MÉNÉTRIER'S DISEASE

# Ménétrier's Disease Therapy: Rebooting Mucosal Signaling

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**Ménétrier's disease, a rare hyperproliferative disorder of the stomach, is associated with chronic abdominal pain, vomiting, weight loss, and edema, as well as an increased risk of gastric cancer. Therapy, other than surgical resection of the stomach, is limited to supportive measures and reflects the limited understanding of Ménétrier's disease pathogenesis. Data reported in this issue describe a promising targeted therapeutic approach and provide new insight into the causes of Ménétrier's disease.**

Ménétrier's disease is a rare disorder of the gastric mucosa—the mucous membrane layer of the stomach—typified by diffuse hyperproliferation, or hyperplasia, of the mucus-secreting foveolar epithelium and atrophy of glandular cells within the acid-secreting portions of the stomach (*1*, *2*). This hyperplasia leads to excess mucus secretion, cystically dilated gastric glands, decreased acid secretion, and gastric blood and protein loss. Although both pediatric and adult Ménétrier's disease present with abdominal pain, vomiting, weight loss, and peripheral edema due to hypoproteinemia, the clinical courses are markedly different. Pediatric disease, which is often associated with cytomegalovirus (CMV) infection, tends to be self-limited and regresses spontaneously without recurrence. Therapy is, therefore, primarily limited to supportive measures until disease abates. In contrast, adult disease, which most frequently occurs between the ages of 40 and 60, is chronic and progressive and confers an increased risk of gastric cancer. Acute treatment begins with supportive measures but frequently leads to gastrectomy, the removal of all or part of the stomach, as the only means to control the severe blood and protein loss. Although this symptom-based treatment approach is clearly suboptimal, it reflects limited understanding of the pathogenesis and, as a result, a lack of targeted therapies. In this issue of *Science Translational Medicine*, Fiske *et al.* describe a promising new therapy for this disease (*3*).

The search for pathogenic mechanisms of Ménétrier's disease has roots in basic studies of gastric growth factors. Two decades ago, work in the guinea pig, rat, and dog suggested that local transforming growth factor–α (TGF-α), one of seven mammalian ligands that activate the epidermal growth factor receptor (EGFR), was able to stimulate gastric epithelial repair and renewal while inhibiting acid secretion (*4*). Further studies in transgenic mice found that gastric TGF-α overexpression induced the development of histological and clinical features similar to those seen in Ménétrier's disease (*5*, *6*). Histological changes in the stomachs of TGF-α transgenic mice included foveolar hyperplasia as well as atrophy and cystic dilatation of gastric glands (*5*, *6*). These changes were associated with reduced basal and histamine-stimulated rates of acid production, as a result of the reduced mass of acid-secreting parietal cells, secondary to a TGF-α–induced diversion of epithelial cell differentiation toward the foveolar mucous cell lineage (*7*, *8*).

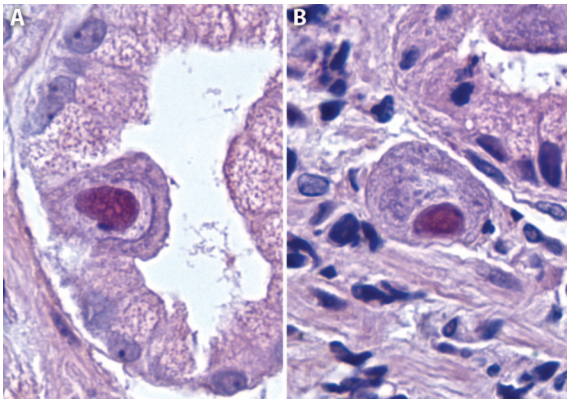


**Fig. 1. CMV infects gastric epithelial and stromal cells.** CMV-infected cells can be recognized by the presence of distinctive red intranuclear inclusions as well as cytoplasmic inclusions. Within the stomach, CMV infects foveolar (epithelial) cells (**A**) as well as stromal cells (**B**) and endothelial cells. CMV does infect stromal and endothelial cells in other parts of the gastrointestinal tract, but epithelial infection is common only in the stomach. This observation may, in part, explain the association of CMV infection with pediatric Ménétrier's disease.

