Autoimmune gastritis results in disruption of gastric epithelial cell development

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Judd, Louise M., Paul A. Gleeson, Ban-Hock Toh, and Ian R. van Driel. Autoimmune gastritis results in disruption of gastric epithelial cell development. Am. J. Physiol. 277 (Gastrointest. Liver Physiol. 40): G209–G218, 1999.—We have investigated the underlying basis of the lesion in murine autoimmune gastritis, a model of the human disease pernicious anemia. The disease is mediated by T lymphocytes and characterized by selective depletion of parietal and zymogenic cells from the gastric unit (gland) together with gastric epithelial cell hyperplasia. The gastric units of gastritic stomachs contained 2.3-fold more cells than normal and accumulated rapidly dividing, short-lived gastric epithelial stem cells and mucus neck cells. Most of these immature cells failed to differentiate into end-stage cells but rather appeared to die by apoptosis. We also found no correlation between anti-parietal cell autoantibody titers and the degree of gastric pathology, providing further evidence that autoantibodies do not play a direct role in the pathogenesis of gastritis. Taken together, the normal developmental pathways of the gastric mucosa are disrupted in autoimmune gastritis, resulting in an amplification of immature cell types. The differentiation of these immature cells appears to be blocked, contributing to depletion of end-stage cells. This scenario provides an explanation for depletion of not only parietal cells but also zymogenic cells even though they are not directly targeted by the immune system.

The majority of the gastric mucosa is a glandular epithelium. The glands or units are composed of three major differentiated cell types (16). Pit (surface mucous) cells occur in the upper pit zone of the unit and secrete protective mucus. Acid-secreting parietal cells are found in the middle and lower regions of the units. Zymogenic (chief) cells that secrete pepsin, and in some species intrinsic factor, predominate toward the base of units. The cells of the gastric units are in continuous turnover. Mature epithelial cells develop from stem cells via a series of well-defined cellular intermediates (18–22). Infiltration of the gastric mucosa by autoimmune inflammatory cells is accompanied by changes to the cohort of cells in the gastric units. Parietal and zymogenic cells are greatly depleted in number, although the total number of cells in the units is increased (24). One of the outstanding questions in the pathogenesis of autoimmune gastritis is why, when there is only evidence for an immune response to parietal cells, other cell types of the gastric mucosa are also affected, in particular the almost complete depletion of zymogenic cells. To address this question, we have investigated the cellular basis of the epithelial lesion in autoimmune gastritis. By examining rates of epithelial cell proliferation, cell death, and the fates of various gastric cell types, we conclude that the normal developmental pathways in the gastric mucosa of gastritic animals are blocked, resulting in the depletion of parietal and zymogenic cells and the accumulation of less-developed epithelial cells. This study has implications for other similar chronic inflammatory diseases.

MATERIALS AND METHODS

Neonatal thymectomy. On day 3 after birth, BALB/c and BALB/cRcSlc mice obtained from the Monash University Animal Facility were thymectomized under cold anesthesia as described previously (2). At the completion of the experiment, mice were examined for thymic remnants. All animal experimentation received prior approval from the relevant institutional ethics committees.

Analysis of autoimmune gastritis. Autoantibodies to tomato lectin-purified (9) porcine H+K+-ATPase α- and β-subunits present in mouse sera were detected by an ELISA as previously described (11). To assess gastritis, stomachs were fixed in 10% Formalin in phosphate buffer and embedded in paraffin wax. Sections (4 μm) were adhered to poly-L-lysine-coated slides and stained with hematoxylin and eosin or by a modification of the Maxwell method as described previously (28). In all analyses, the mucosa of the oxyntic stomach was examined.

In situ DNA nicked-end labeling. In situ detection of nicked-end DNA in sections of stomachs from 12-wk-old mice was performed as described (14). To determine if labeling reagents could access the entire tissue, sections were treated with 1 μg/ml of DNase I for 10 min at room temperature and subsequently exposed to nicked-end labeling reagents.
before the enzyme incubation step. To test the specificity of
the staining, the digoxigenin-labeling step was performed in
the absence of terminal deoxynucleotidyl transferase. Stained
nuclei were counted, and the total area of the mucosa was
measured using an image analysis system with Video Pro 32
software (Leading Edge, Adelaide, Australia). The data were
expressed as stained nuclei per square millimeter of gastric
mucosa. Four sections from each stomach were analyzed, and
sections were at least 25 µm apart to avoid sampling the same
cell twice.

