Etiology of epithelial barrier dysfunction in patients with type 2 inflammatory diseases

Robert P. Schleimer, PhD, and Sergejs Berdnikovs, PhD *Chicago, Ill*

Epithelial barriers of the skin, gastrointestinal tract, and airway serve common critical functions, such as maintaining a physical barrier against environmental insults and allergens and providing a tissue interface balancing the communication between the internal and external environments. We now understand that in patients with allergic disease, regardless of tissue location, the homeostatic balance of the epithelial barrier is skewed toward loss of differentiation, reduced junctional integrity, and impaired innate defense. Importantly, epithelial dysfunction characterized by these traits appears to pre-date atopy and development of allergic disease. Despite our growing appreciation of the centrality of barrier dysfunction in initiation of allergic disease, many important questions remain to be answered regarding mechanisms disrupting normal barrier function. Although our external environment (proteases, allergens, and injury) is classically thought of as a principal contributor to barrier disruption associated with allergic sensitization, there is a need to better understand contributions of the internal environment (hormones, diet, and circadian clock). Systemic drivers of disease, such as alterations of the endocrine system, metabolism, and aberrant control of developmental signaling, are emerging as new players in driving epithelial dysfunction and allergic predisposition at various barrier sites. Identifying such central mediators of epithelial dysfunction using both systems biology tools and causality-driven laboratory experimentation will be essential in building new strategic interventions to prevent or reverse the process of barrier loss in allergic patients. (J Allergy Clin Immunol 2017;139:1752-61.)

Key words: *Epithelial barrier, differentiation, mesenchyme, extracellular matrix, tight junctions, hormones, metabolism, allergic predisposition, allergic sensitization*

Abbreviations used
AD: Atopic dermatitis
CRS: Chronic rhinosinusitis
EDC: Epidermal differentiation complex
EMT: Epithelial-to-mesenchymal transition
EoE: Eosinophilic esophagitis
FLG: Filaggrin
ZO-1: Zonula occludens 1

The epithelial barrier is diverse, occurring *inter alia* in the gastrointestinal tract, urogenital tract, respiratory system, eyes, and skin. Epithelial cells are specialized in each of these organ systems and in the various geographic regions of each system. The main functions of epithelia are to present a physical and immune barrier; maintain a surface that accommodates commensal organisms but not pathogens; remove, degrade, or neutralize environmental toxins and particulates; and maintain the balance of water and electrolytes. Specialized functions of the physical barrier include maintenance of the mucociliary escalator in the airways, production of surfactants in the alveoli and small airways, and production of a protective mucus blanket in the gastrointestinal and urogenital tracts.

The phrase immune barrier refers to epithelial elements that are essential for innate immune resistance to potential pathogens, including constitutive and inducible expression of enzymes, peptides, proteins, lipids, ions, and pathogen recognition receptor systems designed to protect the host. Combined with epithelial tight junctions, these systems present a vigilant and effective barrier to microbial invasion. Many allergic diseases are now known to manifest clear disorders of the immune barrier. The purpose of this review is to discuss the presence of barrier dysfunction, its role in allergic disease, and the molecular and endocrinologic mechanisms that are underlying causes.

BARRIER DEFECTS IN PATIENTS WITH TYPE 2 DISEASES

Introduction

When the immune barrier is predisposed to disruption, microorganisms and antigens can gain access between epithelial cells through the basement membrane to the underlying lamina

From the Division of Allergy and Immunology, Northwestern University Feinberg School of Medicine.

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Corresponding author: Sergejs Berdnikovs, PhD, Division of Allergy-Immunology, Northwestern University Feinberg School of Medicine, McGaw Building, Rm M-302, 240 East Huron St, Chicago, IL 60611. E-mail: s-berdnikovs@northwestern.edu.

