

Cutting Edge Issues in Autoimmune Gastritis

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Abstract Autoimmune gastritis is the outcome of a pathological CD4 T cell-mediated autoimmune response directed against the gastric H/K-ATPase. Silent initially, the gastric lesion becomes manifest in humans by the development of megaloblastic pernicious anemia arising from vitamin B12 deficiency. Cutting edge issues in this disease relate to its epidemiology, immunogenetics, a role for *Helicobacter pylori* as an infective trigger through molecular mimicry, its immunopathogenesis, associated organ-specific autoimmune diseases, laboratory diagnosis, and approaches to curative therapy.

Keywords Autoimmune gastritis · Gastric H/K-ATPase · Pernicious anemia · *Helicobacter pylori* · Parietal cell and intrinsic factor antibody · Gene therapy · Bone marrow transplantation

Autoimmune gastritis or chronic atrophic gastritis is the underlying pathological gastric lesion for the clinical manifestation of vitamin B12-deficient pernicious anemia [1]. Chronic atrophic gastritis is a precursor of intestinal metaplasia leading to gastric cancer, the second leading cause of cancer deaths worldwide. Mouse models of the human disease induced either by neonatal day 3 thymectomy (d3Tx) or by transgenic expression of GM-CSF driven by a stomach-specific promoter [2–4] are excellent animal models. In man as in mice, the gastric H/K-ATPase [5, 6] is the target antigen. The gastric lesion comprises a chronic inflammatory infiltrate with cellular, humoral, and immune responses to the gastric H/K-ATPase. Gastric H/K-ATPase-reactive CD4 T cells are the major drivers of the autoimmune response in man as in mice.

What Is the Incidence of Autoimmune Gastritis Worldwide?

The true incidence of autoimmune gastritis worldwide remains unclear because it is asymptomatic before the clinical manifestation of pernicious anemia. As it is a gastric disease that is relatively inaccessible to detection save by gastric endoscopy and biopsy, studies of its incidence have relied mainly on surrogate serum markers. Incidence estimates have ranged from 0% to 11% per year and consistently below 1% in patients not infected with *Helicobacter pylori*. A 5-year study of 5,229 German women and men, aged 50–74 years, reported on overall incidence of 1.1%, increasing from 0.5% from 50 to 54 years to 2.1% for those aged 70–74 years. *H. pylori* seropositivity was strongly associated with incidence [7]. A study of 1,387 Northern Italian dyspeptic patients revealed a good correlation (94%) between serum studies with a

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“GastroPanel” (comprising tests for pepsinogen 1, pepsinogen 2, gastrin-17, and *Helicobacter* antibody) with biopsy [8]. A study of 4,256 Finnish volunteers using the “GastroView panel” (comprising tests for pepsinogen I and II levels (and ratio) and *H. pylori* IgG antibody level) revealed positive tests in 3.5% and with *H. pylori* infection in 37%. The diagnosis was new in 95% leading to the conclusion that chronic atrophic gastritis is a common largely undiagnosed disease among Finnish adults [9]. These studies suffer from the failure to include tests for parietal cell and intrinsic factor antibodies as serum biomarkers for autoimmune chronic atrophic gastritis.

What Genes Predispose to Development of Autoimmune Gastritis?

Autoimmune gastritis clusters with the organ-specific autoimmune endocrinopathies that include autoimmune thyroiditis and type 1 diabetes mellitus. Its incidence is also higher among identical twins and first-degree relatives. These observations point to a genetic association. Genetic studies in mouse autoimmune gastritis identified *Gasa1* and *Gasa2* located on mouse chromosome 4 as the major susceptibility loci (Fig. 1). Analysis of BALB.B6 congenic strains revealed that *Gasa1* and *Gasa2* can act independently to cause full expression of susceptibility to autoimmune gastritis. The positions of *Gasa1* and *Gasa2* correspond closely to two autoimmune diabetes susceptibility loci, *Idd11* and *Idd9*. This is of interest because of the association of autoimmune gastritis with autoimmune diabetes [10]. However, whether these loci are relevant to human autoimmune gastritis remains unknown.