Immunohistochemical analysis of DNA synthesis. Twelve-
week-old mice were injected with 100 ng of 5-bromo-2'-
deoxyuridine (BrdU)/g body wt (Sigma B5002) 6 h, 4 days, or
7 days before they were killed. Stomach tissue and sections
were prepared as above, and immunohistochemical detection of
BrdU incorporated into DNA was performed as described
previously (31). To quantitate BrdU labeling, five sections at
least 25 µm apart from each stomach were analyzed. From
each section, 20 complete longitudinal profiles of units were
selected at random from body and antrum, and the numbers
of cells both labeled and unlabeled were counted and classi-
fied by type under high magnification. The data were ex-
pressed as the average number of cells per section of gastric
unit for each animal.

Preparation of tissue for electron microscopy. Stomachs
from neonatally thymectomized mice were removed 12 wk
after thymectomy and fixed in 4% paraformaldehyde, 4%
sucrose, and 2% gluteraldehyde in 0.1 M phosphate buffer, pH
7.4, at 4°C overnight. The tissue was postfixed in 1% osmium
tetroxide, dehydrated in graded acetone, and embedded in
hard Spurr’s resin. Sections (90 nm) were examined after
they were stained with 2% uranyl acetate and lead citrate in a
Phillips 400T transmission electron microscope operating at
60 kV.

**RESULTS**

Phenotype of cells in gastric units of gastritic mice. BALB/c mice were thymectomized on day 3 after birth
and analyzed at 12 wk of age. Sera were tested by an
ELISA for the presence of autoantibodies directed to
the parietal cell H⁺-K⁺-ATPase, and stomachs were
examined histologically to detect mononuclear infil-
trates. Mice that had both of these hallmarks were
considered to have autoimmune gastritis. It should be
noted that all animals used in this study had been
thymectomized, including those that did not have auto-
immune disease. The stomachs of mice that did not
have autoimmune gastritis appeared identical to stom-
achs of unthymectomized animals, that is, they did not
have higher numbers of mononuclear cells in mucosal
or submucosal regions and epithelial cell populations
appeared normal.

The gastric units of mice with neonatal-thymectomy-
induced autoimmune gastritis contained more cells
than the gastric units of unaffected mice (1, 15, 24). To
identify the major gastric epithelial cell types in the
lesion, we stained sections of gastritic stomachs with a
modified Maxwell stain (see Fig. 1). As expected, the
(pit to base) length of the gastric units in the gastritic
stomach was increased (compare Fig. 1, A–C). Zymo-
genic cells were virtually absent from severely affected
gastric units, and parietal cells were greatly reduced in
number. There was a large variation in the degree and
characteristics of the epithelial lesion throughout each
gastric stomach and between stomachs from different

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**Fig. 1.** Histochemical staining of sections of stomach from 12-wk-old neonatally thymectomized mice. Stomach
sections were stained with the Maxwell modified technique as described in MATERIALS AND METHODS. A: stomach of
thymectomized but not gastritic mouse. Lumen of the stomach is indicated, and all other sections are in the same
orientation. B and C: gastritic stomachs from different mice. Abundant phospholipids present in the complex
intracellular membrane network and mitochondria of the parietal cells stain deep blue with Luxol fast blue. Zymo-
genic cells present at bases of the units stain pink/purple with pyronin, which binds to RNA in the abundant
rough endoplasmic reticulum and free ribosomes of this cell type. Pit cells (located on luminal surface) and
immature cells (located immediately below the pit cell layer) also stain with pyronin because of their large
nuclear-to-cytoplasmic ratio. Alcian yellow stains carbohydrates present in the lumen and granules of pit, mucous
neck, and mucus-rich cells. Bar = 50 µm (applies to all panels).
gastritic animals (compare Fig. 1, B and C). In the majority of the affected regions of the gastritic stomachs, small, pyronin-staining cells reminiscent of immature epithelial precursors were apparent (Fig. 1B). Other regions mostly consisted of large cells that stain with Alcian yellow, indicating abundant carbohydrates (Fig. 1C). Mucous granules were obvious in these Alcian yellow-stained cells when sections were observed at higher magnification (not shown) or electron optically (see below). We shall refer to these cells as “mucus-rich” cells. Therefore, in gastritic mice, there was an accumulation of a number of cell types that were either rare or absent in the unaffected gastric units.