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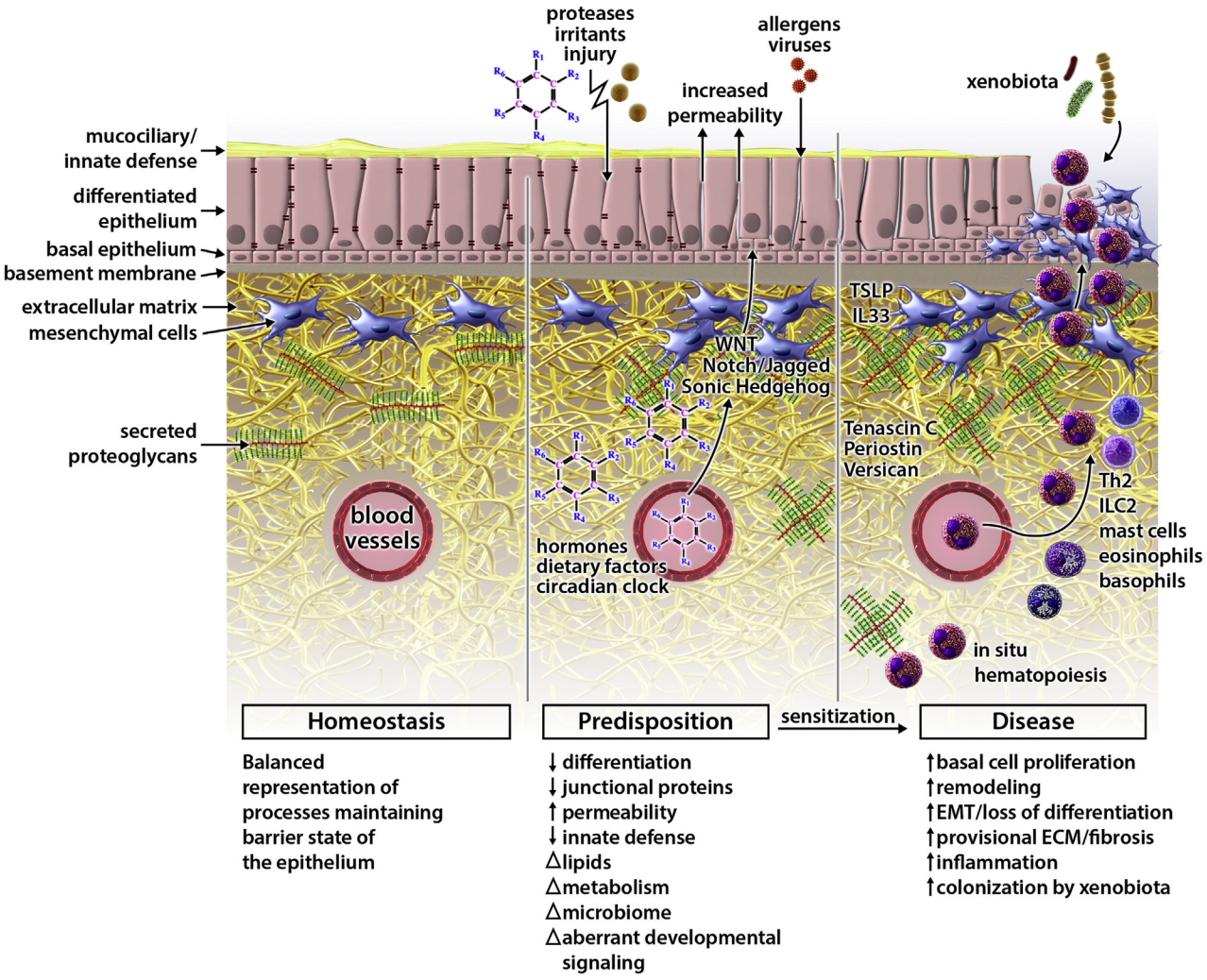

FIG 1. Key features of epithelial dysfunction common to all allergic disease. Epithelial barriers predisposed to type 2 allergic disease are characterized by increased permeability and aberrant behavior of morphogenetic programs that maintain epithelial homeostasis. Both exogenous (inhaled allergens, respiratory viruses, chemical sensitizers, and air pollutants) and endogenous (hormones, dietary factors, and altered circadian clock) disruptors of epithelial homeostasis can drive predisposition to allergic sensitization by altering homeostatic activity of developmental pathways (WNT, Notch, and Hedgehog) that maintain proper epithelial-to-mesenchymal communication, epithelial differentiation, and barrier integrity. Transition to a remodeling state in disease typically follows allergic sensitization and inflammatory responses. This transition features further loss of differentiation signals, downregulation of innate defense molecules, profibrotic processes, deposition of extracellular matrix, and potentiated activity of the mesenchymal unit. *ILC2*, Group 2 innate lymphoid cell; *TSLP*, thymic stromal lymphopoietin.

propria and connective tissue. Penetration of microbes triggers strong innate immune responses by pathogen recognition receptors on epithelial cells and immune cells, such as macrophages, innate lymphoid cells, and mast cells, residing among epithelial cells or on the basolateral side of the lamina reticularis. Subsequent sensitization and activation of adaptive immune responses can result, including type 2 immune responses of relevance to the allergic diathesis. Epithelial function can become compromised by alterations in numerous key functional or structural elements, such as epithelial junctional or filamentous proteins. Loss of protective anti-proteases, antimicrobial peptides or compounds, or disturbances in transport of ions, protons or water can also disrupt barrier function. Profound activation of sensory nerves important in manifestation of disease experienced by the patient is also associated with loss of barrier and sensitization. In this section we briefly discuss some of the salient mechanisms and features of barrier loss commonly shared by all patients with allergic diseases (summarized in Fig 1).

Atopic dermatitis

Atopic dermatitis (AD) is characterized by loss of barrier function of the skin, culminating in a clinical phenotype characterized by formation of skin lesions. Skin barrier dysfunction is induced by disruption of the stratum corneum, a dense protein-lipid matrix that functions as a barrier to water loss, environmental insults and allergens. Filaggrin (FLG), a filament-associated epidermal differentiation complex (EDC) protein essential for regulation of epidermal homeostasis, is highly deficient in the skin of many patients with AD.[1] Similarly, the FLG-like proteins hornerin and FLG2 are detected at