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Regulation of immune responses at mucosal surfaces: Allergic respiratory disease as a paradigm

HOLT

The epithelial surfaces of the respiratory tract represent a fragile interface between the immune system and the outside environment. In order to maintain local homeostasis, the adaptive immune system must continuously discriminate between innocuous antigens which are ubiquitous in the atmosphere, and antigens associated with microbial pathogens. Any breakdown in this discrimination process can potentially lead to chronic inflammatory disease. The mechanisms employed by the mucosal immune system to maintain this delicate balance are many and varied, and a comprehensive understanding of how they collectively operate would provide novel insight into a wide variety of diseases. This discussion reviews recent progress in this area, focusing on allergic respiratory disease as a model for the study of immune regulation at mucosal surfaces.

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Introduction

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Interest in mucosal immunology as a distinct subdiscipline has grown rapidly over the last 10 years. This branch of immunology provides unique experimental models for the field at large, particularly for the *in vivo* study of effector mechanisms defined at the growing molecular edge of the discipline. It is pertinent to reflect in this context, that when Burnet first proposed the clonal selection theory, the cellular source of antibodies was completely unknown – the modern era of immunology did not really begin until the demonstration by James Gowans in the early 1960s that removal of the small lymphocytes from rats resulted in the loss of all immune responses, and restoration of immune function rapidly followed lymphocyte replacement. The technique used by Gowans (chronic thoracic duct drainage) is one of the methodological cornerstones of modern mucosal immunology.

Allergic respiratory disease: Dysregulation of mucosal immune responses to environmental antigens

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The early 1960s witnessed major changes not only in experimental immunology, but also in as yet undefined 'environmental factors' which have had profound effects on population patterns of immunologically mediated diseases. Notably, each cohort of children born subsequent to this period has manifested progressively increased prevalence rates of allergic diseases, in particular atopic asthma and atopic dermatitis,¹ such that current rates are approximately three times those of 1960. Remarkably, this increase has been largely restricted to the developed countries of the West, in particular to the higher socio-economic subgroups of the populace.^{1, 2} The impact on the healthcare system in these countries has also been profound, with asthma treatment alone now being a multi-billion dollar industry.³

The principal antigenic triggers for these diseases have been identified and comprehensively characterized, and comprise a range of airborne proteins ('environmental allergens') that are ubiquitous in dusts, particularly inside the home.⁴ Earlier notions that immunological hyper-responsiveness to allergens impacting on mucosal surfaces was the basis for the atopic phenotype have now been supplanted by evidence indicating that T cell immunity to these agents is universal, responder phenotype instead being determined by the cytokine patterns of the Th cells which dominate respective T memory populations.^{5–8} Notably, allergy is associated with Th memory which is polarized towards the Th2 or (Th0) cytokine phenotype, whereas non-atopics express low-level Th1-polarized immunity.

However, it is also clear that while Th2 polarized memory against these airborne allergens is necessary for expression of (for example) atopic asthma, it is not sufficient in its own right, given that the majority of subjects who produce IgE (and respond by skin prick test [SPT]) to these agents, never develop asthma.^{5–8} It is now believed that the expression of asthma symptoms (essentially reversible airways obstruction triggered by severe local inflammation in the airway mucosa) is the end result of repeated cycles of intense allergen-induced Th2 cell activation within the mucosa itself. Accordingly, mucosal control mechanisms which regulate the intensity and duration of local T cell responses may play a significant role in limiting the expression of symptoms in individuals with 'sensitized' Th2 memory cells.

Thus, the expression of the atopic phenotype may require the consecutive failure of two distinct sets of control mechanisms which operate at the level of the airway mucosa, and these are considered separately in the following discussion.

T cell activation in the airway mucosa: Interactions between T cells, dendritic cells and macrophages

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Regulation of APC functions

☐ IgE☐ immune deviation☐ respiratory tract☐ T cells☐ tolerance☐

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A variety of bone marrow-derived and mesenchymal cell types (e.g. epithelial cells) expressing MHC class II antigen are present within respiratory tract tissues, and all theoretically have the potential for local antigen presentation to Th memory cells. However, at foci of inflammatory damage in tissues from atopics, the most relevant populations appear to be dendritic cells (DC) and monocytes/macrophages, as B cell blasts are infrequent, and MHC class II positive epithelial cells appear to deliver anergizing (as opposed to activating) signals.⁹

