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Review

New insights into immune mechanisms underlying autoimmune diseases of the gastrointestinal tract

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ABSTRACT

Recent progresses in the immune mechanisms implicated in chronic inflammatory disorders have led to a more in-depth knowledge of the pathogenesis of autoimmune diseases of the gastrointestinal tract, including autoimmune atrophic gastritis, celiac disease, autoimmune enteropathy and ulcerative colitis. While the pathogenic role of specific circulating autoantibodies, i.e., respectively anti-parietal cell, anti-tissue transglutaminase, anti-enterocyte and anti-neutrophil cytoplasmic, is still controversial, some common T-cell mediated mechanisms for inflammation – increase in T helper cell type 1/type 17 pro-inflammatory cytokines- or losing self-tolerance-abnormal regulatory T cell function – are recognized as crucial mediators of the tissue damage causing atrophy of the stomach mucosa in autoimmune atrophic gastritis, villous flattening of the small bowel in celiac disease and autoimmune enteropathy, and mucosal ulceration of the colon in ulcerative colitis. This review deals with novel advances in the immunological bases of the aforementioned autoimmune gastrointestinal disorders, and it also highlights immune mechanisms of progression from chronic inflammation to cancer and implications for new therapeutic targets.

Contents

1. Introduction . . . 0
2. Autoimmune atrophic gastritis . . . 0
3. Celiac disease . . . 0
4. Autoimmune enteropathy . . . 0
5. Ulcerative colitis . . . 0
Take-home messages . . . 0
Uncited references . . . 0
References . . . 0

Abbreviations: AAG, autoimmune atrophic gastritis; AEA, anti-enterocyte antibody; AIE, autoimmune enteropathy; APECED, autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy; ATP-ase, adenosine triphosphatase; CD, celiac disease; ECL, entero-chromaffin-like; FasL, Fas ligand; HLA, human leukocyte antigen; HNE, human neutrophil elastase; HP, *Helicobacter pylori*; IFN, interferon; IEL, intraepithelial lymphocyte; IL, interleukin; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked; LPMC, lamina propria mononuclear cell; MAd-CAM, mucosal addressin cell-adhesion molecule; MHC, major histocompatibility complex; MMP, matrix metalloproteinase; p-ANCA, perinuclear anti-neutrophil cytoplasmic antibodies; PCA, parietal cell autoantibody; RCD, refractory celiac disease; STAT, signal transducer and activator of transcription; TCR, T-cell receptor; TGF, transforming growth factor; Th, T helper cell type; TNF, tumor necrosis factor; TSLP, thymic stromal lymphopoietin; tTG, tissue transglutaminase; UC, ulcerative colitis.

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1. Introduction

The increasing epidemiologic burden of autoimmunity in the Western world has led to a more in-depth dissection of the immune mechanisms underlying chronic inflammation in a number of autoimmune diseases [1]. The latter are a group of disorders sustained by an abnormal immune response against own tissues, which results in tissue damage and autoimmunity, and clinically characterized by a long-term and often disabling outcome, and a possible evolution into cancer [2,3]. Although autoimmune diseases display significant clinical differences, many pathogenic mechanisms overlap among them, including losing self-tolerance due to reduced deletion of autoreactive $CD4^+$ T lymphocytes and defective regulatory T cell function, or an abnormal immune response due to an exaggerated production of pro-inflammatory

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cytokines which mediate organ-specific lesions [4]. The comprehension of these pathogenic mechanisms has guided the development of new treatment modalities for patients with autoimmune disorders aimed at reversing lymphocyte dysfunction, neutralizing pro-inflammatory signaling or restoring self-tolerance [5,6].

From the gastrointestinal tract, which plays a crucial role in modulating the immune system homeostasis [7], a number of autoimmune disorders may arise, such as autoimmune atrophic gastritis (AAG), celiac disease (CD), autoimmune enteropathy (AIE) and ulcerative colitis (UC). Apart from AIE, which is a rare disorder mainly affecting children, although cases in adults have been described [8], the other three conditions are characterized by a quite high prevalence, especially in the case of AAG [9,10] and CD [11] (Table 1). Even if the four abovementioned disorders display many differences according to location, type and diagnostic accuracy of circulating autoantibodies, and specific targets of the humoral immune response, they share female predominance, common pathogenic mechanisms in terms of up-regulated pro-inflammatory cytokines and epithelial cell apoptosis, and a common predisposition to tumor development (Table 1).

This review focuses on novel advances in the immune pathogenesis of autoimmune gastrointestinal disorders, and highlights immune mechanisms implicated in their progression to cancer and new treatments based on rational targeting of immune pathways.

2. Autoimmune atrophic gastritis

AAG is an organ-specific autoimmune disease affecting the corpus–fundus mucosa of the stomach, and in the majority of patients it is associated with serum anti-parietal cell (PCA) and anti-intrinsic factor autoantibodies [12,13]. The pathology of AAG is characterized by mucosal lymphocyte infiltration, destruction of specialized parietal and zymogenic cells resulting in mucosal atrophy (reduction or disappearance of native gastric glands), and hyperplasia of immature mucous neck cells. Enhanced differentiation of immature precursor neck cells into histamine-producing enterochromaffin-like (ECL) cells, likely secondary to hypergastrinemia, is a prominent finding of advanced AAG, and this results in ECL cell hyperplasia which, in turn, predisposes to an increased risk for ECL cell tumors [13,14].

