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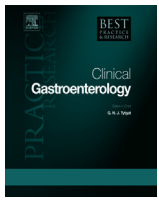

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Innate immunity: Actuating the gears of celiac disease pathogenesis

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A B S T R A C T

Celiac disease is a T cell mediated immune disorder characterized by the loss of oral tolerance to dietary gluten and the licensing of intraepithelial lymphocytes to kill intestinal epithelial cells, leading to villous atrophy. Innate immunity plays a critical role in both of these processes and cytokines such as interleukin-15 and interferon-α can modulate innate processes such as polarization of dendritic cells as well as intraepithelial lymphocyte function. These cytokines can be modulated by host microbiota, which can also influence dendritic cell function and intraepithelial lymphocyte homeostasis. We will elaborate on the role of interleukin-15, interferon-α, and the microbiota in modulating the processes that lead to loss of tolerance to gluten and tissue destruction in celiac disease.

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Introduction

Celiac disease (CD) is a T cell-mediated enteropathy with an autoimmune component that occurs in the small intestine of genetically predisposed individuals in response to gluten protein found in wheat, barley, and rye. The critical events required for disease pathogenesis are the induction of a gluten-specific inflammatory T helper-1 (Th1) CD4 T cell response as well as the targeted killing of intestinal epithelial cells (IEC) by licensed T cell receptor (TCR) αβ intestinal epithelial lymphocytes (TCR αβ IEL) [1]. These immunological events translate into a wide disease spectrum, ranging from potential CD to refractory sprue [2].

The role of innate immunity is highlighted by the enrichment of CD susceptibility loci in gene ontology pathways associated with innate immune processes [3]. Understanding the role of innate immunity in the inductive and effector phases of disease is critical to understanding the disease as a whole. To that effect, we structure our discussion on innate immunity in CD around the two central processes implicated in disease pathogenesis: (A) the triggers that implicate innate immunity in the loss of tolerance to gluten, and (B) the factors that can unleash the innate-like lymphokine killer activity (LAK activity) of TCR αβ IEL.

Defining the players

Our view of innate immunity in the small intestine is one that encompasses dynamic interactions between cytokines, antigen presenting cells (APCs), microbiota, IEC, and IEL. In the context of CD this takes the form of interrogating the role of interleukin 15 (IL-15) and type I interferons (type-1 IFNs), two cytokines produced primarily by innate immune cells, in polarizing innate immune responses by acting on dendritic cells (DCs), IEC, and or IEL. We do not discuss IL-21 below, despite its potential impact on IEL and regulatory T cells, as it is a cytokine produced by adaptive gluten-specific CD4 T cells in CD [4] and acts downstream of type-1 IFNs [5] and IL-15 [6]. In addition, we comment on the potential for the microbiota to influence the intestinal microenvironment in a manner that would favor either the loss of tolerance to gluten or the activation of TCR αβ IEL. We are aware of the studies demonstrating the innate stimulatory properties of gluten and wheat components, but we do not discuss these studies as they are reviewed in detail in another section of this issue [7,8].

Innate cytokines and their role in CD

The immune system is a complex entity that is constantly integrating signals from a multitude of sources. The language that is understood by all immune cells is cytokines and under homeostatic conditions in the intestine the conversation being dictated by these cytokines is one of a neutral nature. In CD this conversation takes a different tone as the immune system initiates processes that lead to the loss of tolerance to gluten and licensing of TCR αβ IEL to kill IEC. The observation that negatively charged gluten peptides generated by active transglutaminase 2 (TG2) [9,10] have a higher affinity for binding HLA-DQ2 and HLA-DQ8 [11,12] is critical but does not explain why an inflammatory, rather than a regulatory, immune response to gluten is induced in CD. Furthermore, it has become evident, from both human and mouse studies, that TCR αβ IEL are the effector cells mediating IEC destruction [1]. Yet TCR αβ IEL are not gluten-specific, suggesting they destroy IEC based on recognition of stress signals/molecules. We believe these processes are in particular dictated by IL-15 and type-1 IFNs, two cytokines produced by innate cells that have the potential to influence multiples levels of the system by acting on IEC, APCs, and IEL.

IL-15

The dysregulated expression of IL-15 has been implicated in CD for quite some time [13–16]. Of particular importance to the topic of this review is IL-15's ability to polarize DCs and impact the function of TCR αβ IEL. Importantly, IL-15 acts in a cell contact dependent manner [17] and is upregulated in active CD in both the lamina propria (LP) and epithelium, where it exerts its effects on DCs and TCR αβ IEL, respectively [15].