A number of changes in the cell populations were observed by electron microscopy in the gastritic mucosa compared with normal mucosa. The stomachs of three gastritic mice were examined, and very similar observations were made for each. Cells resembling the previously described granule-free undifferentiated stem cells (19) were present in larger numbers in gastritic compared with normal mucosae (Fig. 2A). These cells likely correspond to the small, pyronin-staining cells (Fig. 1B). Pit cells were also abundant toward the luminal surface of the gastric units (Fig. 2B). The final major cell type in the mucosa of gastritic mice contains cored diphasic granules, typical of mucous neck cells of the normal mucosa (21) (Fig. 2, C and D). However, these cells were more abundant than mucous neck cells in normal mucosae, and each individual cell contained more granules. The location (central regions of the units) and morphology of these cells suggest that they correspond to the mucus-rich cells observed by carbohydrate histochemistry and light microscopy (Fig. 1). The morphology of the granules in these cells varied in different regions of the mucosa from one animal and between animals. In some granules, very little darkly stained material was present (Fig. 2C), in others the
darkly stained material was more prevalent (Fig. 2D). Small numbers of parietal cells were present in the gastritic mucosa, and very few zymogenic cells were detected.

Quantitation of cell division in mucosa of gastritic mice. The extent of the hypercellularity of the units of gastritic stomachs was determined by counting cells in 4-µm sections. The average cell number (calculated from data in Fig. 3) in sections of gastritic units was 106 ± 27 (average ± SD) compared with 46 ± 4.7 in unaffected gastric units (P < 0.0005, t-test assuming variances unknown and not equal). We estimated the mitotic rates by labeling cells in vivo with BrdU followed by detection of incorporation by immunocytochemistry 6 h, 4 days, and 7 days after BrdU injection. These time points were chosen on the basis of the generation times and half-lives of mucosal cell types (18-22). Figure 4 shows representative sections of BrdU-labeled tissue. In stomachs of animals killed after 6 h, a far greater number of BrdU-labeled cells were present in the gastric units of gastritic vs. unaffected animals (compare Fig. 4, A and B). In unaffected stomachs, most of the labeled cells were located in the isthmus region of gastric units as expected (19), representing the region of proliferating immature cells. In gastritic stomachs, BrdU-labeled cells were located throughout much of the length of the gastric unit. At 6 h, the proportion of BrdU-labeled cells per gastric unit varied from 13.5 to 21.2% [average of 16.2 ± 6.5 (SD)] in gastritic stomachs and from 1.2 to 2.5% (1.7 ± 0.37) in unaffected stomachs (calculated from data in Fig. 3). In data derived from gastritic mice, there is a high correlation (r = 0.95) between the number of BrdU-labeled cells per unit and the total cell number per unit (Fig. 3). This correlation is not evident at later time points due to a decrease in BrdU-labeled cells (see below).

In mice killed 4 days and 7 days (representative histology in Fig. 4, C and D) after injection, the proportion of BrdU-labeled cells in the gastric units of affected mice had dropped substantially [4 days: range of 2.3–3.3%, average of 3.0 ± 0.4% (SD); 7 days: range of 0.6–1.9%, 1.1 ± 0.72%, calculated from data in Fig. 3]. The number of BrdU-labeled cells in gastric units of unaffected stomachs also decreased but to a lesser extent (4 days: range of 0.9–1.2%, 1.1 ± 0.2%; 7 days: range of 0.56–1.0%, 0.84 ± 0.24%).

Quantitation and fate of cells in gastritic mucosa. To determine the type of cells labeled with BrdU and their developmental fate, stained sections of tissue were examined using high-magnification light microscopy, which allows unambiguous assignment of the mature pit (Fig. 4E), parietal (Fig. 4F), or zymogenic (Fig. 4G) cells. Cells grouped as small immature cells (Fig. 4H) appeared to have large nuclear-to-cytoplasmic ratio and a cytoplasm that stained strongly with eosin. The cells grouped as mucus-rich cells (Fig. 4I) were relatively large cells with a cytoplasm that stained weakly and diffusely. These two groupings of cells may contain heterogeneous populations at various stages of development. Using these classifications, we were able to account for all epithelial cells in the gastric units.

