Celiac disease (CD) is a common autoimmune enteropathy triggered by the ingestion of gluten in genetically susceptible individuals. Although the mechanisms underlying gliadin-mediated activation of adaptive immunity in CD have been well-characterized, regulation of innate immune responses and the functions of certain immune cell populations within the epithelium and lamina propria are not well-understood at present. Innate lymphoid cells (ILCs) are types of innate immune cells that have lymphoid morphology, lack antigen-specific receptors, and play important roles in tissue homeostasis, inflammation, and protective immune responses against pathogens. Information regarding the diversity and functions of ILCs in lymphoid organs and at mucosal sites has grown over the past decade, and roles of different ILC subsets in the pathogenesis of some inflammatory intestinal diseases have been proposed. However, our understanding of the contribution of ILCs toward the initiation and progression of CD is still limited. In this review, we discuss current pathophysiological aspects of ILCs within the gastrointestinal tract, findings of recent investigations characterizing ILC alterations in CD and refractory CD, and suggest avenues for future research.

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Celiac disease (CD) is an autoimmune enteropathy induced by the ingestion of gluten in genetically susceptible individuals, which is prevalent in approximately 1% of the population in many parts of the world.1,2 In individuals with this condition manifest characteristic histopathologic features of the small intestinal mucosa, reflecting damage induced by the adaptive and innate immune responses.3,4 CD patients may be asymptomatic or exhibit intestinal and extraintestinal symptoms such as diarrhea, constipation, anemia, osteoporosis, and dermatitis herpetiformis.5 Lifelong adherence to a strict gluten-free diet (GFD) is the only effective treatment that leads to mucosal healing and remission of symptoms.6 However, a proportion of CD patients are nonresponsive to GFD, and up to 5% are deemed to have refractory CD (RCD), which is defined as persistent or recurrent small intestinal damage and malabsorptive symptoms despite a strict GFD for >12 months, after exclusion of other etiologies for the symptoms as well as malignancies.7–9 RCD is further subdivided into 2 types, RCD I and RCD II, on the basis of molecular and immunophenotypic differences.10 The intraepithelial lymphocytes (IELs) in RCD I constitute polyclonal expansions of T cells displaying a normal phenotype (surface CD3+ and CD8+), whereas RCD II is characterized by clonal expansions of phenotypically aberrant IELs (surface CD3+, cytoplasmic CD3+, and CD8+).10 Unlike RCD I patients, those with RCD II do not respond well to immunosuppressive therapy and have higher morbidity and mortality.11 RCD II is considered a precursor of enteropathy-associated T-cell lymphoma (EATL), with approximately 50% of RCD II patients developing EATL within 5 years.10,12

Innate lymphoid cells (ILCs) are types of innate immune cells of the lymphoid lineage that lack somatic rearrangements of immune receptor genes and, hence, surface antigen-specific receptors.13 They respond rapidly to environmental cues and play important roles in maintaining tissue homeostasis and facilitating inflammatory responses.13 Recent studies have implicated alterations of ILCs in the pathogenesis of inflammatory intestinal diseases.14,15 In this review, we will summarize the functional heterogeneity of ILCs in the human gastrointestinal (GI) tract, highlight the emerging roles of ILCs in the pathogenesis of CD and RCD, and discuss future research prospects.
Pathogenesis of CD and RCD

A gluten-specific adaptive immune response plays a central role in CD pathogenesis.16 Gluten peptides that enter the lamina propria via transcytosis or paracellular routes are deamidated by tissue transglutaminase (tTG) and subsequently presented by HLA class II molecules (HLA-DQ2/8) on antigen-presenting cells (APCs) to CD4+ T cells.17-29 Intraepithelial ILC1s (ieILC1s) expressing the transcription factor T-bet, produce IFN-γ, which interact with IL15-induced MICA and HLA-E on small intestinal epithelial cells. This results in enterocyte killing in a T cell receptor (TCR)-independent manner.30 In addition, ILC1s enhance production of IL21 by IELs and lamina propria CD4+ T cells,32 which further promotes IEL proliferation and cytotoxicity33,34 and amplifies the Th1 response in CD.23

The etiology of and immune mechanisms underlying RCD are unclear. The cumulative dose of gluten that an individual with CD is exposed to is considered a risk factor.10 HLA-DQ2 homozygosity, which results in increased presentation of gliadin peptides by APCs,19,35 has been reported more frequently in RCD patients (25%-40% in RCD I and 44%-67% in RCD II) than in uncomplicated CD (21%).26,37 An increased frequency of infections has also been documented in RCD patients.38 Evolution of a gliadin-dependent immune response to an autoimmune response is presumed to underlie some cases of RCD I.39 A recent genome-wide association study has revealed a novel susceptibility locus for RCD II on chromosome 7q14.3.40 A single nucleotide polymorphism (rs2041570) at this location was associated with increased expression of C2orf114 (BPIFB1) and alterations of epithelial innate immune genes and antimicrobial defenses.

