Dynamics and clinical significance of intestinal intraepithelial lymphocytes

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ABSTRACT
Intestinal intraepithelial lymphocytes (IELs) are one of the largest populations of lymphocytes and comprised of heterogeneous populations with varying phenotypes and physiological/pathological functions. IELs located between the basolateral surfaces of the epithelial cells and then potentially provide a first line of immune defense against enteric pathogens, although, the precise roles of each IEL populations are not well defined. A variety of molecules are involved in the IEL-homing to the intestinal epithelium. Conventional IELs originate from circulating T cells activated in lymphoid organs and imprinted for gut homing. On the other hand, unconventional IELs derive from thymocytes and migrate to the intestinal epithelium, although, some of them may arise extrathymically. Regarding the interaction between IELs and epithelial cells, IELs are known to be highly motile and actively migrate along the basement membrane, suggesting their roles in immune surveillance. In addition, there has been growing evidence to support that IELs are involved in the pathogenesis of gut disorders such as celiac disease and inflammatory bowel diseases. In this review, we provide a comprehensive overview of IEL dynamics and their clinical significance.

1. Introduction
Intestinal intraepithelial lymphocytes (IELs) are a diverse population of lymphoid cells localized between the intestinal epithelial cells that form the intestinal mucosal barrier. IELs distributed in the small intestine and large intestine, and the small intestine contains at least ten times more IELs than the colon [1]. In the mouse, it is estimated that one IEL is present for every 10 intestinal epithelial cells in the small intestine [2]. It is assumed that IELs play crucial roles in regulating gut inflammations and host defense against intestinal pathogens. These lymphocytes have been complicated by the incredible heterogeneity of their function and these are represented by conventional (induced) and unconventional (natural) T-cell subsets. In this review, we focus on recent advances in IELs, especially on their dynamics and roles in physiological and/or pathological conditions.

2. Diverse population of IELs
In the murine intestinal IELs, two major groups of lymphocytes can be distinguished based on their expression of either a γδT-cell receptor (TCR) or an αβ TCR. These subsets are further subdivided on the basis of CD8 coreceptor expression. The overwhelming majority of TCRγδ+ IELs is predominantly Vγ7+ and expresses the CD8αα homodimer. This is very different from TCRγδ+ T cells located in lymphoid tissues, which predominantly lack CD8 expression. In humans, about 10% of the small intestinal IELs express TCRγδ+ [3]. However, the percentage of TCRγδ+ T cells in IELs drastically increases under certain inflammatory conditions, suggesting pathological roles of TCRγδ+ IELs [4]. Unlike T cells in other tissues, TCRαβ+ IELs in the small intestine mainly consists of CD8αα, CD8ββ, and CD4. CD8αα+ IELs that express TCRγδ or TCRαβ but do not express either CD4 or CD8β are so-called natural IELs [5]. Unconventional CD8αα+ IELs do not express some surface markers typically expressed by conventional T cells but express natural killer (NK) cell receptors such as NK1.1 [5]. Moreover, similar to tissue-resident type 1 innate lymphoid cells (ILC1), CD8αα+ IELs require the transcription factor T-bet for their development [6] and constitutively tissue-resident markers CD69 and CD103 [7]. On the other hand, conventional CD4+ or CD8β+ TCRαβ+ T cells are so-called induced IELs. In contrast to the natural IELs, induced IELs acquire an activated phenotype in response to cognate antigens encountered in the periphery [5]. In humans, IEL numbers are several-fold higher in the proximal compared with the distal
small intestine, decreasing even further in the colon [8]. To support these human data, mice studies revealed that the distribution of IELs and their different mucosal T-cell subtypes varies based on location and housing conditions [9]. Specifically, IEL numbers are descending from duodenum to ileum, with few found in the colon [10]. In addition, although, unconventional IELs are the dominant T cell population along the length of the small intestine, their proportions are higher in the proximal compared with distal small intestine [11]. Furthermore, although, germ-free mice have dramatically reduced numbers of IELs, the regional variations in subset composition are largely maintained in these mice [8].

Recent papers described another population of IELs, which expresses CD4 and CD8αα [6,12–14]. This CD8αα+CD4+ IEL population is peripherally-converted and categorized as induced-type IEL [5]. Similar to peripheral Foxp3-expressing regulatory T cells, Foxp3+CD8αα+CD4+ IELs depend on retinoic acid signaling for their development and have anti-inflammatory properties [6,15,16].