In normal stomachs at 6 h, almost all labeled cells were of the small immature phenotype (Figs. 4A and 5A) as expected from previous studies (19). In gastritic...
stomachs, in addition to labeled small immature cells, a small number of the mucus-rich cells (Fig. 5B) were also stained, and overall the number of cells that had incorporated BrdU was much greater than in unaffected gastric units.

At day 4, the number of labeled small immature cells present in the gastritic stomachs had decreased dramatically, and the number of mucus-rich cells was also generally lower (Fig. 5A and B). Labeled pit cells were present in both gastritic and unaffected animals, but the number per gastric unit was about twofold greater in gastritic stomachs (based on average values, Fig. 5C). If data were calculated as a percentage of total cells per unit that were labeled pit cells, then, because the number of cells in the gastritic units is larger, little difference was observed between the two groups (gastritic, 1.42%; unaffected, 1.51%; 0.94-fold). In both affected and unaffected groups, parietal cells were labeled at day 4 (Fig. 5D). A low number of zymogenic cells were labeled in the unaffected group, whereas no zymogenic cells were found in gastritic stomachs (Fig. 5E).

By day 7, few labeled small immature cells remained in both affected and unaffected stomachs; there were also some labeled mucus-rich cells remaining in the gastritic stomach (Fig. 5, A and B). Labeled pit cell numbers had decreased relative to 4 days (Fig. 5C), consistent with their short half-lives (20). Parietal cell numbers were 2.6-fold greater in unaffected than in gastritic animals (based on average values, Fig. 5D). If data were calculated as a percentage of total cells per unit that were labeled parietal cells, then the difference observed between the two groups was more substantial (gastritic, 0.07%; unaffected, 1.12%; 16-fold). Small numbers of BrdU-labeled zymogenic cells were present in the unaffected stomachs but were absent from gastritic stomachs (Fig. 5E). This result is consistent with the slower rate of development of zymogenic cells compared with parietal and pit cells in normal gastric units (18, 20, 21).

Overall, in gastritic stomachs, the large size of the gastric units is primarily due to a large population of small immature cells and mucus-rich cells. The number of BrdU-labeled cells at 4 days was 23% of that at the 6-h time point (based on average values), suggesting that most of these cells died. A small percentage of small immature cells appeared to have differentiated by day 4 and day 7 into terminally differentiated cells.

Fig. 4. Immunochemical detection of BrdU incorporation in neonatally thymectomized mice. Mice were neonatally thymectomized and at 12 wk of age were injected with BrdU before they were killed 6 h (A, B, H, I) or 7 days (C–G) after injection. A and C and E–G: thymectomized but not gastritic mice. B, D, H, and I: gastritic mice. Sections of stomach were incubated with a mouse anti-BrdU antibody and then with horseradish peroxidase-conjugated anti-mouse immunoglobulin antibody. Binding of antibody was detected by incubation with diaminobenzidine, which is metabolized to a brown precipitate, and sections were counterstained with hematoxylin and eosin. Arrows indicate pit (E), parietal (F), zymogenic (G), small immature epithelial (H), or mucus-rich (I) cells, which have a labeled nucleus. Bar in A = 50 µm (applies to A–D). Bar in E = 15 µm (applies to E–I).
Considering the large number of precursor cells in gastritic stomachs, the rate of appearance of differentiated cells was far less than in unaffected stomachs. Of significance, no zymogenic cells were visible in gastritic stomachs, indicating a complete cessation of development of this lineage.

Cell death in gastric units of gastritic mice. The rapid disappearance of the immature population led us to examine if rates of apoptosis were greater in gastritic vs. unaffected gastric units. Apoptotic cells were detected by the transferase UTP nick-end labeling (TUNEL) technique (14), which involves labeling and detection of 3'-ends of fragmented DNA, which abound in cells undergoing apoptosis. Stained cell remnants/nuclei were examined by light microscopy at high magnification and scored if they exhibited the typical morphological features of apoptosis. An example of TUNEL staining of gastritic mucosa is shown in Fig. 2F. The number of apoptotic cells per unit area in gastritic stomachs (Fig. 6) was on average 5.1-fold greater than that in unaffected stomachs. Apoptotic profiles in both gastritic and unaffected stomachs were located mostly in the neck-isthmus region of the gastric units, which contained many small immature cells. Apoptotic bodies in gastritic mucosa were also identified by electron microscopy (Fig. 2E), and in nearly all cases these bodies were observed in regions of the units that contained predominantly granule-free stem cells or other cells with only rudimentary characteristics of differentiated cells. Hence, it appears likely that the majority of apoptotic activity is the result of the death of precursor cell types.

