveness and greater sensitivity to inhaled irritants in patients with asthma (8). Overexpression of IL-5 in airway epithelium results in eosinophils surrounding the large airways and increased vagally mediated bronchoconstriction (9). Clinically, treatment with eosinophil-targeting biologics is associated with a lower rate of asthma exacerbations, less oral corticosteroid use, and lung function improvements. Inhibition of eotaxin signaling also ameliorated AHR in patients with asthma (10). It is noteworthy that bronchoconstriction alone, without additional inflammation, leads to subepithelial collagen deposition in the airway wall of patients with asthma (11). Thus, the effect of increased vagal reflex–mediated bronchoconstriction acquired *in utero* on airway remodeling in later life requires further investigations.

The results by Lebold and colleagues provide a solid basis for additional mechanistic studies that may reveal avenues for novel preventative strategies (1). Specifically, a role of other cytokines acting at the feto–maternal interface as determinants in the early origins of increased bronchoconstriction remains to be determined. IL-5 and GM-CSF (granulocyte-macrophage colony-stimulating factor) are principal mediators in the early and late stages of eosinophilopoiesis. IL-33 and TSLP (thymic stromal lymphopoietin)—epithelium-derived alarmins—may also promote eosinophilopoiesis directly and independently of IL-5 (12, 13). Thus, a range of cytokines could be assessed in the future as experimental targets *in utero* to ameliorate vagal reflex bronchoconstriction in the offspring.

Viral infections of the lung commonly cause bronchiolitis in infancy and asthma exacerbations in later life. Macrophages, TNF-α and IL-1β are involved in mediating virus-induced loss of M2 muscarinic receptor function. This results in more acetylcholine release from the parasympathetic nerves to increase vagal bronchoconstriction and potentiate AHR, even in the absence of allergic airway disease (14). An increased vagal reflex bronchoconstriction may predispose to symptoms of lower airway obstruction during infection with viruses that typically cause upper airway symptoms only, for instance rhinovirus. Vagal reflex bronchoconstriction that is acquired *in utero* may predispose to, or worsen the severity of, bronchiolitis and rhinovirus-induced asthma exacerbations and may be particularly responsive to treatment with long-acting muscarinic antagonists.

Asthma in pregnancy is the most common medical complication in pregnancy, and its control and management are associated with respiratory outcomes in the offspring. More than one-third of pregnant women may stop or reduce their asthma medication because of concerns regarding safety. The Managing Asthma in Pregnancy (MAP) trial randomized pregnant women with asthma to a treatment approach where the dose of inhaled corticosteroids was adjusted monthly according to levels of the fraction of exhaled nitric oxide, a surrogate variable of T2 immune response–induced eosinophilic airway inflammation (15).

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Compared with a control group managed on the basis of clinical symptoms only, the group of women with asthma managed with fraction of exhaled nitric oxide experienced a marked reduction in asthma exacerbations during pregnancy, and their offspring had a 90% reduction in recurrent bronchiolitis episodes in infancy and a 40% reduction in early childhood asthma prevalence (16, 17). These benefits seemed to be mediated by more appropriate use of inhaled steroids that corresponded with the level of T2 airway inflammation currently present. The mechanisms whereby a tighter control of eosinophilic inflammation in pregnancy may potentially prevent recurrent episodes of bronchiolitis and childhood asthma remain elusive. However, it is tempting to speculate, on the basis of the intriguing findings by Lebold and colleagues, that uncontrolled eosinophilic asthma in pregnancy may be associated with an increased risk in the offspring to develop vagal reflex bronchoconstriction that is acquired *in utero* (1). Maternal T2 cytokine release may increase airway sensory innervation by promoting fetal eosinophilia. The clinical relevance of a novel role of eosinophils in the early origins of bronchoconstriction and AHR could be far reaching, as obstructive airway diseases are common throughout life. ■

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