HLA associations have been identified for the autoimmune endocrinopathies such as type 1 diabetes mellitus, but similar associations have for sometime eluded their identification in autoimmune gastritis. Two recent studies in

Italian and Finnish subjects suggest an association with HLA-DRB103 and HLA-DRB104. A study of 89 Italian patients with chronic atrophic gastritis reported a prevalence of 28.1% for HLA-DRB1*03 compared to 15.9% for controls ($p=0.01$) and of 25.8% for HLA-DRB1*04 vs. 14.4% for controls ($p=0.01$; Fig. 1). HLA-DRB1*01 occurred more frequently in controls than in AG patients (11.5% vs. 3.4%, $p=0.01$) suggesting a protective effect. Patients carrying the HLA-DRB1*03 or *04 alleles also more frequently had autoimmune thyroid disease (70.4% vs. 42.2%, $p=0.01$) and intestinal metaplasia (86.4% vs. 62.2%, $p=0.01$). Thus, over 50% of these patients carry HLA-DRB1*03 or *04 alleles [11]. A study of 12 Finnish patients with autoimmune gastric corpus atrophy revealed significantly more HLA-DRB1*04 (58%) and DQB1*03 (83%) than the general Finnish population (28% and 51%, respectively; $p=0.045$ and 0.034). No patient was positive for HLA-B8-DRB1*03, a well-established autoimmune marker. These findings led to the conclusion that HLA-DRB1*04 and DQB1*03 alleles, but not HLA-B8-DRB1*03, predispose to autoimmune gastritis [12]. Whether these HLA associations hold true for other European and non-European populations remain to be determined.

Is *H. pylori* a Microbial Trigger?

H. pylori is a common gastric pathogen affecting almost half the population of the world. Its infection is associated with the development of chronic atrophic gastritis. Molecular mimicry between *H. pylori* antigens and gastric H/K-ATPase has been invoked as a mechanism for the genesis of autoimmune gastritis [13] (Fig. 1). The proposal is based on the observation that *H. pylori*-infected patients with autoimmune gastritis harbor in vivo-activated gastric CD4+ T cells that recognize both H/K-ATPase and cross-reactive epitopes from nine *H. pylori* proteins. The cross-reactive *H. pylori* peptides induced T cell proliferation and production of Th1 cytokines. Furthermore, autoantibodies to the H/K-ATPase were identified in 20–30% of *H. pylori*-infected patients. The presence of *H. pylori* autoantibodies is associated with increased severity of corpus gastritis, atrophy, and apoptosis with histopathological and clinical features similar to autoimmune gastritis [14]. *H. pylori* infection was found in a study of serum markers of gastric atrophy (pepsinogen I, pepsinogen I/II, and gastrin) and autoimmunity (parietal cell and intrinsic factor antibodies) in 23 patients with different grades of atrophic gastritis [15]. While these studies support a causative link, they do not provide definitive evidence. The suggestion is confounded by reports of an inverse association between a proinflammatory genetic profile and *H. pylori* seropositivity. Clearance of *H. pylori* infection with progression of

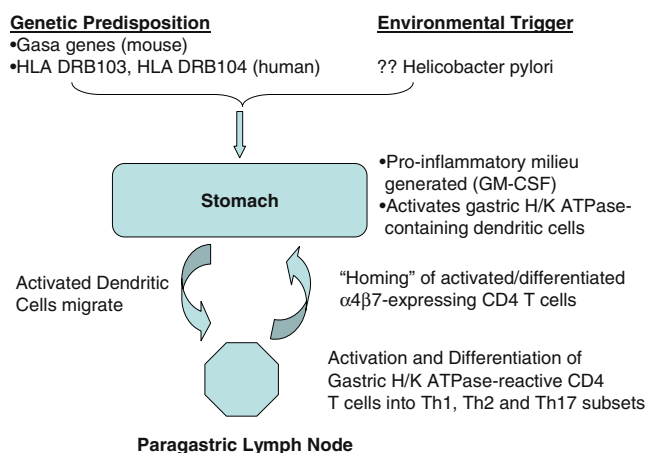


Fig. 1 Immunopathogenesis of autoimmune gastritis

gastritis to corpus atrophy [16] suggests a major underestimation of its association with chronic atrophic gastritis [17]. A “hit and run” for *H. pylori* remains possible in which infection begins in the antrum but is lost with progression to the corpus and the consequent loss of acid secretion. What is required to test this hypothesis is a longitudinal study. The study should document the inception of *H. pylori* infection with antral gastritis followed by extension to corpus autoimmune gastritis and loss of *H. pylori* infection with achlorhydria.