Most of the knowledge underlying the pathogenic mechanisms of AAG derives from studies conducted on experimental models. In particular, it has been shown that the gastric proton pump H^+/K^+ adenosine triphosphatase (ATP-ase) located on parietal cells is the major autoantigen recognized by mucosal T cells, which can be elicited in non-thymectomized mice by immunization with either gastric mucosal extracts or gastric ATP-ase [15–17], or by neonatal thymectomy [18]. Among the different T cell subsets, gastric H^+/K^+ ATP-ase $CD4^+$, but not $CD8^+$ T cells, seems to play a dominant role [19] and there is evidence that various pro-inflammatory cytokines are over-expressed in murine inflamed gastric mucosa, including interferon (IFN)-γ, interleukin (IL)-21 and tumor necrosis factor (TNF)-α [20,21]. Recently, thymic stromal lymphopoietin (TSLP), an epithelial-derived anti-inflammatory cytokine with polarizing effects on dendritic cells [22], has been implicated in experimental AAG [23]. In particular, deficiency of TSLP receptor exacerbated the severity of gastric lesions, thus suggesting that, at least in experimental models, TSLP receptor-mediated signaling negatively regulates organ-specific T helper cell type (Th)1-dependent autoimmunity [23]. Finally, the recent demonstration of high levels of IL-17A in the gastric mucosa and stomach-draining lymph nodes of mice with severe AAG [24] supports the involvement of Th17 cells in experimental AAG.

Less is known regarding molecular mechanisms underlying AAG in humans, and these are schematically reported in Fig. 1. T cells isolated from gastric biopsies of patients with AAG showed that most T cell clones are $CD4^+$, whereas $CD8^+$ T cells represent a minority of the lymphoid infiltrate [25]. Accordingly, a considerable proportion of $CD4^+$ T cell clones proliferate in response to gastric H^+/K^+ ATP-ase, whereas no proliferation was evident for $CD8^+$ T cell clones. Most of the H^+/K^+ ATP-ase-specific T cell clones produce IFN-γ, but not IL-4 or IL-5, while only a few clones secrete both T helper cell (Th)1 and Th2 cytokines [25].

From a translational point of view, TNF-α together with IL-21 represents the only two targets which have been in vivo neutralized in experimental AAG with amelioration of gastric lesions; [21] however, no data are available attempting to counteract specific inflammatory mediators of in AAG patients.

Autoreactive Th1 cells may induce gastric epithelial cell death through both Fas–Fas ligand (FasL) and perforin/granzyme B pathway. Th1 cytokines can increase the expression of Fas and major histocompatibility complex (MHC) class II molecules on gastric epithelial cells [26], thus inducing them to function as antigen presenting cells, as proved by cathepsin expression on gastric epithelial cells [27]. Fas expression in the corpus–fundus mucosa co-localizes with the expression of H^+/K^+ ATP-ase [28]. Killing of Fas^+ target cells by FasL-expressing H^+/K^+ ATP-ase specific Th1 cells isolated from the gastric mucosa of AAG patients was demonstrated in vitro [25]. Fas-mediated parietal cell death may favor the expansion of immature progenitors which fail to differentiate into zymogenic cells [14,29].

There is evidence that humoral immunity may also have a role in AAG. Chronic T cell dependent activation of B cells seem to be responsible for the local production of PCA, which are usually detected in the serum of AAG patients (Table 1) [25], and an increase of IgG4-positive plasma cells has been detected in gastric biopsies (Fig. 2) [30]. The *primum movens* of autoimmunity in AAG is still unknown, and it is

Table 1
Main characteristics of autoimmune diseases of the gastrointestinal tract.

Disease	Prevalence	F/M	Circulating autoantibody	Autoantibody target	Autoantibody pathogenicity	Autoantibody SE/SP	Dominant cytokine	Mechanism of epithelial damage	Neoplastic complication	Current therapy
Autoimmune atrophic gastritis	1.9/100	3:1	PCA	H^+/K^+ ATPase	Uncertain	90%/50%	IFN-γ	Apoptosis	Gastric tumors	Vitamin B12 supplementation
Celiac disease	1/100	2:1	tTGA	tTG	Uncertain	99%/100%	IFN-γ, IL-17A, IL-15	Apoptosis	EATL	GFD
Autoimmune enteropathy	Rare	1:1	AEA	Enterocyte	Yes	Unknown	Unknown	ADCC	EATL	Steroids, immunosuppressants
Ulcerative colitis	0.01/100	2:1	p-ANCA	Perinuclear neutrophil protein	No	90%/40%	TNF-α, IL-17A	Apoptosis	Colorectal cancer	Mesalazine, steroids, immunosuppressants, anti-TNF-α antibodies

ADCC, antibody-dependent cell-mediated cytotoxicity; AEA, anti-enterocyte antibody; p-ANCA, perinuclear anti-neutrophil cytoplasmic antibody; EATL, enteropathy-associated T cell lymphoma; F, female; GFD, gluten-free diet; IFN, interferon; IL, interleukin; M, male; PCA, parietal cell autoantibody; SE, sensitivity; SP, specificity; TNF, tumor necrosis factor; tTG, tissue transglutaminase; tTGA, anti-tissue transglutaminase antibody.

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