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VIEWPOINT

The Ins and Outs of Body Surface Immunology

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Rather than being confined to the secondary lymphoid tissue of the spleen and lymph nodes, large numbers of lymphocytes are intrinsically associated with the epithelial surfaces of the body. The best studied is gut-associated lymphoid tissue, but distinct epithelium-associated lymphoid tissue also exists in the reproductive tract, the lung, and the skin. The multiple cell types and functions composing these lymphoid tissues are increasingly seen as the key to how antigens delivered to body surfaces can elicit either immunogenic or tolerogenic responses. In some instances, these responses occur purely within the local body surface tissue, yet in other cases both local and systemic responses are elicited.

The immune system at body surfaces has become a contemporary paradigm for understanding systemic immune function, because local and systemic immune responses are probably connected via an "informational relay" (Fig. 1). The relay starts locally, where body surface antigen-presenting cells, such as dendritic cells (DCs), can be provoked to take up, process, and present antigens locally, or to differentiate and migrate to draining lymph nodes to present antigen to systemic T cells (*1*). The same relay system is also likely to be operational for systemic B cells, which can be also activated by DCs bearing intact antigen from elsewhere (*2*). Migration of the systemically activated cells back to infected body surface areas is facilitated by changes in the expression of homing molecules and chemokine receptors, and the informational relay is completed. Understanding this relay paradigm is critical for aiding the development of vaccines against pathogens [such as mycobacteria, human immunodeficiency virus (HIV), and influenza] that enter hosts across epithelial layers, and for targeting the pernicious cancers that also strike epithelia. But attempts to transform the body's surfaces into crucibles of immunoresponsiveness must respect the immunological tolerance that the host displays toward myriad innocuous agents (such as commensal bacteria, food antigens, pollen, or fertilized embryos) that reside at or engage our epithelia (Fig. 1). Indeed, systemic tolerance to body surface antigens can be so durable that antigen delivery via oral or nasal routes has been actively pursued as a way to reduce pathologic autoimmunity (*3*). To understand the variable outcomes of antigen exposure at body surfaces, the relay paradigm must be built upon by considering the protective and regulatory functions that are constitutively resident at body surfaces.

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Purely Local Responses

Body surfaces inherently limit infection. Absorptive mucosal epithelia are covered in a thick electrostatically charged glycocalyx, but essential absorptive functions preclude epithelial layers from being impervious. Additional protection is provided by various means. Paneth cells, for example, are provoked by bacterial products to secrete lysozyme, type II phospholipase A2, and α-defensins, which combine within minutes to insulate their neighboring epithelial cell progenitors from infection (*4*). Such rapid-acting innate responses seem particularly appropriate at body surfaces, where epithelial cells survive for only a few days. Nonetheless, local protection is also provided by cells of the adaptive immune system, notably B cells that produce secretory immunoglobulin A (sIgA) (*5*, *6*). The effectiveness of mucosal IgA (and IgM) is not limited to pathogen neutralization in the gut lumen but is extended by its capacity to bind endocytosed pathogens during transcytosis across epithelial cells (*7*). This encounter occurs at the apical recycling endosome, where low pH may release pathogens from lipid carriers and expose novel pathogen-associated epitopes, beyond those displayed ex-

tracellularly, the importance of which is highlighted by the high titers of IgA specific for such epitopes on HIV glycoprotein (gp) 41 detected in uninfected chronically exposed partners of HIV-positive individuals (*7*, *8*). Although some sIgA production is T cell–independent (*6*), T cells are a conspicuous feature of body surfaces and are considered in the following sections.

Epithelial Cells and Intraepithelial Lymphocytes (IELs)

Epithelial cells directly regulate in several lymphoid interactions, not least because of their proximity to IELs. After pathogenic bacterial infection, epithelial cells are activated via the nuclear factor kappa B (NF-κB) pathway to synthesize cytokines and chemokines [such as interleukin-8 (IL-8), MIP2α, and MIP3α] and other molecules that activate and/or recruit effector cells. Induction of this inflammatory cascade can be prevented by nonpathogenic bacteria, which, on binding directly to the epithelium, mediate an anti-inflammatory effect by interfering with the NF-κB–dependent response through a factor thought to inhibit IκBα ubiquitination/degradation (*9*). Epithelial cells also secrete cytokines, such as IL-7 and IL-15, that support the development and/or survival of resident IELs, with which they are directly juxtaposed in situ. IELs are primarily T cells, of either the αβ or γδ T cell receptor (TCR) subtype; and given the gargantuan surface area of epithelia, there may be more IELs than any other type of T cell. Most are rich in cytotoxic granules, which has led to the premise that IELs recognize and kill infected epithelial cells (*10*, *11*).