How Is Tolerance of CD4[±] T Cells to Gastric H/K-ATPase α and β Established?

There is unequivocal evidence that the gastric H/K-ATPase is the causative autoantigen in human and in mouse autoimmune gastritis [1] (Fig. 1).

The gastric H/K-ATPase comprises α and β 2 subunits. While the α subunit is “promiscuously” expressed in the thymus, the β subunit is not [18]. Transgenic expression of the β subunit in the thymus prevents the development of d3Tx-induced autoimmune gastritis [18]. The prevailing view is that promiscuous intrathymic expression of tissue-specific self-antigens is an evolutionarily conserved process. Activation of a promiscuous gene expression program, in part mediated by the autoimmune regulator (Aire) gene, leads to synthesis of a diverse set of >400 genes that cluster along chromosomes. “Promiscuous” expression appears to be a unique property of medullary thymic epithelial cells rather than bone marrow-derived antigen-presenting cells, although recent interest in peripheral lymphoid organs and their role in immune tolerance may challenge this view [19]. Expression of these genes is considered crucial for selecting a T cell receptor repertoire purged of self-reactive specificities. Cognate interactions occur between CD4⁺ thymocytes carrying autoreactive T cell receptors and medullary thymic epithelial cells displaying autoantigen–MHC class II complexes [20–23]. The case of the gastric H/K-ATPase α subunit is an exception. Neither promiscuous expression of thymic HK α in wild-type mice nor its transgenic overexpression in bone marrow-derived cells negatively select pathogenic anti-H/K α T cells [24]. Negative selection of anti-H/K α T cells was only observed with thymic overexpression of H/K β . A plausible explanation rests on the suggestion that H/K α epitopes fail to access MHC class II-loading compartments in cells of the normal thymus because of its inability to be exported from the endoplasmic reticulum and its rapid degradation in the absence of H/K β [25].

Tolerance to either subunit presumably has to rely on peripheral mechanisms (Fig. 2). For the α subunit, extra-thymic peripheral deletion has been reported [25]: CD4⁺ T

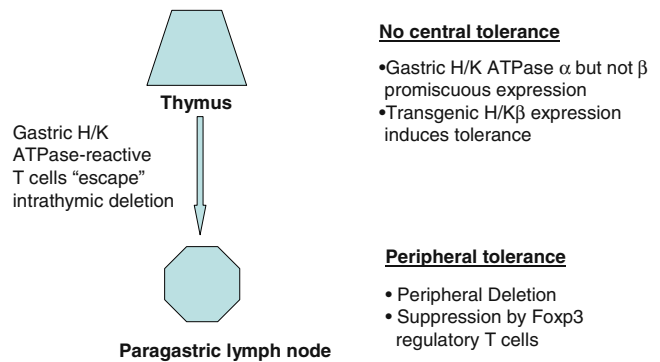


Fig. 2 Tolerance to gastric H/K-ATPase

cells from H/K-ATPase-deficient mice were highly effective in inducing gastritis, but exposing them to H/K-ATPase in WT mice decreased their ability to induce gastritis. Peripheral deletion of CD4⁺ T cells reactive to the H/K-ATPase α subunit was formally demonstrated by transfer of CD4⁺ T cells from TCR transgenic mice with α subunit specificity into WT mice. However, peripheral deletion of CD4⁺ T cells reactive to the H/K-ATPase β subunit has not been demonstrated. While antibody to the HK β subunit has been demonstrated, T cell clones to this subunit have not been reported.