3. IEL homing and dynamics

IELs in the small intestine are distributed throughout the epithelium that overlies small intestinal villi. Even under homeostatic conditions, IELs actively migrate almost in the space between the epithelial layer and the basement membrane and occasionally showed transient movements in close association with epithelial cells (Figure 1) [17–19]. 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 (Table 1). β7 integrin and CC-chemokine receptor 9 (CCR9) have been well-known to be gut-homing receptors under homeostatic conditions [20]. In particular, the number of IELs was significantly reduced in all small intestinal segments of β7 integrin-deficient mice when compared to controls. In addition, the

Table 1. Gut-homing molecules on intestinal intraepithelial lymphocytes.

| Molecules       | Phenotypes in deficient mice                                                                 |
|-----------------|------------------------------------------------------------------------------------------------|
| CCR9/CCL25      | Reduced number of IELs (mainly due to the low number of TCRαβ+ IELs) in the small intestine. |
| β7 integrin     | Reduced number of IELs and lamina propria lymphocytes in the small intestine.                |
| CXCR3/CXCL10    | Decreased number of CD8αα+IELs and increased number of CD8αα+IELs.                          |
| IL-15/IL-15Rα/IL-2Rβ | Reduced number of CD8αα+IELs and CD8αα+CD8αα+IELs.                                       |
| Vitamin D receptor | Reduced number of CD8αα+IELs (remarkable in CD8αα+IELs).                          |
| GPR18           | Reduced number of CD8αα+IELs and more extensive interaction between IELs and epithelial cells in the small intestine. |
| GPR55           | Increased number of CD8αα+IELs and less interaction between IELs and epithelial cells in the small intestine. |
| occludin        | Decreased number of TCRαβ+IELs and less interaction between IELs and epithelial cells in the small intestine. |
| GPR15           | Reduced homing of regulatory T cells to the large intestine mucosa.                         |
gut-associated lymphoid tissues (GALTs), comprising Peyer’s patches and lamina propria lymphocytes of the intestine, appeared hypoplastic in β7 integrin-deficient mice [21,22]. In CCR9-deficient mice, the total numbers of IELs was diminished 2-fold in comparison with wild-type mice and these decrease in IELs was mainly due to the presence of low numbers of TCRγδ+ IELs [23]. Natural IEL precursors such as CD8αα+ IELs have been reported to develop and express gut-homing receptors in the thymus [24–26]. On the other hand, induced IELs such as CD8ββ+ IELs and naive T cells generally do not express mucosal homing receptors are normally not detected within the intestinal epithelium. However, in these populations, gut-homing molecules β7 integrin and CCR9 are induced in GALTs, such as Peyer’s patches [27] and in mesenteric lymph nodes [28]. In these processes, the vitamin A metabolite, retinoic acid, is a key inducer of gut-homing-related molecules, upregulating β7 integrin and CCR9 [29].

Regarding the ligands for β7 integrin and CCR9, E-cadherin and CC-chemokine ligand 25 (CCL25) expressed in small intestinal epithelial cells, respectively [25]. The number of IEL in CCL25-deficient mice was reduced to the similar extent in CCR9-deficient mice [30].