How T cells, with highly diverse antigen receptors, might find rare cognate specificities among largely sessile epithelial cells presented a paradox that prompted the "first line of defense" hypothesis, in which it was proposed that IELs recognize generic immunological distress signals rather than unique pathogen-specific epitopes (*11*). Proteins related to, but distinct from, major histocompatibility complex (MHC) class I molecules were considered to be good candidates for these signals (*11*), a prediction supported by the discovery that the MHC class I chain-related antigens MICA and MICB are up-regulated on the surface of human enterocytes by heat shock and can activate TCRγδ$^+$ human intestinal IELs (*12*). There is no evidence that MICA or MICB presents antigen (*13*); rather, IELs are thought merely to recognize the difference in MICA and MICB expression levels on normal versus stressed epithelial cells. Although the physiological stimuli that up-regulate MICA and MICB remain to be defined, they must presumably be tightly regulated so as to prevent the constitutive activation of γδ$^+$ IELs. Given that epithelial cells do not live for long, the stimuli for MICA and MICB activation may primarily be infections, or transformation events, that threaten the integrity of the whole organism. MICA and MICB are likely prototypes for other MHC-related molecules [including murine TL (*14*), RAE, H60 (*15*), and ULBP1/2 (*16*)] that may costimulate IELs through interactions with NKG2D, an "activating-type" natural killer (NK) receptor expressed on γδ$^+$ IELs, cytotoxic αβ T cells, and NK cells (*17*, *18*).

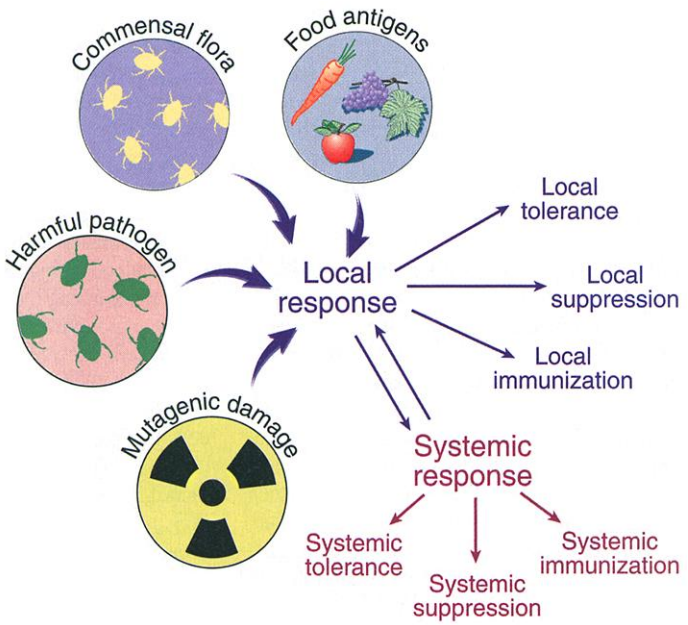

Fig. 1. The informational relay in the gut. The mucosal surfaces of the gut are exposed to myriad antigens that require very different types of responses, ranging from tolerance to suppression to active immunity. The nature of the response required is primarily determined by whether the antigen is likely to be beneficial or detrimental to the body. Once initiated, antigen responses can either be limited to the local regional tissues or be extended beyond the local site to elicit responses at distant systemic areas as a complement to the local response. The likely purpose of the systemic response is to mediate antigen-specific immune function at distal sites, or, if help is needed at the body surface, the systemically triggered cells may be required to feed back into the locally challenged area.