In addition to peripheral deletion mechanisms, suppression by Foxp3 expressing regulatory T cells also has a major role. Studies of gastric autoimmunity induced by d3Tx were the first to implicate a role for regulatory T cells in tolerance [26, 27]. Natural occurring regulatory T cells (nTreg) inhibit both the induction of d3Tx autoimmune gastritis and the effector functions of cloned autoantigen-specific effector CD4⁺T cells [28]. These nTreg inhibited the differentiation of autoantigen-specific T cells to Th1 effector cells, as reflected by a decrease in antigen-stimulated IFN γ production and reduced T-bet expression [29]. However, they did not inhibit migration and expansion of effector cells in the gastric lymph node nor did they inhibit their migration to the stomach. TGF β -induced H/K-ATPase-specific T regulatory cells (iTregs) inhibited the initial priming and proliferation of autoreactive T cells, and appear to do so by acting on H/KATPase presenting dendritic cells [30]. Antigen-specific regulatory T cells are more potent than polyclonal regulatory T cells in suppressing autoimmune gastritis [31]. TGF- β complexed to latency-associated peptide (LAP) is expressed on the cell surface of activated but not resting Treg cells. Treg cell LAP-TGF- β plays an important role in suppressing the proliferation of activated T cells, but it is not required for suppressing naive T cell activation. Treg cell-derived TGF- β could generate de novo suppressive CD4⁺FoxP3⁺ T cells in vitro from naive precursors in a cell contact-dependent, antigen-presenting cell-independent, and α (V)

integrin-independent manner. The data suggest that the generation of these TGF- β -dependent CD4⁺FoxP3⁺ cells by “infectious tolerance” may represent a major mechanism by which Treg cells maintain tolerance and expand their suppressive abilities [32].

What Are the Mechanisms of Activation of H/K-ATPase-Reactive CD4[±] T Cells?

An enlarged paragastric lymph node is a prominent feature of experimental autoimmune gastritis. A physical association of CD11c⁺dendritic cells with gastric parietal cells has been reported [33]. H/K-ATPase protein was found within vesicular compartments of a few CD11c⁺dendritic cells only in the draining gastric lymph node and increased markedly in number with gastric mucosal destruction. Constitutive *in vivo* processing and presentation of H/K-ATPase were only seen in gastric but not peripheral dendritic cells. The presumption is that uptake of the H/K-ATPase by these gastric dendritic cells follows the normal turnover of gastric parietal cells from their apoptotic cell death. These data support a model of antigen uptake in the gastric mucosa by gastric dendritic cells followed by their trafficking to the draining paragastric lymph node [33] (Fig. 2). These studies beg the question of the mechanisms that lead to activation of these dendritic cells. One possible mechanism is suggested by studies that showed that local transgenic expression of the dendritic cell activating cytokine, GM-CSF, led to spontaneous autoimmune gastritis [4]. In these studies, lymphocytes that proliferate in response to stimulation by the gastric H/K-ATPase were also restricted to the draining paragastric lymph node.

Homing of activated H/K-ATPase-reactive CD4 T cells studied in the d3Tx model of autoimmune gastritis identified $\alpha 4\beta 7$ /MAdCAM-I interaction as a key pivotal event [33]. MAdCAM-1 in the mucosal endothelium of gastritis mice was significantly increased in the gastritis mice [34]. The incidence of autoimmune gastritis was reduced from 80% to 26% by treatment of d3Tx BALB/c mice with MAdCAM-1-specific monoclonal antibody (MECA 367). The incidence of gastritis was reduced to 40% by treatment with a monoclonal antibody directed to the MAdCAM-1 ligand, $\alpha 4\beta 7$.

What Is the Contribution of CD4 T Cell Subsets in Immunopathogenesis?

Th1, Th2, and Th17 CD4⁺ T cells reactive to the gastric H/K-ATPase are implicated in the pathogenesis of autoimmune gastritis (Fig. 2). Freshly explanted paragastric lymph node cells from mice with d3Tx-induced autoimmune

gastritis reacted to the H/K-ATPase α chain, but only marginally to the β chain. Two H/K-ATPase-reactive CD4⁺T cell lines derived from this lymph node recognize distinct peptides from the H/K-ATPase α chain. While one cell line secreted Th1 and the other Th2 cytokines, both are equipotent in inducing gastritis with distinct profiles of cellular infiltration in nude recipients [35]. TCR transgenic mice generated from T cell clones were generated from these two cell lines. The TCR transgenic mouse derived from the Th1 clone spontaneously developed severe autoimmune gastritis, with disease detected as early as day 10 of life and could be transferred to immunodeficient recipients [36]. With the TCR transgenic mouse derived from Th2 T cell clone, only a proportion of these mice spontaneously develop autoimmune gastritis by 10 weeks of age, with disease characterized by eosinophilic infiltration of the gastric mucosa and Th2 differentiation of transgenic T cells in the paragastric lymph node. The Th2 phenotype of this autoimmune response seems related to a low availability of MHC class II–self-peptide complexes. This *in vivo* model of spontaneous Th2-mediated, organ-specific autoimmunity provides a unique example in which clonotypic TCR conveys the Th2 disease phenotype [37]. The capacity of fully differentiated Th1, Th2, and Th17 cells derived from the Th1 TCR transgenic mouse to induce autoimmune gastritis was evaluated by transfer to immunodeficient recipients. Th17 cells induced the most destructive disease with cellular infiltrates composed mainly of eosinophils with high serum IgE levels. Polyclonal Treg suppressed Th1 cells, moderately suppressed Th2 cells, but suppressed Th17 cells only at early time points [38]. The precise contribution of each of these CD4 Th subtypes in the induction of gastritis and whether they operate synergistically remains unclear.

