

Review

Recent advances in roles of G-protein coupled receptors in intestinal intraepithelial lymphocytes

Hayakazu SUMIDA¹¹Department of Dermatology, Faculty of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

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Intestinal intraepithelial lymphocytes (IELs) potentially provide the first line of immune defense against enteric pathogens. In addition, there is growing evidence supporting the involvement of IELs in the pathogenesis of gut disorders such as inflammatory bowel diseases. Various kinds of molecules are involved in the dynamics of IELs, such as homing to the intestinal epithelium and retention in the intestinal mucosa. G protein-coupled receptors (GPCRs) comprise the largest family of cell surface receptors and regulate many biological responses. Although some GPCRs, like CCR9, have been implicated to have roles in IEL homing, little is still known regarding the functional roles of GPCRs in IEL biology. In this review, we provide a concise overview of recent advances in the roles of novel GPCRs like GPR55 and GPR18 in the dynamics of IELs.

Key words: intestinal intraepithelial lymphocytes, dynamics, G-protein coupled receptors, gut immunology

INTRODUCTION

Intestinal intraepithelial lymphocytes (IELs) are a heterogeneous T cell population localized within the intestinal epithelial layer, where they carry out various effector, regulatory, and protective functions [1]. IELs are distributed in the small intestine and large intestine, and it has been estimated that there is one IEL for every 4 to 10 intestinal epithelial cells (IECs) seen in the small intestine and for every 30 to 50 IECs found in the large intestine [2, 3]. These intraepithelial lymphocytes have been complicated by the heterogeneity of their functions, and these are represented by conventional (induced) and nonconventional (natural) T-cell subsets. On the basis of recent information, it is assumed that IELs play key roles in the induction and regulation of mucosal immunity. Therefore, revealing the mechanisms of the dynamics of IELs should be useful for providing novel therapeutic strategies for inflammatory bowel diseases and for understanding the gut mucosal immune system.

The G protein-coupled receptors (GPCRs) represent the largest and most versatile family of cell surface communicating molecules and are currently the most common targets in the pharmaceutical industry. GPCRs can be activated by a diverse array of ligands, including chemokines and lipid mediators. Therefore, GPCRs are involved in various key pathological and/or physiological processes. A variety of GPCRs and their mediators have been found to be involved in the immune system. Regarding gut immunology, the C-C chemokine receptor type 9 (CCR9), also known as CD119, is a member of the GPCR

supergene family selectively and functionally expressed on human and murine small-intestinal lymphocytes [4]. Murine data suggest that interactions between CCR9 and its ligand, CCL25, specifically contribute to IEL homing to the small intestine. However, given that CCR9- or CCL25-deficient mice showed decreased numbers of IELs in the small intestine [5], it has been assumed that other GPCRs besides CCR9 must be involved in the dynamics of IELs. Moreover, T-cell homing to the large intestine does not require CCR9, which is not expressed on colonic IELs. In this review, we focus on recent advances in IELs and related GPCRs such as CXCR3, GPR18, GPR55, and GPR15, especially on their dynamics and roles in physiological and/or pathological conditions.

HETEROGENEOUS POPULATION OF IELS

IELs are a heterogeneous population of T lymphocytes in the human and murine intestine and include both TCR $\alpha\beta$ ⁺ and TCR $\gamma\delta$ ⁺ IELs. These subsets are further subdivided on the basis of CD8 coreceptor expression. In the small intestine, the overwhelming majority of TCR $\gamma\delta$ ⁺ IELs are predominantly V γ 7⁺ IELs and express the CD8 $\alpha\alpha$ homodimer in mice, whereas about 10% of the small intestinal IELs express TCR $\gamma\delta$ in humans [6]. On the other hand, in the colon, the majority of CD8⁺ cells bear TCR $\alpha\beta$ and express the CD8 $\alpha\beta$ heterodimer [3, 7]. TCR $\gamma\delta$ ⁺ IELs are very different from TCR $\gamma\delta$ ⁺ T cells located in lymphoid tissues, which predominantly lack CD8 expression. Unlike T cell populations in other tissues, most TCR $\alpha\beta$ ⁺ IELs in the small

Corresponding author. Hayakazu Sumida (E-mail: sumida-tyk@umin.ac.jp)