The observations in mice prompted analyses of human tissues, which showed that the expression of both TGF-α and EGFR was increased in gastric mucosa from Ménétrier's disease patients (*9*). Thus, a combination of mechanistic studies in mice and correlative studies in human tissue cemented the hypothesis that TGF-α is central to Ménétrier's disease pathogenesis (*9*). On that basis, a single patient with Ménétrier's disease was treated with a monoclonal antibody raised against EGFR (anti-EGFR) (*10*). The U.S. Food and Drug Administration approved the compassionate use of this therapy because a coexisting condition, primary pulmonary hypertension, excluded gastrectomy as a treatment option for this patient. The results were impressive; vomiting fell from 70 episodes to 1 episode per week, serum albumin increased dramatically, and stool protein loss was reduced by more than 60% (*10*). Gastric biopsies documented that parietal cells, which were absent before therapy, were present after treatment. Moreover, a limited analysis of signal transduction events downstream of EGFR activation suggested that these were reduced by treatment. Despite these impressive clinical, histological, and biochemical effects of anti-EGFR treatment, gastric pH remained at 7.0 after therapy, as compared with pH ≤ 3 in a normal stomach. However, this elevated pH may have reflected the short 1-month course of treatment, which was limited by the patient's demise from unrelated complications. Thus, despite being a single case report, this study suggested the potential of anti-EGFR as a rational, mechanism-based, targeted therapy for Ménétrier's disease. This idea received further support from a study by the same group that reported successful treatment of Ménétrier's disease with anti-EGFR in two more patients with treatment durations of 4 months and 1 year, respectively (*11*). One of the patients in that study presented with hypoalbuminemia and peripheral edema that were severe enough to require total parenteral nutrition (nutrition given intravenously) and albumin infusions (*11*). In this patient, the electron-dense dye ruthenium red leaked abnormally across the tight junctions of the gastric glandular

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epithelium. Anti-EGFR treatment corrected this permeability defect, as demonstrated by the exclusion of ruthenium red from tight junctions. This change correlated with improvement of hypoalbuminemia to such an extent that albumin infusions were no longer required. This observation suggests that defective tight junction barrier function may be related to gastric protein loss in Ménétrier's disease, although the signaling pathways responsible have not been defined. Although the study did provide further evidence that anti-EGFR therapy might have broad utility in the treatment of Ménétrier's disease, it was not a controlled clinical trial with detailed quantitative analysis and, therefore, could not serve as a basis for use of this approach outside of an experimental setting.

Now, Fiske *et al.* report a study of nine Ménétrier's disease patients treated with anti-EGFR (*3*). As suggested by the previous three patients, the response rate was high and results were seen within 1 month in all but two patients. One of these failed to respond to two antibody infusions, and re-review of his biopsies identified a focus of gastric cancer. He was removed from the study along with a second patient who reconsidered trial enrollment and withdrew. The remaining seven patients all experienced significant improvement, with normal gastric acid secretion in six and either minimal or no residual foveolar hyperplasia in four. Remarkably, three of the patients continued to do well as much as 38 months after initiation of therapy. The remaining four underwent gastrectomy due to the risk of malignancy, as discussed below, or infusion reactions—complications related to treatment with antibodies—that limited ongoing therapy. However, even in the cases of the two patients with infusion reactions, the anti-EGFR treatment was beneficial because anemia and hypoproteinemia improved, making the patients far better operative candidates than at presentation.