As aforementioned, CCR9 and β7 integrin are involved in the migration of IELs into the intestinal mucosa under homeostatic conditions. Besides these, other molecules have been implicated to be involved in IEL recruitment to the small intestinal epithelium. For example, CXCR3 is expressed on the surface of activated T cells including CD8+ IELs, and this CXCR3 expression by gut IELs had been attributed to chronic activation of these cells by luminal pathogens [31]. CXCR3-deficient mice showed decreased number of CD8αβ+ IELs and increased number of CD8αα+ IELs [32]. Then, it is assumed that IEL recruitment is preferentially guided by CXCR3 and its ligands such as CXCL10, which have been suggested to be one of the most relevant chemokine axes promoting cells into inflamed gut tissues [33]. This axis is known to be active not only in inflammatory bowel diseases/celiac disease [34–38] but also in different chronic inflammatory processes such as rheumatoid arthritis [39]. If we return to the discussion under homeostatic condition, IL-15 has been shown to induce maturation and enhance survival and proliferation of both CD8αα+ TCRββ+ and CD8αβ+ TCRγδ+ IELs [40]. In the absence of IL-15, IL-15Rα, or IL-2Rβ, CD8αα+ TCRββ+ and CD8αβ+ TCRγδ+ IEL numbers are severely reduced [41–43]. In addition, vitamin D and vitamin D receptor (VDR) have recently been shown to regulate IEL numbers. Specifically, there are fewer total numbers of TCRββ+ T cells in the guts of VDR-deficient mice, and this reduction is remarkable in the CD8αα+ TCRββ+ IELs. Conversely TCRγδ+ T cells were normal in the VDR-deficient mice [44]. Although, this report explained that decreased maturation and proliferation of CD8αα+ TCRββ+ cells in VDR-deficient mice results in fewer functional CD8αα+ TCRββ+ T cells, another report stated that in VDR-deficient mice, the lack of CD8αα+ TCRββ+ IELs was due in part to decreased CCR9 expression on T cells, resulting in the failure of VDR-deficient T cells to home to the small intestinal epithelium [45].

Regarding local dynamics in the small intestine, it is not fully understood how each IEL population move and contact with epithelial cells in the physiological and/or pathological conditions. γδ IELs, a major population of IELs, are highly motile and actively migrate along the basement membrane and into the lateral intercellular space between epithelial cells [19]. Further morphometric analyses of intravital microscopy data showed that γδ IELs rapidly localized to and remained near epithelial cells in direct contact with pathogen such as Salmonella typhimurium. In terms of functions, this interaction between IELs and pathogens is essential to γδ IEL surveillance and immediate host defense [46]. As for the interaction between IELs and epithelial cells, another report showed that occluding, a tight-junction protein, positively regulates TCRγδ+ IEL migration within epithelial monolayers and this interaction was attenuated by tumor necrosis factor administration. Furthermore, in vivo analyses demonstrated that occluding-deficient TCRγδ+ T cells are defective in the accumulation within the intraepithelial compartment and showed less interaction with intestinal epithelial cells [19]. When it comes to CD4+ regulatory T cells, one paper reported difference of γδ T cell and CD4+ regulatory T cell movement in the small intestine. Concretely, more than 80% of γδ IELs preferentially remained in the epithelium, while 68% and 14% of CD4+ regulatory T cells were considered lamina propria and intraepithelial residents, respectively [14].

With respect to the roles of G protein–coupled receptors in IEL homing and/or dynamics, recent report showed that G protein-coupled receptor 18 (GPR18) is abundantly expressed in CD8αα+ IELs and that mice lacking this orphan receptor have reduced numbers of CD8αα+ TCRγδ+ IELs [47–49]. Further analysis suggests that GPR18 has a role in augmenting the accumulation of CD8 T cells in the intraepithelial versus lamina propria compartment [47]. Moreover, another recent paper demonstrated that GPR55, a receptor that mediates migration inhibition in response to lyso phosphatidylinositol, negatively regulates CD8αα+ TCRγδ+ IEL accumulation in
the small intestine. Intraval imaging studies, in this report, showed that GPR55-deficient IELs migrate faster and interact more extensively with epithelial cells [18].

4. Clinical significance of IELs

This strategic localization and migration within the intestinal mucosa (Figure 1) might be able to make them easy to interact with enterocytes to maintain epithelium integrity and prevent pathogenic incursion. IELs have an ability to produce antimicrobial factors and tissue repair factors in response to bacteria. Therefore, IELs can help to preserve the integrity of damaged epithelial surface [50]. In particular, TCRγδ⁺ subset of IELs can produce a variety of proinflammatory cytokines, anti-inflammatory cytokines, and antimicrobial proteins [51]. A number of recent studies have shown that TCRγδ⁺ IELs are highly motile for an efficient immune surveillance, and this is driven by commensal bacteria [17,19,46] and negatively regulated by GPR55 [18]. Following infection with microbial pathogens, TCRγδ⁺ IELs quickly change their motility and pattern of movement within the epithelium [17]. Cross-talk between TCRγδ⁺ IELs and intestinal epithelial cells is critical for immune surveillance/protection against a wide variety of intestinal species. For instance, the importance of this interaction is previously implicated in infection of Salmonella typhimurium [46,51], Toxoplasma gondii [46,52] and clearance of Nippostrongylus brasiliensis parasites [53]. In addition, IELs are implicated to contribute to viral immunity in the gut. At least, TCRβ⁺ IELs take part in viral clearance in the mucosa [54,55]. In IELs, stimulation with anti-CD3 can upregulates IFN genes and the supernatant of activated IELs can reduce viral infection [56,57]. In terms of clinical significance, given that most of these pathological findings come from mouse studies, further studies using human samples are needed for verification because there are considerable differences in physiology and anatomy between mice and humans.