T cell activation is observed in atopic lung tissues in the alveolar regions and particularly in and around the epithelium of the conducting airways, and epithelial desquam represents one of the hallmarks of this disease process. This localization mirrors precisely the distribution of resident DC populations, which exist as contiguous networks within and directly below the airway epithelium and throughout the alveolar interstitium in humans and experimental animals.^{10–14} However, studies in the rat indicate that, analogous to what has been described in relation to epidermal Langerhans cells,¹⁵ resting respiratory tract DC are restricted to the 'sentinel' functions of antigen uptake/processing, and they do not express their full potential for T cell activation until they are cultured in a source of granulocyte/macrophage colony stimulating factor (GM-CSF).^{16–18} This functional maturation is believed to normally occur *in vivo* only after migration of the DC to regional lymph nodes (RLN), thus limiting the potential for T cell cytokine-mediated damage to airway tissue sites.¹⁷

Consistent with their 'sentinel' role at the airway mucosal interface with the outside environment, airway epithelial DC populations turn over extremely rapidly in the steady state (half-life ≤ 2 days¹⁹), and respond rapidly to local challenge with a variety of microbial and non-microbial antigens via accelerated recruitment of large numbers of additional precursors.^{20, 21} It has not yet been established whether the *in situ* functional phenotype of the DC change under these circumstances of local stress.

Immunoregulatory role of lung macrophages

At least one potent endogenous control mechanism has been described for down-regulation of GM-CSF-mediated functional maturation of airway DC, in the form of nitric oxide (NO) production by lung macrophages.¹⁷ These latter *in vitro* studies are supported by *in vivo* observations indicating that depletion of alveolar and airway luminal macrophage populations via intratracheal dichloromethylene diphosphonate leads to both rapid up-regulation of the APC activity of lung DC,¹⁷ and hyperresponsiveness of the depleted animals to intratracheal²² or aerosol²³ challenge with recall antigen.

It is important to note that within the lung macrophage population, cells at the monocytic end of the differentiation spectrum function as efficient APC. However, in virtually all species except the guinea-pig,²⁴ mature lung wall and alveolar macrophages (AM) directly inhibit the capacity of T cells to proliferate in response to activation signals.^{25–27} The AM effector mechanism in rodents is again NO secretion,^{26, 28, 29} and a further (as yet undefined) mechanism operates in humans.²⁷ Recent studies in our lab indicate that NO functions in this system by dephosphorylation of Jak3/Stat5 kinases, via a cyclic GMP-dependent mechanism.³⁰

We have also recently established that the effects of NO are limited to reversible inhibition of proliferation, as the T cells secrete normal levels of cytokines including IL-2, IFN- γ and GM-CSF.^{27, 29} The role of this mechanism may thus be to limit the expression of local effector function by individual T cells to a 'single hit', while preserving their capacity to contribute to Th memory cell generation after migration from the lung microenvironment into RLN.

It is also of interest to note that down-regulation of Th memory cell proliferation by the AM is not a constitutive mechanism, but requires initial activation in the form of an IFN- γ signal³¹ which we have previously determined as emanating from bystander T blasts.³² Additionally, the mechanism can be at least temporarily shut-off via the combination of GM-CSF and TNF- α , or particularly via TGF- β .^{25, 33}

The airway mucosa in atopic asthmatics

The precise role of these cellular processes in the pathogenesis of human atopic asthma remains to be established. However, it is noteworthy that airway mucosal DC have recently been shown to be increased in number in subjects with allergic respiratory disease,^{34–37} and to express activation markers such as the low affinity receptor for IgE.^{35, 36} In addition, the atopic asthmatic airway mucosa is also characterized by high level production of both GM-CSF³⁸ and NO.³⁹

The hallmark of this tissue in atopics is the relatively high frequency of activated T cells, especially Th2 cells. It is tempting to speculate that the mechanisms described above may contribute towards the local accumulation of these T cells, during the disease process.

Development of Th memory against airborne environmental allergens: Animal models

A variety of experimental animal models are now available for the study of the effector phase of allergic respiratory disease. In general, these involve parenteral immunization of animals with soluble protein antigen plus Th2-selective adjuvants, followed by repeated aerosol challenge, to set up foci of T cell-driven inflammation in the airways.