In addition to its role in uncomplicated CD, dysregulated expression of IL15 is believed to play integral roles in the pathogenesis of RCD I and II. IL15 stimulates the proliferation of innate IELs by blocking transforming growth factor-β-Smad-3-dependent transcription,41 augments CD4+ and CD8+ T cell resistance to forkhead box protein 3 (FoxP3-) regulatory T cells by activating phosphoinositide 3-kinase signaling,42 and extends the survival of IELs by increasing expression of Bcl-xL via activation of the JAK3-STAT5 signaling pathway.30,43 Continual cytokine stimulation in RCD II is thought to induce genotoxic stress, which leads to acquisition of mutations and chromosome abnormalities, fueling the transformation to EATL.10

ILCs Background and Classification

ILCs are types of innate immune cells, derived from bone marrow progenitors, that have lymphoid morphology, lack antigen-specific receptors, and play important roles in tissue homeostasis, inflammation, and protection against pathogens.13,34 ILCs do not express lymphocyte-lineage surface molecules and thus are referred to as lineage marker negative (Lin-) cells.13 Certain ILC subsets have been known for a while, such as tissue-resident NK cells45 and lymphoid tissue-inducer (LTI) cells,16 whereas others have been discovered more recently. Currently, 6 ILC subsets are recognized: NK cells (conventional and tissue-resident), LTI cells, ILC1s, ILC2s, ILC3s,13 and regulatory ILCs (ILCregs).47 NK cells express the transcription factor eomesodermin, exhibit cytotoxic potential, and secrete IFN-γ.48 LTI cells are crucial initiators of secondary lymphoid tissue development and produce IL22 and IL17A in response to bacterial infection.49 ILC1s, ILC2s, and ILC3s have functions analogous to Th cells.50 ILC1s mirror Th1 cells, express the transcription factor T-bet, and produce IFN-γ and TNF in response to intracellular pathogens and as anti-tumor defense mechanisms.51 ILC2s express GATA3, secrete Th2 cytokines (IL4, IL5, IL9, IL13) and amphiregulin (AREG), provide anti-helminth immunity,52 and orchestrate allergic responses.53 ILC3s express RORγt, produce Th17 cytokines (IL17A, IL22), as well as granulocyte-macrophage colony-stimulating factor and TNF-α, and protect against extracellular pathogens at mucosal sites.54,55 ILCregs have been reported to function similarly to regulatory T cells (Tregs) in suppressing immune responses in murine and human intestines.47

The presence of limited numbers of mature non-NK ILCs in the fetal liver or adult bone marrow44,56,57 suggests that the majority of peripheral tissue ILCs are descendants of ILC precursors that have already egressed from the bone marrow. The mechanism of ILC tissue tropism has been reviewed in detail elsewhere.58,59 Circulating human ILCs have been identified in the blood,60,61 and although trafficking of ILCs between different organs has not been described in humans, murine studies have demonstrated that at least certain types of ILCs can migrate to other tissues under experimental conditions and determined the underlying mechanisms.52 ILCs are widely distributed throughout the body.59 NK cells constitute the most abundant ILC group in humans53 and can be subdivided into two populations on the basis of the relative expression of the surface markers CD56 and CD16; the CD56bright CD16dim/- subset is mainly tissue-resident (lymph nodes, spleen, gut, liver, and lung), whereas CD56dim CD16bright NK cells represent the dominant subset in the peripheral blood.48 LTI cells are found in fetal lymph nodes,64 and intestinal cryptopatches, tiny mucosal lymphoid aggregates close to the bottom of the crypts.57 Helper ILC1s, which express the IL7 receptor alpha chain (IL7Ra, CD127), are present in the tonsils and intestines.13 Intraepithelial ILC1s (iILC1s) expressing NKP44 and CD103, but not CD127, reside in the gut.
epithelium,66 ILC2s are the dominant population in the lung, particularly in the collagen-rich interstitial tissue,67 and ILC3s mainly populate the small and large intestinal lamina propria.59,68