Celiac disease, or gluten sensitive enteropathy, occurs when an inappropriate immune response, thought to be controlled by T cells, is initiated towards dietary gluten. The apparent T-lymphocytic infiltration associated with the disease has previously been determined [4]. Frequencies of TCRγδ⁺ IELs are significantly elevated within the epithelial layer in both active and treated celiac patients [58]. In another report, in active celiac patients, CD4⁺CD8⁺ human small intestinal T cells were significantly decreased in both the epithelial layer and lamina propria, which may play a critical immunoregulatory role in the gastrointestinal tract and contribute to the breakdown of oral tolerance to harmless dietary antigens [59]. Regarding the roles of CD8αβ⁺ TCRαβ⁺ IELs, in humans with celiac disease, CD8αβ⁺ TCRαβ⁺ IELs contribute to disease pathogenesis by inducing the enterocyte apoptosis [60]. These studies suggest that each IEL populations have unique roles in pathogenesis or healing process after tissue damage in celiac disease.

Regarding inflammatory bowel disease (IBD), there is limited data for a role of IELs in IBD. Disease severity is reported to correlate with increase in the number of TCRγδ⁺ IELs in ulcerative colitis [61] and Crohn’s disease [62]. One recent paper defined a novel subset of human γδ T-cells expressing CD8αβ and reported that the numbers of this CD8αβ⁺ TCRγδ⁺ IELs correlate inversely with disease severity, and the numbers are restored to levels observed in healthy controls upon treatment [63], suggesting its important role in mucosal healing in inflammatory bowel disease. As described here, although, there are several studies on the roles of IELs in the pathological situation, the data on a role for IELs in preventing or reducing susceptibility to IBD still remain unclear.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective anti-inflammatory drugs and are the most widely consumed classes of medications worldwide. However, a major limitation to their use is the adverse reaction they cause to serious dose-dependent gastrointestinal (GI) complications, including the formation of gastric lesions and the impairment of gastric ulcer healing [64]. The gastrointestinal toxicity by NSAIDs is mainly caused by inhibiting cyclooxygenase, which is well known as the major protective factor of gastrointestinal system. In addition to gastric injury, the more distal parts of the GI tract are also frequently affected, which have been revealed as a result of the development of the capsule endoscope and double-balloon endoscope. For instance, serious injury to the small intestine has been estimated to account for one third of all NSAIDs-associated complications [65,66]. Although, there is not enough human studies, given that mouse studies showed that IELs have protective roles in the intestinal barrier dysfunction [18,51], IEL could be a therapeutic target for the treatment of gut epithelial injury or integrity in the human.

5. Conclusion

IELs in the gut have a heterogeneous population and, especially in human IELs, future studies are required to define detailed IEL populations and its location for further analysis to reveal their roles in physiological and pathological conditions. IELs and its interaction with epithelial cells have been
reported to be crucial in the intestinal homeostasis, immune surveillance, and maintenance in epithelial integrity. These crucial roles contribute to host-microbial relationships, protection against invasion, tissue damage, and inflammatory diseases. As described in this review, a lot remains unclear, and there are controversial arguments which need further studies. Previously, experimental difficulties in IEL such as isolating IELs, complicated their populations, and their uneasy accessible location, have made us difficult to promote IEL-related researches. However, recent technological advantages, such as multicolor flow cytometry and intravital two-photon microscopy at the mucosal sites [17–19,46], now help us and must help us to make further advance in functions of IELs and related gut immunology. Furthermore, given the diverse functions of IELs in the gut, previous and future insights may aid in the rational design of novel treatments.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

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