The Chemokine Receptor CCR7 Expressed by Dendritic Cells: A Key Player in Corneal and Ocular Surface Inflammation

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ABSTRACT Dendritic cells (DCs) are highly potent stimulators of the immune system, and their contribution as such to the pathogenesis of corneal and ocular surface inflammatory disease has been well established. These vigorous antigen-presenting cells are reliant upon their effective migration from peripheral tissues (e.g., those of the ocular surface) to the lymphoid organs, where immune responses are triggered and can then cause disease. The chemokine receptor CCR7 expressed on DCs has emerged as the master mediator of this highly complex migratory process, and thus it is important in causing corneal and ocular surface inflammation. Furthermore, CCR7 has received considerable attention as a potential therapeutic target, as topically instilled antagonists of this receptor are quite effective therapeutically in a mouse model of ocular allergy. These findings and more are reviewed in the current article. In addition, the understanding regarding CCR7 function in mice and humans, and the biology of DCs that populate the ocular surface are also detailed herein. The involvement of DCs and their expression of CCR7 in corneal and ocular surface diseases such as in ocular allergy, dry eye disease, immune rejection and more, are also reviewed here.

KEY WORDS allergic conjunctivitis, CCR7, CD103, conjunctivitis, dendritic cells, dry eye disease, keratitis, ocular surface, ocular allergy, T cells

I. INTRODUCTION

Work in dendritic cell (**DC**) biology has expanded considerably in the last 5-7 years. The awarding of the 2011 Nobel Prize in Physiology or Medicine to the late Ralph Steinman for his contribution in the identification of these unique antigen-presenting cells indeed underscores this. The recent increase in information in DC biology has had a profound impact on the current understanding of immunity, inflammation, and disease. Similarly, the importance of DCs is indisputable in pathobiology of ocular inflammatory diseases, including those that involve the tissues of the ocular surface.

A key attribute of the DC machinery lies within their unequivocal potency for T cell stimulation, and the chemokine receptor CCR7 plays an essential role in this. In preclinical models of corneal and ocular surface inflammatory diseases, such as in ocular allergy and dry eye disease (**DED**), the role of antigen-charged DC from the cornea and ocular surface in activation of pathogenic T cells has been established.[1-7] Furthermore, other such conditions that are associated with pathogenic T cells, including ocular involvement in graft-versus-host-disease (**GVHD**), keratolimbal allograft rejection, mucous membrane pemphigoid, and Stevens-Johnson syndrome, could implicate a role for DCs as well.

In animal models and in humans, the chemokine receptor CCR7 and C-C motif ligand (**CCL**)-19 and CCL21 interaction has emerged as one of the most—if not the most—important known chemokine systems in the migration of DCs from the affected tissue to the lymph node (**LN**) paracortex.[7-13] This allows for encounter and consequent activation of cognate T cells to initiate/perpetuate adaptive immune responses and thus establishes a link for CCR7 and DCs with pathogenic T cell activation in corneal and ocular surface inflammatory diseases (Figure 1). As such, the involvement of CCR7 expression and function

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OUTLINE

Abbreviations

AKC	Atopic keratoconjunctivitis
CDP	Common DC progenitors
DC	Dendritic cell
DED	Dry eye disease
ELC	EBV-induced molecule 1 ligand chemokine
GVHD	Graft-versus-host-disease
HEV	High endothelial venules
LN	Lymph node
MHC	Major histocompatibility complex
PAC	Perennial allergic conjunctivitis
SAC	Seasonal allergic conjunctivitis
SLC	Secondary lymphoid chemokine
Treg	T regulatory cell
TSP-1	Thrombospondin-1
VKC	Vernal keratoconjunctivitis

by DCs in ocular tissues has recently received considerable attention.[2,7,14-22]

This article reviews recent literature that sheds light on how DC subsets that populate the cornea and conjunctiva utilize this chemokine receptor machinery to efficiently migrate to the LN in a highly coordinated fashion, and how this process contributes to the pathogenesis of corneal and ocular surface diseases, such as in ocular allergy. Furthermore, recent work validating the use of topical CCR7 antagonist as a therapeutic measure in ocular allergy is also reviewed.

II. FUNDAMENTALS OF CCR7 AND DC MIGRATION

Appreciation for the role of CCR7 requires an understanding of certain fundamentals of DC biology. For example, it is important to know that DCs populate the interstitial tissues throughout the body in normal physiologic conditions, where they continuously sample antigen from their environment. During inflammation and exposure to "danger signals," such as Toll-like receptor signaling, DCs are stimulated to undergo phenotypic maturation, a process that is triggered in part via their loss of thrombospondin-1 expression.[23] Maturation of DCs involves upregulation of the major histocompatibility complex (**MHC**) class II (or histocompatibility leukocyte antigen complex in humans) and CD80/CD86 costimulatory molecules. This maturation process prepares DCs to be able to prime/stimulate T cells, as MHC II is necessary for antigen presentation and CD80/CD86 are costimulatory molecules. Mature DCs also play a role in triggering secondary immune response, via activation of memory T cells also found in the LN.

However, maturation is merely an upstream event that is reliant upon CCR7-CCL19/21-mediated migration to the lymph node, where pools of naïve T cells and memory T cells are found. This is a highly complex chemotactic process that involves gaining access to terminal lymphatics, entry into the LN parenchyma, and trafficking to the T cell-rich paracortex. The sections below explain the manner by which this is accomplished.

A. CCR7 Ligands

CCR7 is a 7-transmembrane-spanning domain which signals through G protein-coupled receptors, with only known ligands including CCL19 and CCL21.[24-42] Previously referred to as EBV-induced molecule 1 ligand chemokine (**ELC**), CCL19 is expressed by fibroblastic reticular cells in the paracortical regions of the LN where T cells are found.[36,37] Migratory DCs also express CCL19 within the paracortical region, which is presented on the luminal side of high endothelial venules (**HEV**).[38] Previously referred to as *secondary lymphoid chemokine* (**SLC**), CCL21 is the other CCR7 ligand.[38-43] It is encoded by two functional variants in mice.[40] One is CCL21-Leu (containing a leucine at position 65), which is expressed on lymphatic vessels in nonlymphoid tissues. The other is CCL21-Ser (containing a serine at this position), which is expressed in fibroblastic reticular cells of the LN paracortex, as well as by endothelial cells of HEV.[40-43]

B. Coordinated CCR7-Mediated Migration of DCs

How are the different CCR7 ligand sources coordinated to accomplish DC migration? Entry into the lymphatic vessels is facilitated by DC maturation. During an inflammatory response, DCs are activated to mature and upregulate their expression of CCR7. Concurrently in inflammation,