ILCs in the GI Tract

ILCs are particularly abundant in the GI tract mucosa, where they play critical roles in intestinal homeostasis and modulation of immune as well as inflammatory responses through cytokine secretion.69 Studies in mice and humans indicate heterogeneity in the timing and mechanisms of gut homing receptor expression and differences in receptor- ligand interactions that are responsible for retention of distinct ILC subsets in the GI tract.51,58,59,66,70–74

The proportion of small intestinal intraepithelial ILCs decreases with age, with a concomitant expansion of T- IELs.75 The composition of intestinal ILCs also changes over the life course, with age-associated decreases in the frequencies of conventional NK cells and ILC3s having being reported in the duodenal epithelium and ileal lamina propria, respectively.75,76

Intestinal tissue-resident NK cells are predominantly located in the epithelial layer.74 A fraction (<10%) of peripheral blood NK cells that bear the chemokine receptors CCR6 and CCR9 can also migrate to the intestines.2 CD103+, CD127+, Nkp44+ ieILCs, and CD127+ helper ILC1s represent the major non-NK cell ILC subsets within the small intestinal epithelium, while CD127+ ILC3s account for only a minor component.66,77 An increase in lamina propria helper ILC1s, however, has been observed in active Crohn’s disease.78 Both tissue-resident NK cells and ILC1s are the main sources of IFN-γ required for early defense against intracellular pathogens such as Toxoplasma gondii80 and Salmonella typhimurium.81 IFN-γ activates macrophages and other immune cells that aid in the clearance of infected cells.81 ILC2s appear to be limited to the gut lamina propria.82 Helminth infection induces secretion of IL25 and IL33 by intestinal epithelial cells, which stimulate IL13 production by lamina propria ILC2s,82–84 potentiating Th2 responses,82 goblet cell differentiation,85 and mucus production.86 ILC2s have also been shown to respond to neurons via certain peptides such as neuropeptide U and calcitonin gene-related peptide that lead to the elaboration of type 2 cytokines.87–90 In addition, ILC2s synthesize AREG, which binds to epithelial growth factor receptor and promotes tissue healing.88,89 ILC3s are the dominant subset in the lamina propria of the small and large intestines,91 where they mediate immune tolerance toward gut commensal bacteria.92 IFN-γ production by ILC3s via activation of herpesvirus entry mediator (HVEM) signaling is considered important for initiating an immune response against Yersinia enterocolitica.93 ILC3s are the main source of intestinal IL22, which performs myriad activities, supporting epithelial tissue repair,94–97 intestinal stem cell regeneration,96 production of mucus and antimicrobial peptides,98 tight junction maintenance,99 and fucosylation of proteins.100,101 Besides IL23 and IL1β, vasoactive intestinal peptide and glial cell line-derived neurotrophic factor (GDNF) family ligands can fine tune IL22 production by ILC3s in the cryptopatches and isolated lymphoid follicles.102–104 In conjunction with IL22, ILC3-derived IL17A induces the expression of antimicrobial C-type lectins (RegIIIγ and RegIIIβ) by the epithelial cells.98 A role of ILC3s in the pathogenesis of Crohn’s disease has been proposed.105

Recently, ILCregs were identified in the human intestine, mainly in the duodenum.4 ILCregs do not express genes encoding markers specific for the aforementioned ILC groups or the key transcription factor of Tregs, FoxP3, but they assist in the resolution of intestinal inflammation through IL10 production and the suppression of ILC1 and ILC3 activation.

ILCs and CD Pathogenesis

ILCs constitute a relatively small population of lymphoid cells in the GI tract and account for approximately 10% of total IELs, yet these cells play an important role in orchestrating intestinal inflammation by rapid cytokine production in response to environmental signals.65 Previously identified as non-T cells, an altered composition of ILCs in CD was first described in 1989,106 Early investigations suggested that these cells represented precursors of T cells that underwent extra-thymic maturation.107,108 Subsequent studies revealed the cytoketopic capacity of CD3+ CD103+ IELs, suggesting NK-like attributes.109,110 Until recently, the roles of ILCs in the pathogenesis of CD and RCD were not known.