What Autoimmune Diseases Frequently Segregate with Autoimmune Gastritis?

Of the autoimmune diseases in the autoimmune endocrinopathy cluster, type 1 diabetes mellitus and autoimmune thyroiditis are the two standouts that are not uncommonly associated with autoimmune gastritis (Table 1).

Thyroid autoimmunity is evident in up to one third and gastric autoimmunity in up to a quarter of patients with type

Table 1 Associated diseases

Autoimmune gastritis	Autoimmune endocrinopathy
Iron-deficiency anemia	Autoimmune thyroiditis
Pernicious anemia	Type 1 diabetes mellitus
	Vitiligo

1 diabetes. Relatives of diabetic patients, particularly mothers, have higher frequencies of these autoimmune conditions. Conversely, gastric autoimmunity is present in one third and islet autoimmunity in one tenth of patients with autoimmune thyroid disease [39]. These observations suggest that patients with these autoimmune diseases should be screened for the presence of their associated diseases as a subset of patients with these autoantibodies will develop clinical disease and screening could prognosticate morbidity relative to unrecognized clinical entities. The close follow-up of patients with organ-specific autoantibodies could lead to identification of those requiring therapy [40]. This suggestion is further supported by a cross-sectional study into the occurrence of and risk factors for autoimmune thyroid disease in atrophic body gastritis patients [41]. Of 319 atrophic body gastritis patients, 169 (53%) had an associated thyroid disorder, and 89 (52.7%) of these were unaware of it. The thyroid disease was autoimmune in 128 patients (75.7%) and nonautoimmune in 41 patients. Logistic regression showed that risk factors for having autoimmune thyroid disease in atrophic body gastritis patients were female sex, presence of parietal cell antibodies, and presence of metaplastic atrophy. These studies indicate that autoimmune thyroid disease and atrophic body gastritis are closely linked, suggesting that atrophic body gastritis patients should be investigated for an occult autoimmune thyroid disease, in particular women and those with positive parietal cell antibodies. The association of autoimmune thyroid disease with autoimmune gastritis is further reflected in studies of vitamin B12 levels. In a study of serum B12 levels in 115 patients with autoimmune thyroid disease, 32 patients (28%) had low B12 levels. Fasting serum gastrin was measured in 26 and was higher than normal in 8 patients [42]. Parietal cell antibody measured in 27 patients with B12 deficiency was positive in 8 patients. Five patients with high gastrin levels underwent gastroscopy with biopsy, and atrophic gastritis was diagnosed in all. The prevalence of pernicious anemia as assessed by high serum gastrin levels in patients with low B12 was 31%. The study concluded that patients with autoimmune thyroid disease have a high prevalence of B12 deficiency and particularly of pernicious anemia. The evaluation of B12 deficiency can be simplified by measuring fasting serum gastrin and, if elevated, referring the patient for gastroscopy.