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intestine belong to the CD8⁺ subset [8]. Moreover, a sizeable fraction of TCR $\alpha\beta$ ⁺ IELs are CD8 α ⁺CD8 β ⁻ cells [9], which are referred to as CD8 $\alpha\alpha$ IELs based on their expression of the CD8 $\alpha\alpha$ homodimer. In brief, TCR $\alpha\beta$ ⁺ IELs in the small intestine mainly consist of CD8 $\alpha\alpha$, CD8 $\alpha\beta$, and CD4. CD8 $\alpha\alpha$ ⁺ IELs that express TCR $\gamma\delta$ or TCR $\alpha\beta$ but do not express either CD4 or CD8 $\alpha\beta$ are so-called natural IELs [1]. Regarding surface markers, unconventional CD8 $\alpha\alpha$ ⁺ IELs do not express molecules typically expressed by conventional T cells but instead express natural killer cell receptors such as NK1.1 [1]. Moreover, CD8 $\alpha\alpha$ ⁺ IELs constitutively express tissue-resident markers CD69 and CD103 [10].

IELS AND INTESTINAL PATHOGENS

The intestine contains a dynamic community of trillions of pathogens. The intestinal immune system has a crucial role in limiting tissue invasion by the resident microbiota and is fundamentally important for preserving the symbiotic nature of these interactions [11]. For these roles, the intestinal immune system must avoid potentially harmful overreactions that could unnecessarily damage intestinal tissues or alter the crucial metabolic functions of the microbiota [12, 13]. Regarding the contribution of IELs to the system, these cells play a major role in protection against invasion and systemic dissemination of enteric pathogens and commensal bacteria [14, 15]. Although the microbiota has an effect on the composition and number of TCR $\alpha\beta$ IELs, TCR $\gamma\delta$ IEL numbers are unaffected in germ-free mice, indicating that the intestinal microbiota has little to no effect on maintaining TCR $\gamma\delta$ IEL homeostatic numbers [16]. However, intestinal TCR $\gamma\delta$ IELs have high expression of several cytolytic genes, such as granzymes A and B, indicating a cytotoxic potential towards pathogens and infected cells [17, 18]. Thus, TCR $\gamma\delta$ IELs provide early protection of intestinal tissue against resident bacteria [19, 20]. Furthermore, $\gamma\delta$ TCR-deficient mice, but not $\alpha\beta$ TCR-deficient mice, are more susceptible to infection than control WT mice [17, 19, 21]. In particular, IELs play key roles in the host defense against intestinal pathogens such as *Salmonella typhimurium* and *Toxoplasma gondii* [22]. Thus, revealing the mechanisms of the dynamics of IELs should be useful for understanding how IELs contribute to early protection against pathogen entry from the intestinal surface.

DEVELOPMENT AND MATURATION OF IELS

IELs seem to have a unique development pathway, although controversy remains as to the extent to which IELs are thymus dependent. Conventional IELs, i.e., those originating from circulating T cells, are activated in lymphoid organs and imprinted for gut homing using $\alpha 4\beta 7$ and CCR9. On the other hand, unconventional IELs derive from CD8 $\alpha\beta$ thymocytes that migrate to the intestinal epithelium and undergo further differentiation into IELs, although some of these IELs may also arise extrathymically [23, 24]. Of note, naive CD8 $\alpha\beta$ recent thymic emigrants already express $\alpha 4\beta 7$ and CCR9 when they leave the thymus, and they directly home to the small intestines in a CCR9- and $\alpha 4\beta 7$ -dependent fashion [25].

The molecular mechanisms regulating gut homing receptor expression on primed T cells in Peyer's patches (PPs) and/or mesenteric lymph nodes (mLNs) still remain to be fully

understood. However, one of the key inducers of gut homing receptors seems to be retinoic acid (RA), a vitamin A (retinol) metabolite [26]. Migratory intestinal DCs in the mLNs or PPs have an ability to process vitamin A to RA for presentation. RA imprints small-intestine homing properties on T cells activated in the mLNs, by inducing expression of integrin $\alpha 4\beta 7$ and CCR9 [27–29]. In *in vitro* experiments, addition of RA to anti-CD3 and anti-CD28 antibodies can induce expression of $\alpha 4\beta 7$, CCR9, and GPR55 on stimulated T cells in a dose-dependent manner [26, 30].