Specificity of IEL Recognition

Conventional αβ T cell recognition of antigen in the context of MHC class I or II is classically guided by CD8αβ and CD4, respectively. The observation that IELs are usually positive for only CD8α in the absence of CD8β (CD8α$^+$β$^-$) or negative for both CD4 and CD8 (CD4$^-$CD8αβ$^-$) is consistent with the hypothesis that IELs may preferentially recognize nonclassical MHC-like molecules. The CD4/CD8αβ coreceptors also play a critical role in conventional T cell development and selection, so quite how IELs that are reactive to autologous determinants such as MICA or TL are selected has yet to be resolved. It is possible that epithelia directly support extrathymic development of IELs from bone marrow–derived progenitors (*19*–*21*). An alternative model for consideration is that IEL might develop in the thymus during the fetal or neonatal periods, when negative selection events operate less effectively than in adults (*22*). Such cells would be subsequently deleted in peripheral lymph nodes and spleen but could be selected in epithelia by low-level autoantigen expression (*22*). This model of pre-exposure might also explain why IELs can respond rapidly to epithelial cells that are unable to prime conventional T cells de novo and fits with the prediction that a series of tissue-specific MHC class I–related antigens positively retain IELs with particular tissue-associated TCRs (*23*). The fact that IEL repertoires are established during the early stages of life raises the interesting possibility that IELs have an age-dependent function primarily directed toward protecting the neonate rather than the adult (*24*).

IELs and the Systemic Response

Although we do not know whether the systemic response is uncoupled from IEL interactions with epithelial cells, we know that the reverse is not true. γδ$^+$ IELs secrete chemokines (*25*), which can regulate cell trafficking and have been implicated in down-regulating infiltrating systemic effectors. After infection with epithelia-tropic coccidia, γδ cell–deficient mice show an exacerbated pathology attributed to the unregulated actions of systemic αβ T cells (*26*). And γδ cell–deficient mice successively challenged with autoreactive CD4$^+$ αβ T cells show more aggressive epidermal infiltration than control mice, possibly because they lack γδ$^+$ dendritic epidermal T cells (DETCs) that ordinarily suppress systemic infiltration (*27*). It will be important to resolve whether DETCs exert similar regulation over physiologic contact sensitivities, and if so, which cells might provide an analogous function in humans where DETCs are less evident. The importance of local and systemic immunoregulation by

IELs is underscored by the observation that mice with IEL defects are susceptible to developing inflammatory bowel disease (IBD) (*28*).

Controlling the Information Relay to Systemic Responses

Local control of information being relayed systemically would seem to be key for determining whether responses to antigens encountered at body surfaces induce tolerance or immunization and whether the responses remain purely local or disseminate systemically. Control is probably mediated by the resident antigen-presenting cells (APCs) and the resident T cells. It was assumed for many years that the outcome of mucosal tolerance or immunity was determined purely by the nature of the antigen and the APCs. Soluble protein antigens taken up by epithelial cells were thought to be preferentially presented by nonprofessional/unconventional APCs, such as B cells/epithelial cells, whereas particulate antigens taken up in the Peyer's patches were thought to be preferentially presented by professional APCs. Today, these views have been refined (*29*). Intestinal DCs have been shown to be capable of taking up fed soluble protein antigen and priming naïve T cells (*30*), and conversely, DCs that have taken up apoptotic enterocytes have been shown to be poor at T cell priming (*31*). This latter observation proffers an intriguing candidate mechanism for anergizing systemic T cells that are reactive to enterocyte autoantigens or associated commensal bacterial flora. Other studies on APCs have shown that this singular cell type (the DC) may tolerize under normal default circumstances but has the capacity to immunize after the up-regulation of costimulatory molecules (such as CD80, CD86, CD40, and OX40L) by proinflammatory mediators (*32–34*). It is also worth considering that inflammatory mediators can induce expression of MHC class II antigen-processing machinery within epithelial cells, although the physiological consequences of this in vivo remain uncertain (*35*).