Autoantibody titer and pathology. The titer of anti-H⁺-K⁺-ATPase autoantibodies varies between different
mice and is often used as a quantitative index of gastritis (examples are given in Refs. 3 and 12). In this study, we quantitatively assessed gastric pathology by determining gland size and apoptotic rates. We wished to determine whether autoantibody titer, assayed by H\(^+\)-K\(^+\)-ATPase-specific ELISA, correlated with the severity of pathological features (Fig. 7). The correlation coefficients were 0.02 and 0.51 for antibody titer vs. total cell number or apoptotic cells per unit, respectively, suggesting no relationship between these parameters.

**DISCUSSION**

Autoimmune gastritis induced by neonatal thymectomy is an organ-specific autoimmune disease mediated by CD4\(^+\), helper T lymphocytes (3, 13, 28, 32, 35, 38) directed toward the parietal cell H\(^+\)-K\(^+\)-ATPase (2, 4, 5, 15, 29, 33, 39). The cytotoxic activities of CD8\(^+\) cytotoxic T lymphocytes (13) or antibodies (15, 36) do not appear to play a role in disease induction or ongoing pathology. Although abundant information has been amassed concerning the cell types of the inflammatory lesions that mediate gastritis at this stage, we know little about the pathogenic mechanisms of these cells. In autoimmune gastritis, there is evidence for T and B cell responses to parietal cell proteins alone. However, in gastritic mucosae, not only are parietal cells depleted, but there is also considerable hypercellularity and a complete loss of zymogenic cells. We are attempting to discern the molecular and cellular mechanisms that result in this phenotype. To determine the cellular basis for this phenotype, we examined cell types, cell production, and death rates.

Hypercellularity of the gastric units appeared to be primarily the result of a marked increased rate of cell division and accumulation of immature cells. A high correlation was observed between the total number of cells per gastric unit and the number of cells that had incorporated BrdU in a 6-h period (r = 0.95). On average, 17% of cells in gastric units were labeled with BrdU within 6 h, of which >91% were of the small immature phenotype (Figs. 3–5). These cells were without the characteristics of differentiated gastric epithelia (Figs. 2A and 5A) and therefore appear to be similar, if not identical, to the “granule-free” stem cells (19). After 4 days, BrdU-labeled small immature cells were quite rare (Figs. 4 and 5), suggesting that most cells had died.

We examined cell death in the gastritic mucosae by detecting cells or cellular remnants with abundant fragmented DNA, a method that would preferentially detect apoptotic cells (Fig. 6) and by electron microscopy. Most apoptotic bodies were found in the neck-isthmus region of the units and were surrounded by immature epithelial cells, which strongly suggests that...
many of these cells were dying. Interestingly, Li et al. (26) also observed a high rate of apoptosis in immature gastric epithelial cells (preparietal cells) that had been blocked in their normal developmental pathway. Our data contrast with that reported by Nishio et al. (30) who claimed that they did not observe apoptotic cells in 12-wk-old mice with advanced gastritis. In our hands, apoptotic cells were readily observed in gastritic stomachs of 12-wk-old mice by both TUNEL staining and electron microscopy.

Cells that appear to be similar to mucus neck cells found in normal gastric units also accumulated in gastritic units but to a lesser extent than the small immature cells. These cells, termed mucus-rich cells, have abundant granules in their cytoplasm that often contain dark cores typical of mucous neck cells in transition to zymogenic cells (Figs. 1C, 2C, 2D, and 4F) (21). Because zymogenic cells are absent from the gastritic units, we suggest that mucus-rich cells accumulate because of a cessation of the normal developmental pathway that leads to zymogenic cells. However, mucus-rich cells were not identical to mucous neck cells of normal mucosa. They appeared to have a greater number of mucous granules, which had a different carbohydrate content as they stained with Alcian blue (which does not stain mucus neck cells from normal mucosae, not shown), but failed to bind the mucous neck cell-specific lectin Bandeiraea simplicifolia isolecitin B3 (not shown).