GPCRS INVOLVED IN IEL HOMING TO AND RETENTION IN THE INTESTINE

IEL homing to the intestine and retention in the intestinal mucosa are critically dependent on the expression of a variety of gut-specific homing molecules [31]. As for GPCRs, it is well known that T-cell homing to the small intestine requires CCR9 under homeostatic conditions [32]. However, during the inflammatory process, cell recruitment seems to be preferentially guided by other GPCRs, such as CXCR3, which has been suggested to be one of the most relevant chemokine axes that promotes the arrival of cells into inflamed gut tissues [33]. Recently, GPR18 and GPR55 have been reported to be other GPCRs that positively and negatively regulate CD8 $\alpha\alpha$ ⁺TCR $\gamma\delta$ ⁺ IEL accumulation in the small intestine, respectively [30, 34]. These findings on the unique division of reverse roles by GPCRs suggest a complicated and elaborate mechanism underlying IEL homing to the small intestine. In addition, as for colonic IELs, GPR15 controls the specific homing of T cells to the large intestine [35, 36].

CCR9

The CCR9–CCL25 axis in mice plays a key role in the homing of CD8⁺ T lymphocytes to the small intestine [29], which is supported by studies using CCR9- or CCL25-deficient mice [5]. On the other hand, the situation in the large intestine is different, as colonic IELs require either $\alpha 4\beta 7$ or $\alpha 4\beta 1$, but not CCR9 [37]. In agreement with this, CCL25 was found at a higher concentration in the small intestine but not in the colon within the murine and human small intestine [38–40]. Remarkably, CCL25 expression decreases from the proximal to the distal small intestine in mice [41], and this is consistent with the abundance of IELs in the proximal part compared with the distal part in the small intestine. Of note, CCR9 is also highly expressed on IgA antibody-secreting plasma cells in the mLN and PP. Given this, CCL25 might selectively attract and direct these cells to the small intestine, where CCR9 is downregulated upon arrival [42–44]. Whether IELs recirculate or not is subject to debate. However, given that human IELs express CCR9 [4], peripheral blood CCR9⁺ T cells may include recirculating IELs.

CXCR3

As mentioned above, CCR9 is involved in the migration of IELs into the intestinal mucosa under homeostatic conditions. In addition to this, other GPCRs have been implicated to be involved in IEL recruitment to the small intestinal epithelium. For example, CXCR3 (GPR9/CD183), an interferon-inducible

chemokine receptor, is expressed on the surface of activated CD8⁺ IELs, and this CXCR3 expression by gut IELs has been attributed to chronic activation of these cells by pathogens in the lumen. CXCR3 knockout (KO) mice showed a decreased number of CD8 $\alpha\beta$ ⁺ IELs and increased number of CD8 $\alpha\alpha$ ⁺ IELs [45]. It is assumed that IEL recruitment is preferentially guided by CXCR3 and its ligands, such as CXCL10, especially in inflamed gut tissues [33, 46–48]. In humans, the CXCR3/CXCL10 signaling axis is overactivated in the small intestinal mucosa in untreated celiac disease patients with increased production of CXCL10 in the epithelium primarily by enterocytes [49]. This axis is known to be active not only in inflammatory bowel diseases but also in different chronic inflammatory processes [50]. Given the significance of CXCR3 in the inflamed condition rather than the homeostatic condition, this GPCR might be an ideal target for the treatment of inflammatory bowel diseases.

GPR18

Recently, several novel GPCRs have been reported to play roles in the T cell homing to the small intestine. The orphan receptor, G protein-coupled receptor 18 (GPR18), has been considered to be a putative cannabinoid receptor. Considering the high expression of GPR18 in immune cells, including CD8⁺ T cells, GPR18 is proposed and reported to have an immunological function, especially in CD8 T cells [51]. GPR18 is abundantly expressed in CD8 $\alpha\alpha$ ⁺ IELs in the murine small intestine. GPR18 KO mice showed reduced numbers of CD8 $\alpha\alpha$ ⁺TCR $\gamma\delta$ ⁺ IELs [34, 51, 52], showing that GPR18 and CCR9 have roles in augmenting the accumulation of CD8 T cells in the intestinal intraepithelial lymphocyte compartment compared with the lamina propria compartment. In detail, the GPR18-deficient TCR $\gamma\delta$ ⁺ IELs that remained had elevated Thy1, and there were fewer granzyme B⁺ and V γ 7⁺ cells, indicating a greater reduction in effector-type cells [34]. Therefore, GPR18 is possibly involved in IEL maturation.