How oral feeding might lead to systemic tolerance has been a difficult question to answer. What are the precise molecular signals that accompany antigen exposure at body surfaces and which cells provide them? Recent information implicates the mucosal T cells themselves in at least a part of the story. Studies tracking T cells in the gut have indicated that recognition of orally administered antigen by T cells occurs throughout the gut-associated lymphoid tissue: in the lamina propria, in the Peyer's patches (PP), and in the mesenteric lymph nodes (*36–39*), which are sites where cells are under strong influence from the local milieu. Integrins such as $\alpha_E/\beta7$ and $\alpha4/\beta7$, together with cytokines and chemokines, are thought to recruit and/or retain epithelium-associated T cells in situ, without the prior exposure to antigen that ordinarily facilitates T cell entry into tissues. Now data indicate that oral feeding leads to interferon-γ production by mucosal T cells, a process that is thought to down-regulate systemic homing molecules and induce chemokines or chemokine receptors that inhibit T cell migration (*39*). However, it is difficult to imagine that this T cell sequestration is sufficient on its own to explain long-lived systemic unresponsiveness.

All in all, the molecular signals intrinsic to controlling the response to antigen delivery at body surfaces have, as yet, failed to provide predictive power about the nature of the ensuing immune response. This is evidenced by the fact that some individuals actively respond to organisms tolerated by others (*40*). Host genetic variation in the response to molecular signals will clearly make some contribution, but one intriguing notion is that age-dependent factors may once again play a role; i.e., an adult responds actively to bacteria that would have been tolerated early in life, when the status of epithelial cells, IELs, and APC–T cell interactions and signaling may have been quite different.

Local Regulation of the Type of Immune Response

One means of control that must also be considered arises from observations that various cells have a capacity to alternate T cell responses. For example, by secreting IDO, which catabolizes tryptophan that is essential for T cell survival, cells in the reproductive tract can suppress the proliferation of alloreactive T cells that might otherwise attack the embryo (*41*). Another example of how some cells can suppress T cell responses comes from studies on intestinal regulatory Tr or T helper cell type 3 (T_h3) T cells. Regulatory T cells affect other T cell responses, probably by heterogeneous means: most likely via IL-10 and/or transforming growth factor–β (*42*). The evidence that IL-10 contributes to the tolerogenic phenotype generally observed in the gut is unrivaled. IL-10–deficient mice develop IBD, and exogenous administration of recombinant IL-10 can attenuate intestinal inflammation in most of the experimentally induced models of IBD, as can local delivery of bacteria genetically engineered to secrete IL-10 (*43*)

Lessons can also be learned from the T cell response to allergens encountered in the respiratory tract, where it has been proposed that the development of suppressor cells, rather than effectors, can be directed during antigen presentation by the variable expression of Notch ligands, jagged and serrate, on the APCs (*44*). What regulates that variable expression is undefined, but were it to include locally acting regulators, it could contribute to the default status of suppression at body surfaces versus immunization in the systemic circulation.

It is also important to remember that immunological distinctions at body surfaces extend beyond simple tolerance and responsiveness. Studies of murine systemic DC subsets have revealed that that lymphoid-precursor–derived $CD11c^+$ $CD8\alpha^+$ DCs preferentially direct T_h1 responses (via IL-12), whereas myeloid-precursor–derived $CD11c^+$ $CD11b^+$ DCs preferentially direct T_h2 responses. Although both DC subsets can be found in the PP (*45*), antigen-pulsed DCs isolated from the PP reportedly induce T_h2-type rather than T_h1-type responses (*46*). The latter bias is also true for DCs from the respiratory tract, which will preferentially bias toward a T_h2 response (*47*). Although the different DC subtypes have been shown to localize to distinct areas of the PP (*46*, *48*), there is no evidence that committed Th cells are similarly distributed. Possibly T_h2 skewing is provoked at body surfaces by the strong representation of molecules that under normal circumstances promote tolerance. IL-10 would be a good candidate, because in addition to dampening T cell responses, it promotes IgA production, cytolysis, neutrophil activation, and other aspects of body surface–associated effector responses (*49*).

This review has merely touched on the potential plasticity of responses that are available for body surfaces. The pleiotropy of choice for the epithelial-associated lymphoid tissues highlights how dramatic changes in immunological outcome can ensue swiftly—a process contingent on the physiologic context in which antigens breach body surfaces and possibly on the period in ontogenetic development when those antigens are encountered. The informational relay that exists between local and systemic responses provides a starting point for elucidating how differential immune reactivity is programmed.

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