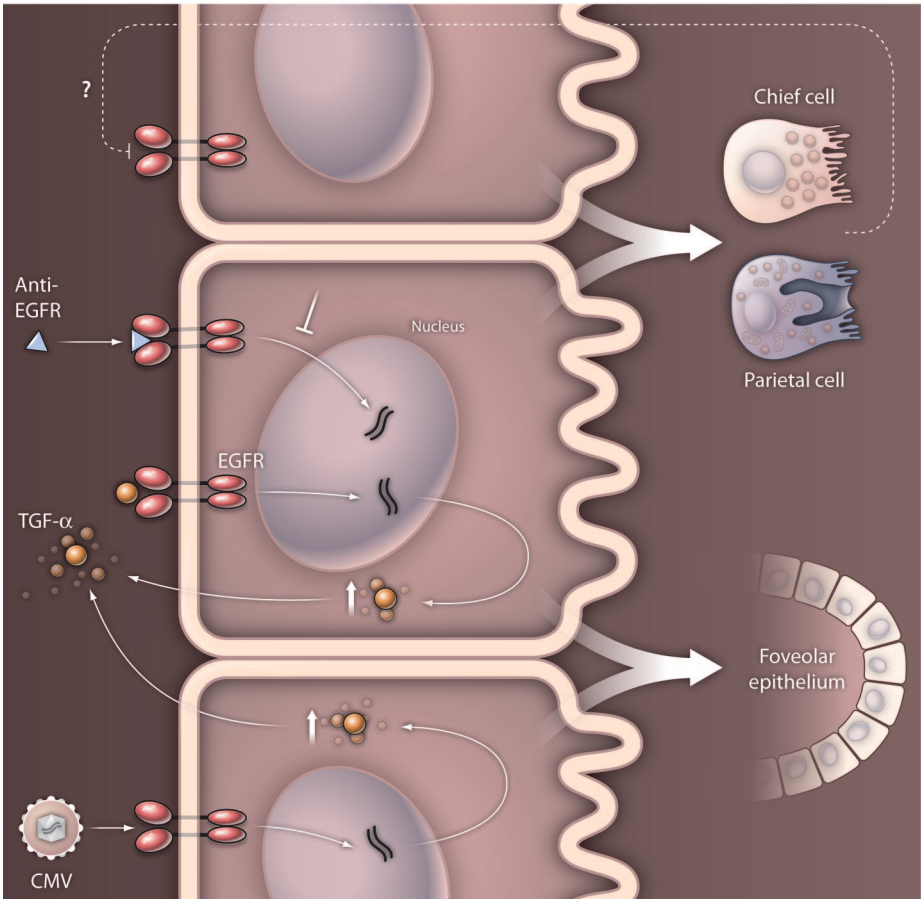


**Fig. 2. Potential mechanisms of TGF-α–driven Ménétrier's disease development in the stomach.** Increased TGF-α engagement of EGFR is central to Ménétrier's disease. This increased EGFR activation may augment local TGF-α production (a positive feedback loop), which drives excessive foveolar differentiation at the expense of chief cells (which release digestive enzymes) and parietal cells (which secrete acid) and causes the foveolar hyperplasia that is typical of Ménétrier's disease. In pediatric Ménétrier's disease, CMV-dependent EGFR activation may be the initial trigger for excessive TGF-α production. Viral clearance and the discontinuation of CMV-dependent EGFR activation may lead to spontaneous disease resolution, which is the norm in pediatric Ménétrier's disease. The initiating factor that causes increased TGF-α production has not been identified in adult Ménétrier's disease. However, once local TGF-α is elevated, it can drive a positive feedback loop whereby EGFR signaling causes excessive TGF-α production and further EGFR stimulation. Anti-EGFR treatment blocks TGF-α signaling through EGFR, which decreases local TGF-α production and allows the restoration of normal differentiation patterns with the emergence of chief and parietal cells. These may, in an unknown manner, reestablish homeostatic TGF-α–EGFR regulation and explain why some patients do well, without recurrent symptoms, after discontinuing anti-EGFR therapy.

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Considering the previously dismal prognosis for Ménétrier's disease, the data are exceptional in that they document the success of medical therapy with anti-EGFR for a relatively large number of patients with this rare disease. However, the increased risk of gastric cancer in Ménétrier's disease remains a concern that requires further investigation. The need for such studies is emphasized by one of the original seven patients who did well for 2 years with treatment and also for an additional year after discontinuation of anti-EGFR therapy. At that time, a 4-cm gastric lesion containing high-grade dysplasia was found during surveillance endoscopy, and she underwent total gastrectomy. Three other patients in the study also underwent gastrectomy, despite a successful medical response to anti-EGFR treatment, due to their anxiety about the risk of malignancy (one of these also had mild infusion reactions). Thus, although the results of the current study are of great importance for initial patient management and stabilization, gastrectomy may ultimately be necessary. Alternatively, a choice to continue without gastrectomy may require routine endoscopic surveillance, as is currently recommended for patients with long-standing Crohn's colitis or ulcerative colitis, inflammatory conditions associated with an increased risk of colon cancer (*12*). It will also be of interest to determine whether the risk of neoplasia is different in Ménétrier's disease patients who require long-term anti-EGFR therapy relative to patients who can be maintained without continued antibody infusion.

