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Early View

Correspondence

Creola bodies and pathogenesis of childhood asthma

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To the Editor,

In their excellent review, Pijnenburg, Frey, De Jongste, and Saglani discuss multiple factors likely involved in inception and pathogeneses of childhood asthma including treatments. They note significant heterogeneity of the disease, highlight inconsistent observations, and suggest that with common modes of classification phenotype stability may be poor. With development of multidimensional and systems biology approaches they envisage that well-defined subgroups of childhood asthma will be possible (1). My comment rather builds on often overlooked clinical observations of association between clusters of epithelial cells, Creola bodies (Cb), in sputum samples in infants and subsequent development of asthma (2,3).

Cb predict development of asthma.
Yamada et al. examined aspirated sputum samples in hospitalized, wheezing infants aged about 5 months. Respiratory Syncytial Virus (RSV) infection was excluded in 23 patients sub-grouped depending on presence (Cb+) or absence (Cb-) of Cb. During a 2-year follow-up period, twelve (80%) in the Cb+ group, but none in the Cb- group, were diagnosed with infantile asthma (2).

RSV bronchiolitis in infancy has been associated with epithelial injury and development of asthma (1,3). Yamada and Yoshihara (3) examined sputum Cb in infants with acute RSV infection. During 5-year follow-up 70% of Cb+ developed asthma compared to 10% in Cb- (sputum granulocytes had not differed).

Epithelial loss in asthma.
Naylor (4) demonstrated hundreds Cb at exacerbations of adult asthma consistent with numerous, small patches of epithelial denudation. Patchy loss of bronchial epithelium though less pronounced is also a basic feature of asthma, apparently also in childhood (5). Nevertheless, 'bedside' observations indicate unincreased penetrability of inhaled molecules in asthma (6). Current cell culture-based research paradigms claiming increased epithelial permeability as well as defect repair of bronchial epithelium in asthma can hardly explain such 'bedside' data (7). The vitro-vivo dichotomy may partly depend on distinct modes of epithelial regeneration in vivo.

Airway epithelial loss-regeneration over intact basement membranes (BM) in vivo.
Studies were carried out in vivo in guinea-pig trachea that differ from mouse models by exhibiting similarities to human airways regarding pseudostratified epithelium and microvascular-epithelial plasma exudation responses. Decisive similarities between the model and asthma further include non-sanguineous, patchy epithelial loss from an intact BM (7).

Epithelial loss may not result in increased penetrability of inhaled toxins
Supporting relevance for human asthma, the experimental in vivo model on epithelial loss-restitution (6,7) reveals modes of maintaining a mucosal barrier in a desquamatory disease: Prompt cover of denuded basement membranes by provisional barrier gels kept in place by fibrin-fibronectin nets; an in vivo milieu where all types of epithelial cells bordering the denuded area participate in intense repair activities (secretory cells, loosing granulae, and ciliated cells, internalizing cilia, dedifferentiate along with basal cells into tethered, poorly

differentiated, rapidly migrating repair cells); as soon as undifferentiated repair epithelium covers the denuded spot, a barrier of interdigitating cell contacts are established (and the fibrin-fibronectin gel cover is shed.) These in vivo observations, coupled with exaggerated, rather than defect, epithelial regeneration and exceedingly patchy loss of epithelial cells, are consistent with the maintained mucosal barrier against inhaled molecules so far demonstrated in adult asthma (6,7).

Asthma-like local effects evoked by epithelial denudation-regeneration alone.
The patchy loss of epithelium results in local asthma-like features (A-E): (A) sustained but minimal plasma exudation establishing both a provisional fibrin-fibronectin barrier and a biologically active milieu suited for defence and speedy epithelial regeneration; (B) mucus hyper-secretion; (C) recruitment and activation of neutrophils; (D) proliferation of epithelial and smooth muscle cells, and thickened reticular basement membrane (7); (E) if eosinophils are present locally they become ultimately activated/disintegrated by primary cytolysis releasing free granules (a prominent feature in asthma that limits the value of mere eosinophil counts (8)).

In vivo data thus indicate that epithelial regeneration alone, in vivo, may evoke several local effects of pathogenic interest. If numerous and wide-spread, hot spots of epithelial loss-regeneration may thus contribute to basic features of asthmatic bronchial mucosa. Human airway epithelial loss/repair is further expected to induce local expression of major upstream T2 alarmins/cytokines that would add pathogenic potential (3,9,10).

Cb an independent factor at inception and exacerbation of asthma?
Both in absence and presence of RSV infection (rhinovirus infection not determined), sputum Cb may predict which infants will develop asthma (2,3). Yamada and Yoshihara (3) saw no role of atopy and discussed Cb as an independent factor potentially deciding which infants with severe RSV infection will develop asthma. They further reviewed intriguing occurrence of Cb in childhood and adult asthma (3). Common to the infant and child studies, neither neutrophil nor eosinophil indices were clearly associated with occurrence of Cb (3).

In summary, a range of research approaches seem warranted at this stage: further establishing occurrence and predictive significance of Cb in inception of asthma; delineating actual causes or innate propensity for producing Cb in infants, with or without viral infections; validating in vivo-roles of shedding-induced Cb and epithelial regeneration in pathogenesis and phenotyping of asthma.
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