In newly diagnosed or active CD, TCR+ IELs expand to a greater degree than CD7(bright)+ iCD3ε+ sCD3– innate IELs, which comprise predominantly ieILCs and helper ILC1s.77,105,111,112 In addition to stimulating T-IELs, IL15 also induces the proliferation and enhanced survival of CD3+ ILC1-like innate IELs in CD.66,75,113,114 On the other hand, Nkp44 and Nkp46-double positive NK cells are decreased in the small intestinal epithelium in active CD.115 We reported activation-induced loss of the NCR Nkp44 by ieILCs (T-bet+ IFN-γ+) in active CD, likely because of protracted inflammation.77 (Figure 1). In contrast to the down-regulation of Nkp44 in functionally exhausted NK cells,116,117 elevations in Nkp44+ ILC1s in CD correlated with increased severity of villous atrophy and enterocyte damage and they produced higher amounts of IFN-γ and cytotoxic granule proteins.77 An increase in small intestinal lamina propria TNF-α and IFN-γ-producing ILCs, likely representing ILC3s and possibly a proportion of helper ILC1s, has also been reported in active CD.118 Because TNF-α has been shown to contribute to increased intestinal permeability,119 these ILCs may facilitate the transfer of luminal antigens to APCs in the lamina propria.

Immunophenotypic and functional plasticity of ILCs is well-recognized.120 Bernink et al15 showed that human tonsilar ILC3s could differentiate into ILC1s upon IL12 stimulation. It is unknown whether a similar conversion occurs in CD. Increased IL12 produced by dendritic cells (DCs) in the lamina propria of CD patients is known to promote Th1 differentiation,121,122 and this cytokine could
potentially assist in the transdifferentiation of ILC3s to ILC1, resulting in reduced IL22 synthesis, up-regulation of IFN-γ, and increased cytotoxicity, which could exacerbate epithelial damage.

Not every HLA-DQ2/8-positive individual develops CD. It remains unclear as to what causes disruption of tolerance to dietary antigens and the initiation of immune and inflammatory cascades. Reovirus infection has been shown to abrogate tolerogenic immune responses and actuate Th1 immunity to gluten via IFN-β-mediated suppression of the conversion of CD4+ T cells to Tregs. Upon viral infection, tolerogenic small intestinal lamina propria DCs have also been reported to switch to an inflammatory phenotype and produce IL12 in a mouse model of CD. This may stimulate the recruitment of NK cells and ILC1s as well as IFN-γ synthesis by these cells. In addition, dysbiosis (an imbalance of gut microbiota), a common occurrence in CD, could trigger proinflammatory innate immune mechanisms and cause epithelial barrier dysfunction. Pseudomonas aeruginosa has been shown to directly impact the breakdown of gluten in vivo in a mouse model of CD, yielding increased immunogenic peptides. ILCs are crucial mediators of host-commensal bacterial interactions at steady-state and during infections. Whether they modulate the host-commensal relationship during development of CD is not known. In Pseudomonas aeruginosa-induced lung injury, ILC3s are an important source of IL17, which increases neutrophil recruitment and is responsible for early immunopathology. By extension, gut ILC3s could conceivably contribute to the onset of CD.

### ILCs and RCD Pathogenesis

In RCD I, similarly to uncomplicated CD, polyclonal expansions of thymus-derived innate cytotoxic CD8+ TCRαβ+ (and TCRγδ+ ) IELs occur, which are thought to mediate epithelial damage. The role of ILCs has not been adequately investigated in this condition. Our observations suggest that similar to active CD, activation-induced loss of NKp44 by cytotoxic ILC1s is associated with increased severity (and persistence) of villous atrophy and epithelial
damage in RCD I. In RCD II, the IELs are clonally expanded, and they exhibit an aberrant immunophenotype. The aberrant IELs were previously considered to originate from conventional intraepithelial TCR\(^{+}\) T cells that had downregulated or lost surface CD3/TCR complexes because of the lack of production or misassembly of TCRs and had extinguished CD8 expression. However, recent flow cytometry and gene expression analyses have revealed transcriptional differences between TCR\(^{+}\) T cells and the aberrant RCD II IELs; the latter bearing similarities to Lin\(^{-}\), CD34\(^{-}\), sCD3\(^{-}\), and iCD3\(^{+}\) that express the activating receptor DNAM-1 (CD226), a mediator of cellular cytotoxicity. It has been shown that the IL15-induced cleavage of NOTCH1 by granzyme B inhibits the expression of T cell differentiation genes in CD103\(^{+}\) Lin\(^{-}\) IELs. RCD II IELs lack the expression of early T cell development markers (eg, terminal deoxynucleotide transferase, CD1a, and CD34\(^{+}\)) and demonstrate limited capacity to differentiate into T cells. The finding of absent or non-productive T cell receptor gene rearrangements in the majority of RCD II cases has supported the notion that the aberrant IELs in RCD II represent ILCs, which fail to commit to a T cell lineage. Whether this paradigm applies to all cases of RCD II is not known at present.

