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Defective Respiratory Tract Immune Surveillance in Asthma

A Primary Causal Factor in Disease Onset and Progression

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The relative importance of respiratory viral infections vs inhalant allergy in asthma pathogenesis is the subject of ongoing debate. Emerging data from long-term prospective birth cohorts are bringing increasing clarity to this issue, in particular through the demonstration that while both of these factors can contribute independently to asthma initiation and progression, their effects are strongest when they act in synergy to drive cycles of episodic airways inflammation. An important question is whether susceptibility to infection and allergic sensitization in children with asthma arises from common or shared defect(s). We argue here that susceptibility to recurrent respiratory viral infections, failure to generate protective immunologic tolerance to aeroallergens, and ultimately the synergistic interactions between inflammatory pathways triggered by concomitant responses to these agents all result primarily from functional deficiencies within the cells responsible for local surveillance for antigens impinging on airway surfaces: the respiratory mucosal dendritic cell (DC) network. The effects of these defects in DCs from children wtih asthma are accentuated by parallel attenuation of innate immune functions in adjacent airway epithelial cells that reduce their resistance to the upper respiratory viral infections, which are the harbingers of subsequent inflammatory events at asthma lesion site(s) in the lower airways. An important common factor underpinning the innate immune functions of these unrelated cell types is use of an overlapping series of pattern recognition receptors (exemplified by the Toll-like receptor family), and variations in the highly polymorphic genes encoding these receptors and related molecules in downstream signaling pathways appear likely contributors to these shared defects. Findings implicating recurrent respiratory infections in adult-onset asthma, much of which is nonatopic, suggest a similar role for deficient immune surveillance in this phenotype of the disease.

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Abbreviations: CTL = cytotoxic T cell; DC = dendritic cell; FcεR1 = high-affinity IgE receptor; IFN = interferon; IL = interleukin; LRI = lower respiratory viral infection; Th = T-helper cell; TNF = tumor necrosis factor; Treg = T-regulatory cell

It has long been recognized that risk for asthma in childhood tracks with intensity of expression of the atopic phenotype,[1] and this association is strongest during the teen years.[1,2] These findings have been replicated in multiple birth cohort studies, some extending to early adulthood (reviewed in Holt and Sly[3]). It is also established that sensitization is an independent asthma risk factor in early childhood[4,5] and that the earlier sensitization occurs the greater the risk of subsequent asthma development.[6-9] This is thought to reflect the differential sensitivity of rapidly growing lung tissues during early life to the persistent inflammation accompanying sensitization to perennial aeroallergens, which has potential to perturb normal patterns of lung differentiation.[3] However, it has been unclear how atopy-associated inflammation in young children can attain sufficient intensity to severely damage airway tissues.

Early sensitization to aeroallergens in this context implies failure to generate protective immunologic tolerance, which is the normal default response of the healthy immune system to de novo allergen exposures (reviewed in Strickland and Holt[10]). Data from birth cohorts exemplified by our findings[11] have pinpointed

the first few years of life as the time when sensitization to ubiquitous aeroallergens is most frequently initiated in atopics, implying that immunoregulatory mechanisms underlying tolerogenesis may be developmentally compromised during this period.

Respiratory Viral Infections

The first years of life are also acknowledged as the period of highest risk for respiratory infections, which, in first-world countries, represent the most frequent cause of hospitalization in this age group. The possible link between early respiratory infections and risk for asthma in children has been recognized since the 1970s, but the full impact of this causal pathway on community disease rates has only become evident through long-term follow-ups from the major prospective birth cohorts.[4-6,12,13] Notably, recurrent symptomatic lower respiratory viral infections (LRIs) have been identified as the strongest independent risk factor for asthma inception and for its persistence through later childhood. Until comparatively recently, the focus of interest was predominantly upon respiratory syncytial virus, particularly in infants,[14] but additional evidence has also demonstrated a major role for rhinovirus,[15] particularly beyond preschool age.

It is pertinent to note that upper respiratory infections, in contrast, are not associated with increased asthma risk,[9] indicating that initial failure of innate immune defenses to contain primary infections at the upper respiratory infection site is a necessary first step toward unmasking the asthmatogenic potential of these pathogens. This may be due in part to an intrinsic defect in the interferon (IFN)-producing capacity of epithelial cells in susceptible subjects.[16,17] However, it is additionally noteworthy that LRIs per se are not associated with increased asthma risk,[9] only those events evoking severe symptoms of wheeze and/or fever,[9,12] suggesting that underlying failure to control the intensity/duration of adaptive immune antiviral responses may also be a key predisposing factor. This hints at deficiencies in T-regulatory cell (Treg) functions, which have been identified as a potential risk factor in asthma pathogenesis,[10,18,19] including in infants and school children.[20,21]

Double Jeopardy

An important issue arising from these epidemiologic findings concerns the potential effects of comorbidity, given that risk for both sensitization to aeroallergens and for respiratory infections are concomitantly maximal during this early life phase. Evidence (reviewed in Holt and Sly[3]) argues strongly that recurrent symptomatic LRI during the first 2 to 3 years of life occurring against a background of preexisting sensitization to aeroallergens results in much higher risk for asthma onset than is associated with either of these factors alone,[4,5,9,15] suggesting synergistic interaction between underlying asthmatogenic inflammatory pathways.

There is a wide body of complementary evidence in the literature for similar interactions at later stages of the disease, including (1) increased susceptibility of atopic children with asthma to intensification and spread of viral infections from the upper to lower respiratory tract with attendant loss of asthma control,[22] (2) amplification of rhinovirus cold symptoms in atopic adults,[23] (3) rhinovirus-induced triggering of T helper cell (Th) 2-associated immunity in the lower respiratory tract of adult patients with asthma,[24] (4) potentiation of Th2-associated airways inflammation in rhinovirus-infected atopic adults by allergen bronchoprovocation,[25] and (5) synergism between atopy and recurrent LRI in relation to risk for de novo onset of asthma in adulthood.[26] However, the most profound examples relate to hospitalization for severe virus-associated asthma exacerbation: Depending upon study methodologies, up to 90% of affected children beyond preschool age and $>$ 60% of affected adults are sensitized and concomitantly exposed to perennial allergens.[3,11,27,28] Moreover, this subgroup of atopics typically comes from the severe end of the sensitization spectrum as defined by IgE titers.[27,28]

An Additional Role for Bacterial Infections in Asthma Pathogenesis?

The question of the role of bacteria, either as independent inducers of airways inflammation or as secondary agents operating in conjunction with viral infections, has been brought sharply into focus by a series of findings. First, in relation to asthma initiation, studies using conventional bacterial culture methodology suggest that nasopharyngeal colonization during infancy with common respiratory pathogens exemplified by *Haemophilus influenzae* and *Streptococcus pneumoniae* is associated with increased risk for early-onset asthma.[29] Second, the application of

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