GPR55

GPR55 was originally identified as an atypical cannabinoid receptor, and lysophosphatidylinositol (LPI) was subsequently found to be an endogenous ligand for GPR55 [53]. GPR55 has been reported to be involved in various physiological and pathological processes, such as in the central nervous system or bone dynamics [54, 55]. Recently, GPR55 was revealed to mediate migration inhibition in response to LPI. LPI inhibited IEL migration to the CCR9 ligand, CCL25, and this effect was lost when using IELs from GPR55-deficient mice. The inhibitory effect of LPI was most potent for $\gamma\delta$ T IELs, which showed remarkably high endogenous expression of GPR55 [30]. In mice lacking GPR55, there was a selective increase in $\gamma\delta$ T IEL cell frequencies and numbers. To support this, multiple forms of LPI were detected in the small intestine by LC-MS/MS. These lines of observation showed that GPR55 negatively regulates CD8 $\alpha\alpha$ ⁺TCR $\gamma\delta$ ⁺ IEL accumulation in the small intestine [30]. Notably, GPR55 is the first reported molecule that can inhibit IEL homing to the small intestine. IELs are distributed throughout the epithelium in the small intestine. Even under homeostatic conditions, IELs actively migrate almost exclusively in the space between the epithelial layer and the basement membrane and showed transient movements in close association with

epithelial cells [30, 56, 57]. Although some molecules, such as transforming growth factor (TGF)- β , are reported to be crucial for IEL retention in the epithelium [58], which GPCRs are involved in IEL retention in the intestinal mucosa has remained obscure. Intravital imaging showed that GPR55-deficient IELs migrate faster and interact more extensively with epithelial cells. From a pathological perspective, GPR55 deficiency in $\gamma\delta$ T IELs protects mice from indomethacin-induced intestinal damage, possibly due to the frequent IEL-epithelial cell crosstalk [30].

GPR15

Compared with IELs in the small intestine, a lot still remains unknown about the factors controlling the dynamics of colonic IELs. The epithelium of the large intestine produces the chemokine CCL28, which binds to the receptor CCR10. Although CCR10 mediates localization of plasmablasts to the colon, CCR10 is not expressed on colonic IELs and does not appear to contribute to their recruitment [59]. However, GPR15 was recently revealed to mediate homing of regulatory T (Treg) cells in the mucosa of the large intestine [35]. In addition, GPR15 is also expressed by mouse Th17 and Th1 effector cells [36]. GPR15-mediated Treg homing is required for efficient control of gut inflammation in a *Citrobacter rodentium*-induced colitis model [35]. Moreover, GPR15-mediated T-effector-cell homing is crucial in the pathogenesis in the T-cell transfer colitis model [36]. In humans, it is noteworthy that GPR15 is expressed by effector cells, including pathogenic Th2 cells, in ulcerative colitis but is not expressed by Treg cells [36]. Thus, GPR15 may help target pathogenic Th2 cells to the colon in humans but is probably less important in humans than in the mouse for the homing and function of Treg cells in the gut wall. Future studies of the role of this chemoattractant receptor in intestinal immune biology are required, and identification of the physiologic ligand(s) for GPR15 might help us understand the dynamics of colonic IELs.

CONCLUSION

As described in this review, gut IELs are a heterogeneous population, and several GPCRs have unique roles in the dynamics of IELs (Fig. 1). Future studies should be performed to define the detailed mechanisms of IEL homing to and retention in the gut epithelium under physiological and pathological conditions. IELs and their interaction with epithelial cells are crucial for intestinal homeostasis, immune surveillance, and maintenance in epithelial integrity [60]. These crucial roles contribute to tissue damage and inflammatory bowel diseases [61, 62] and celiac disease [63, 64]. In addition, IELs contribute to host-microbial relationships. Specifically, intestinal bacteria are linked to the number of IELs and their activation [19, 65, 66]. Several studies suggest that intestinal IELs play roles in limiting mucosal penetration by intestinal pathogens during tissue homeostasis and/or following epithelial damage [19, 21, 22, 67]. As described in this review, although a lot remains unclear, recent accumulating evidence has revealed that novel GPCRs regulate the dynamics of IELs in a unique manner. Recent technological advances will help us to find more novel GPCRs and make further advances in understanding the functions of IELs in the near future. Furthermore, given that GPCRs represent the leading family of validated drug targets in biomedicine, insights concerning the involvement of functional