Autoimmune gastritis can also develop concordant with postpartum thyroiditis. This was investigated in 54 women with postpartum thyroiditis [43]. Parietal cell antibodies to the H/K-ATPase were found in 18 women during pregnancy, and in 10 of them, a 2–9-fold increase in the parietal cell antibody level was observed in the postpartum period. At a 5-year follow-up, the initially parietal cell antibody-positive women still had elevated antibody levels. Hypergastrinemia

and low pepsinogen levels were noted in four women. In two of these women, low serum vitamin B12 levels had developed. In six of nine parietal cell antibody-positive women examined by gastroscopy, biopsy specimens from the gastric body mucosa contained mononuclear cells, mainly T lymphocytes (CD3+) and macrophages (Leu-M3+) combined with aberrant epithelial expression of HLA-DR. In four patients with chronic gastritis, all parietal cells, as defined by a specific monoclonal antibody, were found to have immunoglobulin G (IgG) deposits by a double-immunostaining method. Three of them had microscopic evidence of atrophy, and in one patient, the body mucosa was intact. In one further patient with intact glands at histological examination, the basolateral membrane of some oxyntic glands was coated with IgG.

What Is the Incidence of Iron Deficiency Anemia?

Recent studies have highlighted an association with iron deficiency, as a known complication of achlorhydria that may precede the development of pernicious anemia. Among 160 patients with autoimmune gastritis identified by hypergastrinemia and strongly positive antiparietal antibodies, 83 subjects presented with iron deficiency anemia, 48 with normocytic indices, and 29 with macrocytic anemia [44]. Compared with macrocytic patients, patients with iron deficiency anemia were 21 years younger (41 ± 15 years vs. 62 ± 15 years) and mostly women. All groups had a high prevalence of thyroid disease (20%) and diabetes (8%). Stratification by age cohorts from younger than 20 years to older than 60 years showed a regular and progressive increase in mean corpuscular volume, and serum ferritin and gastrin levels, and a decrease in cobalamin level. The prevalence of *H. pylori* infection was 87.5% at age younger than 20 years, 47% at age 20 to 40 years, 37.5% at 41 to 60 years, and 12.5% at age older than 60 years. These findings challenge the common notion that pernicious anemia is a disease of the elderly and imply a disease starting many years before the establishment of clinical cobalamin deficiency. The implication of these findings is that patients with unexplained iron deficiency anemia should be investigated for autoimmune gastritis and pernicious anemia as autoimmune atrophic gastritis is encountered in 20–27% of patients with obscure or refractory iron deficiency anemia and is 4–6 times more common than celiac disease causing unexplained iron deficiency [45]. These clinical features of iron deficiency anemia associated with achlorhydria and mucosal atrophy sparing the gastric antrum have all been accurately described as the “anemia of achylia gastrica” by Faber and others over 100 years ago, including refractoriness to oral iron treatment, female predominance, relatively young

age, increased prevalence of thyroid disease, and tendency to progress to pernicious anemia.

What is the Incidence of Vitiligo?

Histologic evidence of autoimmune atrophic gastritis was obtained in 10 cases (15%) of 65 unselected patients with vitiligo. These patients had gastric antibodies, elevated gastrin levels, and gastric acid output after pentagastrin stimulation, performed in 7 of them was markedly reduced [46]. The study provided definite evidence of an association of autoimmune atrophic gastritis with a proportion of vitiligo cases and suggests the need for surveillance of these patients in terms of gastric neoplasia.

What Is the Ideal Combination of Tests for Laboratory Diagnosis?

Up to 10% of patients with autoimmune gastritis are predisposed to gastric carcinoid tumors or adenocarcinomas. This provides a strong rationale for screening, early diagnosis, and treatment [47]. Serum biomarker tests should screen for atrophic gastritis and for antibodies that segregate with autoimmune gastritis. Screening tests using a combination of pepsinogen 1 (P1), pepsinogen 2, pepsinogen 1/pepsinogen 2 ratio, and gastrin-17 reliably identify the presence of chronic atrophic gastritis [8, 48]. Loss of zymogenic cells leads to low pepsinogen levels, while loss of acid secretion leads to hypergastrinemia. These serum biomarker tests have been coined the “serological gastric biopsy”. Combination of these tests for corpus atrophy with antibody to *H. pylori* identifies infection with this organism. In one study [49], PGI/PGII ratio gave the best sensitivity (96.1%) and negative predictive value (97.7%), PGI, the highest specificity (94.6%), PGII, a high negative predictive value (90.7%), but IgG anti-*H. pylori* showed poor sensitivity and specificity (58.8% and 26.5%, respectively). The authors concluded that pepsinogen I/pepsinogen II ratio is the most suitable single measurement for screening atrophic gastritis. Concordance between these serum biomarkers and gastric biopsy is excellent [50].