In humans, comparable Th2 responses are only seen in a minority of (atopic) subjects. How is Th2 polarized allergen-specific memory initially established in these individuals?

This process has been modelled by passively exposing mice and rats repeatedly to low levels of aerosolized antigens, mimicking natural exposure of humans to aeroallergens. The key findings (reviewed in^{40, 41}) are that virtually all animals initially manifest a 'default' Th2 response characterized by IgE antibody production which, with continued exposure, spontaneously (and permanently) terminates.

In some animal strains, such as the B6 mouse, this change follows the classical pattern of immune deviation from Th2 to Th1, as exposed animals cease production of IgE/IgG₁ antibody, while boosting the IgG_{2a}/IgG_{2b} subclass.⁴² In contrast, high IgE responder BN rats switch off production of IgE antibody while boosting production of all IgG subclasses (⁴³ and Holt, unpubl. obs., 1997). Concomitant with down-regulation of IgE, aerosol-exposed low IgE-responder strains such as the SJ/L mouse and WAG rats often display loss of production of all IgG subclass antibodies, as well as secretory IgA and DTH reactivity.^{44–46} These differences are paralleled by multilog-scale variations in antigen dose–response curves in various strains in relation to the threshold exposure levels required to mediate tolerance/deviation.^{45, 46} Additionally, a range of environmental factors, including microbial status of the animals, influences the efficiency of this regulatory process.^{46, 47}

Once tolerance/deviation is established, the phenomenon can in most instances be reproduced in naive animals by adoptive transfer of T cells. When aerosol exposure systems are employed which target the lung and airway mucosa, the effector cells are CD8⁺,^{43, 48} and in some models CD8⁺ + TCR γ/δ .^{16,20} In contrast, when intranasal delivery (targeting the nasal mucosa) is employed, the effector cells appear to be CD4⁺.^{49, 50} Comparable heterogeneity with respect to effector cells has been reported in parallel models of oral tolerance.⁵¹

Also, despite the effectiveness of CD8⁺ T cells in transferring established tolerance, the initial induction of IgE-selective tolerance proceeds normally in $\beta_2\text{M}^-/-$ animals and those treated with antibodies against CD8⁺ on T γ/δ cells (McMenamin, Cooper & Holt, unpubl. obs., 1997). Comparable observations have been recently reported from oral tolerance models, where despite the positive role of IFN- γ and CD8⁺ cells in adoptive transfer, IFN- γ -deficient and CD8⁺-deficient animals readily develop tolerance to fed antigens.⁵¹

These findings suggest that the regulatory T cells identified by adoptive transfer are likely to function in the maintenance, as opposed to the initial induction of tolerance/deviation.

Our laboratory is accordingly exploring alternative cellular mechanisms for Th1/Th2 switch regulation during primary immune responses to inhaled antigens. Our current focus is upon the potential role of the major APC population in the airway mucosa, intraepithelial DC.^{12, 14} Accumulating evidence (Stumbles and Holt, unpubl. obs., 1997) suggests that the initial Th2 'default' in these responses may be directly attributable to intrinsic properties of the DC themselves and, further, that these cells play an active role in subsequent deviation towards the Th1 phenotype.

Allergen-specific Th memory development in humans

The available animal model evidence indicates that the key events determining long-term Th memory against airborne allergens occur during the first few cycles of exposure. These findings serve to focus attention on the perinatal period in humans, during which the immunologically naive infant is initially exposed to the outside environment.

Studies from a number of groups (reviewed in⁴¹) suggest that initial priming of the T cell system against aeroallergens occurs *in utero* via transplacental leakage of allergens present in the maternal environment. These early responses are uniformly polarized towards the Th2 cytokine phenotype, and are dominated by high-level production of IL-10.^{52, 53}

After birth, presumably driven by direct exposure to higher levels of inhaled aeroallergen, these early responses are subject to selection/modulation via mechanisms such as high zone and low zone tolerance/immune deviation. By the age of 5 years, allergen-specific Th2 reactivity in approximately 65% of children is replaced by low-level Th1 polarized immunity,⁵⁴ which is consolidated further with age.^{7, 54, 55} However, approximately 35% of 5 year olds amplify their 'foetal' Th2 responses to at least one major allergen specificity,⁵⁴ and many start to express allergy symptoms which become progressively more severe with age. Thus, the development of potentially pathogenic Th2 polarized Th memory against these allergens appears attributable to a failure of the mechanism(s) underlying the low zone tolerance/ immune deviation process which normally redirects these foetal Th2-primed responses towards the Th1 cytokine phenotype.