Given that two previous studies from this group had reported acute efficacy of anti-EGFR therapy in a total of three Ménétrier's disease patients (*10*, *11*), the confirmation of

this result in a larger group might not be surprising. However, it is remarkable that three of the seven patients continued essentially symptom-free up to 1 year after discontinuation of therapy. Although dysplasia prompted gastrectomy in one of these patients, the observation that anti-EGFR therapy could be discontinued without disease relapse suggests that the defect in Ménétrier's disease is one of regulatory disequilibrium and that it may be possible to "reboot" the signals that control gastric TGF-α production. To evaluate this hypothesis, it would be of interest to know whether TGF-α remains elevated in the gastric mucosa of Ménétrier's disease patients after prolonged treatment with anti-EGFR. Even more important would be an understanding of the trigger that initiates TGF-α overproduction. One subtle hint may come from the observation that four of the patients in this study had ulcerative colitis. Although patients with coexisting Ménétrier's disease and ulcerative colitis have been described (*13*, *14*), the data here suggest that the association may be more common than previously recognized. One may, therefore, speculate that increased TGF-α in colonic mucosa involved by ulcerative colitis (*15*) is related to, or even contributes to, the elevated gastric TGF-α that leads to Ménétrier's disease. Because EGF enemas are effective in distal ulcerative colitis (*16*), one might ask whether, conversely, EGFR blockade could trigger ulcerative colitis relapse. This did not occur in any of the patients with both Ménétrier's disease and ulcerative colitis. However, it is interesting to note that, of the three Ménétrier's disease patients who have done well without gastrectomy, the only patient who has required continued anti-EGFR therapy is the one with coexisting ulcerative colitis. Whether this observation is meaningful in a broader context may be a fertile topic for future study, as it might explain why three patients did well after discontinuing anti-EGFR therapy while a fourth required ongoing anti-EGFR treatment.

The events that initially lead to EGFR hyperstimulation and generate the characteristic morphology of Ménétrier's disease remain unknown. Comparison of pediatric and adult Ménétrier's disease may provide insight into this question. CMV infection is strongly associated with the disease in children. EGFR is a surface receptor for CMV (*17*). Moreover, EGFR tyrosine kinase activity is activated by CMV and required for virus entry (*17*). Why then is CMV infection associated with pediatric Ménétrier's disease but not hyperplastic epithelial lesions in other tissues? The explanation for this difference may be that CMV predominantly infects endothelial and stromal cells in most tissues, but also infects epithelial cells in the stomach (Fig. 1). This fact, coupled with the transient nature of Ménétrier's disease in children, suggests that CMV may be the driving force that initiates EGFR signaling in pediatric disease. This could potentially trigger a vicious cycle in which EGFR activation enhances the synthesis and release of TGF-α (*18*) and leads to further EGFR activation and TGF-α release (Fig. 2). Consistent with this hypothesis, increased TGF-α immunostaining within the gastric mucosa has been reported in pediatric Ménétrier's disease (*19*) and even in an adult case of CMV-related Ménétrier's-like disease (*20*). CMV clearance likely removes the EGFR stimulus and therefore results in reduced TGF-α production. Thus, CMV-dependent EGFR activation may explain the self-limited nature of CMV-associated Ménétrier's disease. Translating this concept to adults, it is possible that subclinical gastric injury triggers appropriate TGF-α release and activates downstream EGFR signaling. If the normal feedback loop that prevents this from becoming a vicious cycle of excessive amplification fails, disease develops. This model might also explain the ability of temporary anti-EGFR therapy to provide durable remission. Definition of this regulatory pathway is, therefore, relevant for understanding pathogenesis and improving therapy.

Overall, the study by Fiske *et al.* (*3*) holds great promise for the treatment of Ménétrier's disease. Although questions remain and more studies are needed, this work represents a major advance in the mechanistic understanding and treatment of a rare disease that causes significant morbidity.

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