Serum ghrelin, a molecule mainly produced by endocrine cells of the gastric oxyntic mucosa, is an emergent and promising new test for gastric atrophy. Serum ghrelin was reported to be associated with the highest sensitivity and specificity (97.3% and 100%, respectively) in detecting gastric atrophy and was superior to pepsinogen I/pepsinogen II ratio and gastrin. The study concluded that serum ghrelin represents the most sensitive and specific noninvasive marker for chronic atrophic gastritis [51].

Plasma ghrelin levels correlated with serum levels of PGI and the PGI/PGII ratio, and decrease in accordance with the extent of atrophic change in gastric mucosa irrespective of *H. pylori* infection [52, 53].

Adding the screen for parietal cell antibody and intrinsic factor antibodies to the screen for atrophic gastritis identifies an autoimmune basis for the gastric atrophy. Parietal cell antibody identified by immunofluorescence continues to be used in diagnostic immunology laboratories. Identification of the gastric H/K-ATPase as the target autoantigen for parietal cell antibody has led to the development of an ELISA for the detection of this antibody [54]. While the assay sensitivity was 82% and specificity 90% in this study, a more recent study reported excellent agreement between ELISA and immunofluorescence with results of 75% (type A gastritis) and 100% (pernicious anemia). [55]. In a study of 165 patients with biopsy-proven chronic atrophic gastritis and 113 controls, parietal cell antibody and intrinsic factor antibody were tested by ELISA. The study found parietal cell antibody in 81% of patients and in 10% of controls, and intrinsic factor antibody in 27% of patients. Combining the two tests significantly increased their diagnostic performance yielding 73% sensitivity for pernicious anemia [56]. The findings are at variance with a retrospective study of the frequency of antibody positivity (intrinsic factor antibody and/or parietal cell antibody) over a 3-year period and a prospective study of intrinsic factor antibody in 91 parietal cell antibody-negative patients with low B12 levels. This study found limited value for intrinsic factor antibody in parietal cell antibody-negative patients [57]. Parietal cell antibody was identified by immunofluorescence in this study. Of 847 samples identified in the retrospective study, 4 (0.47%) were positive for intrinsic factor antibodies only, 731 (86.3%) positive for parietal cell antibody alone, and 112 (13.2%) for both. B12 levels had no bearing on autoantibody status. In 91 consecutive patients with low B12 levels, all were negative for gastric parietal cell antibodies and intrinsic factor assay.

In a prospective 5-year study of 208 adult patients with autoimmune thyroid disease, parietal cell antibody identified by ELISA to the gastric H/K-ATPase predicted the subsequent development of chronic atrophic gastritis. The trend analysis showed that autoantibody levels rose progressively over time, reached a peak level, and then fell, following progressive destruction of gastric mucosa and disappearance of the target autoantigen [58]. In another 5-year prospective study of 186 patients with type 1 autoimmune diabetes mellitus, the association of a positive parietal cell antibody and low pepsinogen I identified patients with a higher risk to decrease cobalamin concentrations during follow-up [59].

A case can be made for managing patients with autoimmune gastritis with yearly assessments of serum

biomarkers for gastric atrophy and tests for parietal cell and intrinsic factor antibody (Fig. 3), serum iron, vitamin B12, and a full blood count. Iron or vitamin B12 should be supplemented in patients with iron deficiency or pernicious anemia. Whether there should be regular gastroscopic surveillance and biopsies to monitor for gastric carcinoids and gastric cancer remains controversial. Perhaps, these invasive procedures may be considered at least once in patients with autoantibodies to the parietal cell and/or intrinsic factor, iron or vitamin B12 deficiency anemia, or serum biomarkers of gastric atrophy.

What Are the Optimal Approaches Toward Curative Therapy?

There is no curative therapy for autoimmune gastritis and its attendant complication of pernicious anemia and progression to gastric cancer. Replacement therapy with vitamin B12 only alleviates the macrocytic anemia but has no impact on the underlying destructive autoimmune disease process. Clearly, there is a pressing need to find a curative therapy for this gastric autoimmune disease.

Immunosuppression such as meted by prednisolone only remits the gastric disease with regeneration of the gastric mucosa in so long as drug therapy is continued. Withdrawal of prednisolone promptly results in disease recurrence in man as in the mouse model of autoimmune gastritis [60].

