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Review article

Recent advances in understanding the roles of vascular endothelial cells in allergic inflammation

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Abbreviations:
AD, atopic dermatitis; BA, bronchial asthma; CCR, CC chemokine receptor; COPD, chronic obstructive pulmonary disease; GWAS, genome-wide association studies; ICAM, intercellular adhesion molecule; ICS, inhaled corticosteroid; ILC, innate lymphoid cells; MHC, major histocompatibility complex; PAMPs, pathogen-associated molecular patterns; PMCH, pro-melanin-concentrating hormone; PRRs, pattern-recognition receptors; TARC, thymus and activation-regulated chemokine; TSLP, thymic stromal lymphopoietin; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor

ABSTRACT

Allergic disorders commonly involve both chronic tissue inflammation and remodeling caused by immunological reactions to various antigens on tissue surfaces. Due to their anatomical location, vascular endothelial cells are the final responders to interact with various exogenous factors that come into contact with the epithelial surface, such as pathogen-associated molecular patterns (PAMPs) and antigens. Recent studies have shed light on the important roles of endothelial cells in the development and exacerbation of allergic disorders. For instance, endothelial cells have the greatest potential to produce several key molecules that are deeply involved in allergic inflammation, such as periostin and thymus and activation-regulated chemokine (TARC/CCL17). Additionally, endothelial cells were recently shown to be important functional targets for IL-33—an essential regulator of allergic inflammation. Notably, almost all endothelial cell responses and functions involved in allergic inflammation are not suppressed by corticosteroids. These corticosteroid-refractory endothelial cell responses and functions include TNF-α-associated angiogenesis, leukocyte adhesion, IL-33-mediated responses and periostin and TARC production. Therefore, these unique responses and functions of endothelial cells may be critically involved in the pathogenesis of various allergic disorders, especially their refractory processes. Here, we review recent studies, including ours, which have elucidated previously unknown pathophysiological roles of vascular endothelial cells in allergic inflammation and discuss the possibility of endothelium-targeted therapy for allergic disorders.

Introduction

The global prevalence of allergic disorders, including a range of chronic illnesses, such as bronchial asthma (BA),[1] allergic rhinitis,[2] eosinophilic gastrointestinal disorders[3] and atopic dermatitis (AD),[4] has been increasing in recent decades, leading to serious social and economic burdens.[5] The pathogenesis of these allergic disorders commonly involves both chronic tissue inflammation and remodeling.[6]

The pathogenesis of allergic diseases is characterized by chronically progressive inflammatory reactions that are often triggered by exposure of epithelial surfaces to antigens. Epithelial inflammation leads to responses by tissue structural cells, in addition to activation of a variety of immune cells such as lymphocytes, phagocytes and granulocytes, to the antigens that play essential roles in the pathogenesis of the inflammation. Among

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tissue structural cells, epithelial cells constitute the initial structural and immunological barrier to entry of foreign antigens. In addition, recent studies strongly suggest that epithelial cells also function as important sources of a wide variety of immune mediators. In particular, novel epithelial cell-derived cytokines, including IL-25, IL-33 and thymic stromal lymphopoietin (TSLP), have attracted considerable interest because of their potent functions in promoting type 2 immunity.[7] Fibroblasts, another type of tissue structural cell, play crucial roles in maintaining tissue homeostasis and bringing about wound healing under normal conditions. However, excessive and chronic inflammation as a consequence of activation of immune responses often leads to irreversible tissue fibrosis, resulting in severe and refractory illnesses.[8] Compared to epithelial cells and fibroblasts, the roles of vascular endothelial cells in allergic disorders remain poorly understood. Figure 1A shows a simplified structure of the tissue surface.

Endothelial cells form a one-cell-thick layer called the endothelium (Fig. 1A), which lines the inner wall of blood vessels, forming a selectively permeable barrier between the blood inside the vessels and the surrounding tissues. The endothelium is a highly specialized structure spread throughout the body. It has many vital functions, including blood and oxygen supply, nutrient delivery, metabolic homeostasis and immune cell trafficking.[9–13] On the other hand, we have elucidated several critical roles of pulmonary and skin microvascular endothelial cells in allergic inflammation. In particular, endothelial cells have the greatest potential to produce several key molecules involved in allergic inflammation. The blood levels of periostin[14] and thymus and activation-regulated chemokine (TARC/CCL17)[15] already serve as reliable biomarkers reflecting disease progression of allergic disorders. In addition to being key cellular sources of molecules essential for allergic inflammation, endothelial cells are important functional targets for IL-33,[16] whose gene locus has been reported to be the most consistently associated with BA in all tested ethnic groups. Notably, almost all endothelial cell responses and functions involved in allergic inflammation cannot be suppressed by corticosteroid treatment, a current first-line therapy for various allergic disorders. We, therefore, inferred that endothelial cell responses and functions are crucially involved in the progression of various allergic disorders, especially in corticosteroid-refractory processes.