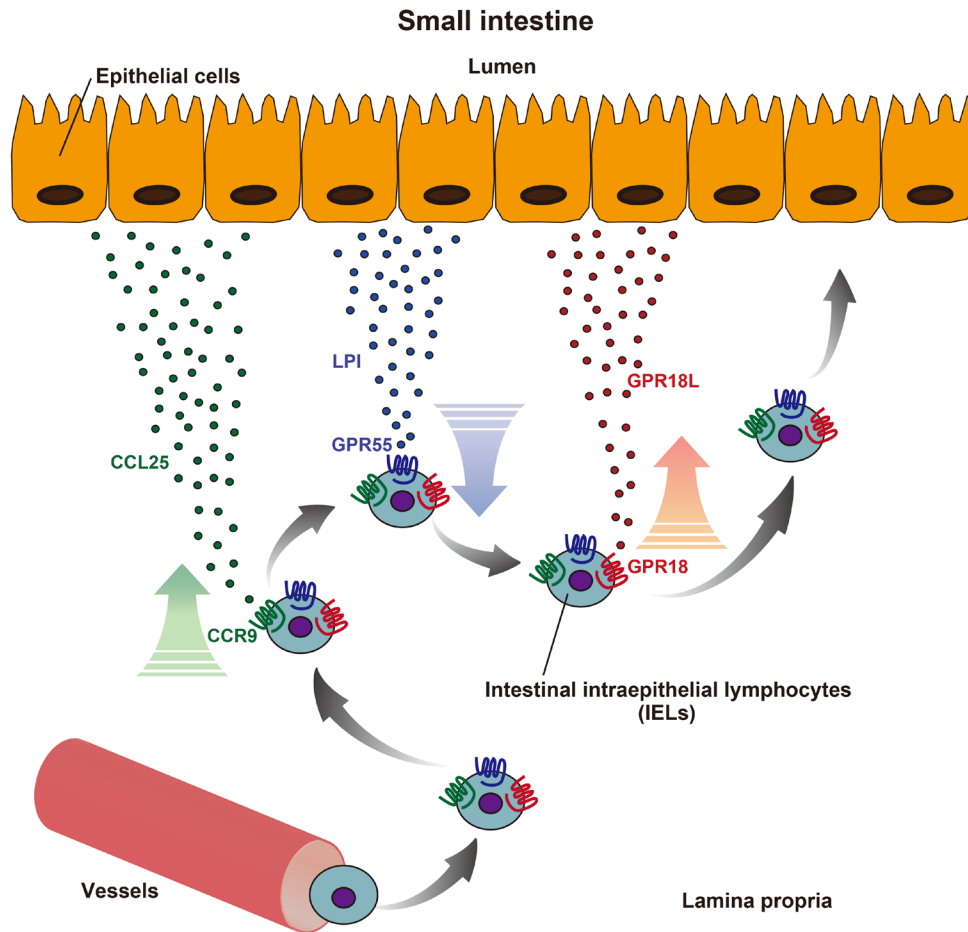


Fig. 1. Dynamics of intestinal intraepithelial lymphocytes (IELs) regulated by G-protein coupled receptors (GPCRs) in the small intestine.

A variety of GPCRs are involved in the IEL homing to the intestinal epithelium. CCR9 and GPR18 have roles in augmenting the accumulation of CD8 T cells in the intestinal intraepithelial lymphocyte compartment. On the other hand, GPR55, a receptor that mediates migration inhibition in response to lysophosphatidylinositol (LPI), negatively regulates CD8 α^+ TCR $\gamma\delta^+$ IEL accumulation in the epithelium. GPR18 L, ligands for GPR18.

GPCRs in the dynamics of IELs may provide new therapeutic strategies for various intestinal diseases, including inflammatory bowel disease and viral/bacterial infections.

CONFLICT OF INTEREST

None.

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