A major subset of the RCD II IELs expresses IL15R\(\beta\), and these IELs proliferate in vitro upon culturing with IL15\(^{+}\) cytokines, such as IL2, TNF-\(\alpha\), and IL21, secreted by gliadin-specific CD4\(^{+}\) T cells in RCD II, can synergistically increase STAT5 phosphorylation as well as the transcription of the anti-apoptotic protein Bcl-xl, enhancing the survival and proliferation of aberrant IELs in a mechanistically similar manner to that of IL15. Direct contact with DCs has also been shown to prolong the survival of RCD II IELs, independent of IL15 or the HLA haplotype. In addition, activating somatic mutations in JAK/STAT pathway genes, documented in the vast majority of RCD II cases, appear to confer increased sensitivity of aberrant IELs to IL15, fostering clonal expansion. It has been hypothesized that decreased expression of proliferating cell nuclear antigen (PCNA) in RCD II IELs can impede DNA-mismatch repair, resulting in acquisition of additional genomic alterations that fuel the transformation to EATL. Because of the recent revelations regarding the cell of origin of RCD II, it is presumed that EATLs evolving from RCD II are also derived from ILCs. Intriguingly, an increase in the intensity of intracytoplasmic CD3 expression by aberrant IELs and a more mature T cell genotype have been proposed to be prognostic factors that predict progression of
RCD II to EATL. Moreover, limited data indicate that RCD II and EATLs may originate from a variety of IEL subsets, including TCR αβ⁺ and TCR γδ⁺ T cells.¹⁰,¹⁴¹,¹⁴² Hence, systematic genomic and immunophenotypic evaluation of large cohorts of RCD II and EATL cases is awaited to clarify whether one or multiple IEL subsets can undergo neoplastic transformation in CD patients.

Unanswered Questions and Avenues for Future Research

Recent advances in our understanding of ILC biology have increased our understanding of the functions of different ILC subsets in inflammatory disorders; however, questions remain regarding their roles in regulating innate and adaptive immune responses in CD. It is not known to what extent the cytokine profiles of ILCs reflect the micro-environmental alterations in CD and what immune (or non-immune) cells they interact with. The relevance of neuronal-ILC cross-talk in the gut to CD and RCD pathogenesis awaits further investigation. Similarly, it is unclear whether changes in ILC composition or phenotypes in CD are a cause or consequence of intestinal inflammation and whether targeting specific ILCs can ameliorate inflammation or prevent neoplastic transformation. ILCs have been implicated in the pathogenesis of human intestinal (and other mucosal) inflammatory diseases, but mechanistic information is lacking. Data from murine models of chemically induced or infection-associated colitis have been discrepant; however, the majority point to functional roles of ILCs in intestinal inflammation.¹¹⁸,¹⁴³,¹⁴⁴

It is challenging to characterize and study the functions of ILCs in human diseases such as CD, because they constitute small populations and tissue samples are limited. Currently, the evaluation of ILCs relies on flow cytometry, requiring a plethora of antibodies for the exclusion of other immune cell lineages and delineating different ILC subsets.¹⁴⁵ Cell lines have been useful for studying transcriptional profiles and signaling mechanisms of ILCs,¹¹³ but they cannot recapitulate tissue location or microenvironment-related phenotypic and functional alterations. The visualization of ILC subsets and their interactions with other cell types (macrophages, DCs, T and B cells) in the small intestine has not been possible because of the limited availability of reagents and relative nonspecificity of many cellular markers.

Newer technologies such as mass cytometry¹⁰⁵,¹⁴⁶,¹⁴⁷ and single cell analytic methods, which are capable of resolving proteomic, transcriptional, and genomic changes in rare cell populations, and allow determination of cellular heterogeneity,¹⁴⁸–¹⁵² are proving useful for analyzing human ILCs and establishing disease state–specific signatures.¹⁰⁵,¹⁴⁹ These methodologies could provide high-resolution maps of the phenotypic and functional status of ILCs in CD and help discern genomic and epigenetic alterations that could potentially predict development of RCD II, which is not currently possible. Dynamic, in vivo real-time imaging tools, which have been used to investigate mechanisms of ILC trafficking in mice,¹⁵³ are not yet available for evaluating human tissue samples. However, studying the recently established, pathophysiologically relevant, gluten- and HLA-dependent mouse model of CD¹⁵⁴ may reveal immune networks and signaling pathways of pertinence to human disease and elucidate the roles of different ILC subsets in the pathogenesis of CD and its complications.

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