Bone marrow transplantation to reprogram the immune system has been mooted as a curative approach to the treatment of the autoimmune diseases [61]. While allogeneic bone marrow transplantation is curative, it is seriously hampered by the toxicity of the preconditioning regimen and by the complication of graft-versus-host disease. Autologous bone marrow transplantation is less toxic, remits disease, but is unfortunately hampered by a high incidence of disease recurrence. Recurrence is most likely due to failure to establish tolerance to culprit antigens that drive the autoimmune response. The concept that ectopic expression of self-antigen in the thymus can be utilized to promote immune tolerance is the basis for our understanding of the role of Aire expression in the thymus. The promotion of “additional” ectopic expression in transgenic mice supports the robust tolerance that can be induced as demonstrated in a number of well-established experimental

Autoimmune gastritis

- Parietal cell antibody to gastric H/K ATPase
- Intrinsic factor antibody

Chronic atrophic gastritis

- Pepsinogen 1
- Pepsinogen 2
- Pepsinogen 1/2 ratio
- Gastrin 17
- Gherin

Fig. 3 Serum biomarkers

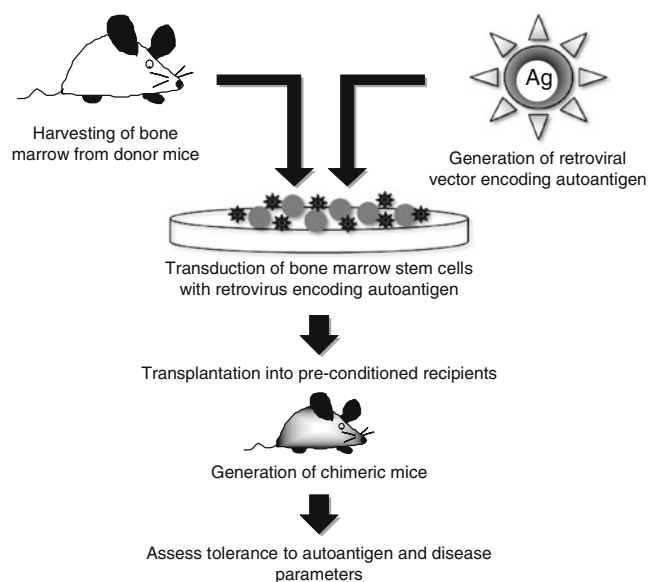


Fig. 4 Experimental approach to curative gene therapy and bone marrow transplantation to establish immune tolerance to self-antigen for autoimmune disease

models of autoimmunity, including type 1 diabetes [62] and autoimmune gastritis [18]. The subsequent demonstration that ex vivo manipulation and transplantation of isolated bone marrow cells can be used to promote immune tolerance reinforces a role for bone marrow-derived cells in immune tolerance and provides an avenue for clinical translation and enhancing existing bone marrow transplantation protocols for the autoimmune diseases. A number of studies have shown that transplantation with bone marrow engineered to encode the culprit antigen can prevent the induction of autoimmune disease [63, 64]. This approach has demonstrated successful establishment of robust intrathymic deletional tolerance and shown to be practical in preclinical and established autoimmune disease models initiated by culprit antigen. The approach of “hijacking” the bone marrow for use as a “molecular Trojan Horse” potentially has wide application to the curative treatment of a range of autoimmune diseases in which the causative self-antigens are known [65, 66] (Fig. 3). However, the full spectrum of tolerogenic mechanisms that may or may not be engaged by this strategy has not been fully elucidated and will provide valuable information. This strategy should be potentially applicable to autoimmune gastritis as the causative antigen has been identified as the gastric H/K-ATPase. The challenge is to design nontoxic bone marrow transplantation approaches that use safe or nonviral vectors to introduce genes encoding self-antigen into the bone marrow. This approach of “hijacking” the bone marrow for use as a “molecular Trojan Horse” potentially has wide application to the curative treatment of autoimmune diseases in which causative self-antigens are known [63,

64] (Fig. 4). This strategy should be potentially applicable to autoimmune gastritis as the causative antigen has been identified as the gastric H/K-ATPase. The challenge is to design nontoxic bone marrow transplantation approaches that use nonviral vectors to introduce genes encoding self-antigen into the bone marrow.

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