It is interesting to note that over this same 5 year postnatal period, high zone tolerance mechanisms operative at the level of the gastrointestinal mucosa appear to efficiently 'tolerize' T cells reactive to common food allergens, evidenced by the age-dependent decline in both lymphoproliferative and cytokine responses.^{54, 55}

Disparate allergen-specific Th memory development in atopics versus normals: What determines the difference?

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Host factors

Recent studies relating to the immunology of pregnancy indicate that the initial polarization of allergen-specific T cell responses in foetal life is part of a homeostatic mechanism which protects the placenta against potentially toxic Th1 cytokines.⁵⁶ The repolarization of the adaptive immune system towards Th1, necessary for protection against microbial pathogens, commences at birth; however, this 're-education' process is relatively slow, and key Th1 functions such as IFN- γ production are acquired relatively sluggishly over the first 5 years of life.^{57, 58}

It is becoming evident that in children genetically at high risk (HR) for atopy, the kinetics of postnatal maturation of Th1 competence is sluggish,

relative to the rest of the (low risk (LR)) population. Thus at birth, IFN- γ production by PBMC from HR infants is reduced relative to their LR counterparts (reviewed in ^{57, 58}), and remains so throughout infancy,⁵⁹ and this transient maturational defect may stall (and in some cases permanently frustrate) immune deviation of foetally primed allergen-specific Th2 responses.

In support of this contention, it has recently been demonstrated in a retrospective study on 900 school children, that expression of atopic disease at age 12 years is inversely correlated with responsiveness to BCG vaccination during early childhood: atopy symptoms were three to four times higher in children who remained Mantoux negative after vaccination at 3 months/6 years, relative to those who successfully developed long-term Th1-dependent tuberculin sensitivity following their first vaccination.⁶⁰

The basis for this maturational defect remains to be elucidated. Our laboratory is currently focusing on both T cells and APC, in this context.

Environmental factors

As noted earlier, the post 1960s explosion in atopy prevalence is a phenomenon related to First World Western lifestyle, which does not appear to be attributable to simple factors such as air pollution.^{1, 2}

One suggestion currently under investigation in many centres is that increasingly efficient public health measures employed in paediatric practice in affluent countries may have had effects on immune function in infants which could not have reasonably been predicted. The nature of this argument is that factors such as provision of microbiologically 'clean' water and food supplies, mass immunization programmes, widespread use (sometimes overuse) of antibiotics, reduction in crowding (family sizes, housing, school classes etc.), while reducing the burden of serious infection in young children, may also have diluted some of the beneficial immunostimulatory effects of normal microbial exposure, removing an important layer of bystander stimulation which assists in driving the acquisition of Th1 'competence' during early childhood (reviewed in ^{58, 61}).

These suggestions rest solely on indirect epidemiological findings, and await confirmation in complex prospective cohort studies which simultaneously track postnatal infection history and the development of allergen-specific T cell immunity. Such studies are in progress in several centres, including our own.

The basic science underlying such a complex set of interactions may not be as obscure as it superficially appears. As argued recently,^{58, 61} it is clear from animal studies that postnatal development of adaptive immune competence is driven largely by stimulation from the microbial environment, partly from infections, but especially from the normal flora of the gut.

An elegant illustration of how this maturation process can impact upon control of Th2 immunity appears in a recent issue of the *Journal of Immunology*, which demonstrates that exposure of infant mice to normal gut flora during the preweaning period is an obligate prerequisite for subsequent development of capacity to down-regulate IgE responses to mucosally delivered allergen.⁴⁷ This finding echoes earlier work from our laboratory on responses to inhaled allergen,⁴⁶ and also has many parallels in the autoimmune disease literature.⁶² In the latter context, it is of interest to note that the First : Second world gradient in allergic disease prevalence is mirrored by a comparable gradient in autoimmune diseases (Björkstén pers. comm.).

The nature of the mechanisms underlying microbial- induced maturation of immune function in neonates remains one of immunology's darker mysteries, which attracts little attention from the research community; given the potential importance of this fundamental process in the aetiology of a range of immunologically mediated diseases, it is a mystery worthy of reinvestigation with the tools now available.

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