The number of parietal and zymogenic cells that arose over 4 or 7 days is generally lower in gastritic units compared with unaffected units (zymogenic cells were absent from gastritic stomachs) (Fig. 5, D and E) despite the large numbers of stem cells that could serve as precursors for these lineages. This strongly suggests a block in the developmental pathways that lead to end-stage cells. It is difficult to rule out the possibility that end-stage cells were very rapidly dying after genesis, although it should be noted that we did not see evidence for increased rates of parietal and zymogenic cell apoptotic death in our electron optical examination of gastritic mucosa.

Both humoral and T cell responses, directed to the gastric parietal cell, are observed in mice with autoimmune gastritis. Because parietal cell autoantibodies appear subsequent to mononuclear cell infiltration, it is assumed that they are not responsible for initiating the disease process (28). We have addressed here if the autoantibody titer can be used as a quantitative measure of disease that correlates with pathological indices. We found no relationship with antibody titer and gastric hypertrophy or apoptosis of epithelial cells. We therefore conclude that autoantibodies are unlikely to play a significant role in the ongoing disease process, again highlighting the importance of CD4+ T cells in the pathology of gastritis. Although the presence of autoantibodies appears to require prior inflammation of the mucosa, our results suggest that autoantibody levels are not a reflection of the degree of gastric pathology and are probably determined stochastically.

CD4+ T lymphocytes mediate most of their biological effects by the secretion of cytokines and growth factors either directly or via activation of macrophages. In an autoimmune disorder, the chronic exposure of a target organ to a complex cytokine mixture could have varying consequences depending on the organ. Parietal cells could be killed by toxic metabolites produced by activated phagocytes or by engagement of tumor necrosis factor receptors or CD95 (Fas). Alternatively, cytokines may alter the normal growth and differentiation of parenchymal cells leading to abnormal growth or deficits in cell populations.

Our data indicate that autoimmune gastritis is associated with a disruption of the normal gastric epithelial cell developmental pathways, which contributes to depletion of parietal and zymogenic cells and the accumulation of large numbers of proliferating epithelial stem cells and intermediate cell populations. Based on recent studies, we propose two models, which are not mutually exclusive, that could explain this phenotype. The first model suggests that cytokines produced by the infiltrating cells either directly or indirectly interrupt the normal mucosal cell development. This hypothesis is supported by recent experiments with genetically manipulated mice. Constitutive expression of transforming growth factor-α in the gastric mucosa of transgenic mice resulted in an accumulation of pit and immature cells and a depletion of the other differentiated cells of the gastric units (6, 34). Abnormally high levels of activins resulted in the arrest of development of all gastric lineages (25). Thus aberrant expression of growth/differentiation factors can also produce pathology similar to that seen in autoimmune gastritis without direct cytotoxic attack on any cell type.

The second model is also based on observations made in genetically manipulated mice. The gastric pathology of autoimmune gastritis is similar to that observed in transgenic systems in which parietal cells have been genetically ablated (10, 27). In these models, zymogenic cells were almost completely lost from the mucosa, despite no apparent direct targeting of this lineage, and there was an accumulation of precursor cell types. This led Li and colleagues (27) to propose that parietal cells provide some “instructive interaction” that promotes development of other lineages in the mucosa. Hence, the disturbance in development observed in gastritis could be a secondary event due to the depletion of parietal cells. Previous work (30) indicated that, in gastritic stomachs, parietal cells but not zymogenic or other cell types express CD95. This raises the possibility that CD4+ T lymphocytes may be able to induce apoptosis of parietal cells by engagement of CD95. Parietal cell depletion could then lead to the developmental disruption documented here and the subsequent depletion of zymogenic cells and the accumulation of precursor cells.

Here, we have described the cellular pathology of autoimmune gastritis and thus provided a mechanism for two hitherto unexplained aspects of gastric pathology, namely, hypertrophy and zymogenic cell depletion. This detailed knowledge will greatly assist in determin-
ing the molecules produced by the chronic inflammatory
infiltrate that are the underlying cause of this autoimmune disease. The mechanism outlined here may also be of relevance to other inflammatory diseases, such as inflammatory bowel diseases, in which alterations in parenchymal cell populations occur.

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