This review article focuses on the contributions of vascular endothelial cells in the development and exacerbation of allergic disorders. Following a brief introduction of the basic biology, we will review how recent reports, including ours, have elucidated the responses of endothelial cells to representative type 2 cytokines and chemokines in allergic airway and skin inflammation. We finally discuss the roles of endothelial cells in corticosteroid refractoriness and the possibility of endothelium-targeted therapy for allergic disorders.

Structure and fundamental functions of endothelial cells

Blood vessels are composed of a sheet of inner endothelium, which is a monolayer of endothelial cells that surrounds functional cells, including pericytes and vascular smooth muscle cells, and extracellular matrix (Fig. 1A).[17] The endothelial and supportive mural cells are tightly bound to each other, partly through integrins, thereby maintaining vascular integrity (Fig. 1A). The endothelium is composed of $1–6 \times 10^{13}$ endothelial cells that cover more than 1000 m^2 of surface area throughout the body.[9,10]

In the absence of inflammation, vascular endothelial cells serve as an essential barrier between the bloodstream and vessel walls. In addition to being a physical barrier, endothelial cells have various indispensable functions, which can be classified into three major groups: 1) modulation of metabolic homeostasis (trophic action), 2) control of vascular hemodynamics (tonic action) and 3) regulation of vascular permeability, coagulation and cell extravasation (trafficking).[18]

These functions of endothelial cells change during the transition from quiescent to inflammatory conditions. The initial change of the vessels in acute inflammation is characterized by increased blood flow secondary to arteriolar and capillary bed dilation (erythema and warmth).[19,20] Increased vascular permeability, as a consequence of either widening of interendothelial cell junctions of the venules or direct endothelial cell injury, results in an exudate of

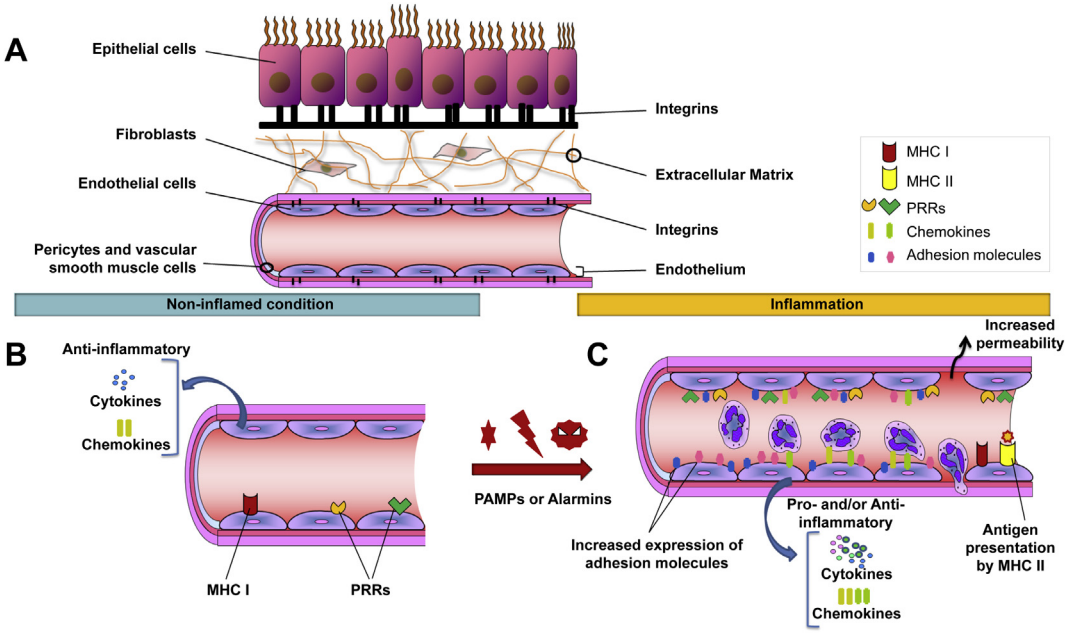

Fig. 1. The basic biology of vascular endothelial cells. (A) Simplified structure of the tissue surface. In addition to being a physical barrier, endothelial cells have several indispensable functions. The different roles of endothelial cells are illustrated in non-inflamed conditions (B) and in inflammation (C).