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Shigeru Oshima, Mamoru Watanabe

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### Commentary

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# Genetic and environmental factors drive personalized medicine for Crohn's disease

Shigeru Oshima and Mamoru Watanabe

Department of Gastroenterology and Hepatology, Graduate School, Tokyo Medical and Dental University (TMDU), Tokyo, Japan.

The introduction of anti-TNF antibody therapy has changed the course of treatment for Crohn's disease. However, the fundamental mechanism for the onset of Crohn's disease is still unknown, and the treatment strategy for this disease remains suboptimal. The assessment of the disease phenotype based on key environmental factors and genetic background may indicate options for the personalized treatment of Crohn's disease. In this issue of the *JCI*, Liu et al. show that consumption of tobacco and the mutation of *ATG16L1*<sup>T300A</sup>, a prevalent Crohn's disease susceptibility allele, drive defects in cells at the bottom of the intestinal crypt, the Paneth cells. These factors may provide novel targets for personalized medicine.

## Making inroads toward personalized medicine for Crohn's disease

Crohn's disease is a chronic inflammatory disease of the intestinal tract that is associated with extraintestinal manifestations and the development of immune disorders (1, 2). Although all segments of the gastrointestinal tract may be affected, the most common site for the onset of Crohn's disease is the terminal ileum and colon. Crohn's disease is characterized by periods of clinical remission alternating with periods of recurrence. Complications (e.g., strictures, fistulae, or abscesses) develop in approximately half of patients, often requiring surgical intervention. Although the approval of the first anti-TNF therapy has revolutionized the treatment of Crohn's disease, several questions still remain unanswered. Current therapeutic strategies are focused on maintaining mucosal healing. The ultimate goal of this approach is to prevent the occurrence of complications and alter the natural history of Crohn's disease (3). As more treatment options for Crohn's disease become available, it is important to identify the patients most likely to respond to different therapies. The validation of

good biomarkers and ability to predict response to therapy are important factors in establishing personalized medicine.

## Autophagy-related protein 16-1 gene and Crohn's disease

Familial aggregation has been linked to Crohn's disease for more than 70 years. In recent years, GWAS identified approximately 200 susceptibility loci, including the *ATG16L1*, *NOD2*, *IRGM*, *IL-23R*, *HLA*, and *STAT3* (4, 5), loci that are involved in intestinal homeostasis, microbial defense, regulation of innate and adaptive immunity, autophagy, generation of reactive oxygen species, and endoplasmic reticulum stress. Familial studies support a genetic contribution to prognosis. However, the evidence showing an association between prognosis and susceptibility loci is currently limited (6). In 2007, research demonstrated an association between the Thr300Ala(T300A) polymorphism within the autophagy-related protein 16-1(*ATG16L1*) gene — one of the most well-analyzed genes — and Crohn's disease. *ATG16L1* is part of a complex that lipidates microtubule-associated protein 1A/1B-light chain 3 (LC3), promoting the formation and function of autophagosomes. *ATG16L1*<sup>T300A</sup>,

a prevalent Crohn's disease susceptibility allele, introduces a caspase-cleavage site that destabilizes the protein product and reduces autophagy in the presence of TNF- $\alpha$  (7, 8). Studies have demonstrated hypomorphic *ATG16L1* protein expression, reduced autophagy, and abnormalities in Paneth cells in mutant mice (9). Importantly, patients with Crohn's disease who are homozygous for the *ATG16L1* allele showed Paneth cell abnormalities similar to those observed in mice. Paneth cells are thought to be the primary site from which intestinal inflammation originates (10). An abnormal Paneth cell phenotype is associated with mucosal dysbiosis and an aggressive disease course (11, 12). Moreover, the Paneth cell phenotype may be a biologically and clinically relevant biomarker, able to stratify patients with Crohn's disease. However, the factors inducing the abnormality in Paneth cells are currently unknown. Currently, it is hypothesized that various environmental factors may be involved in this process.

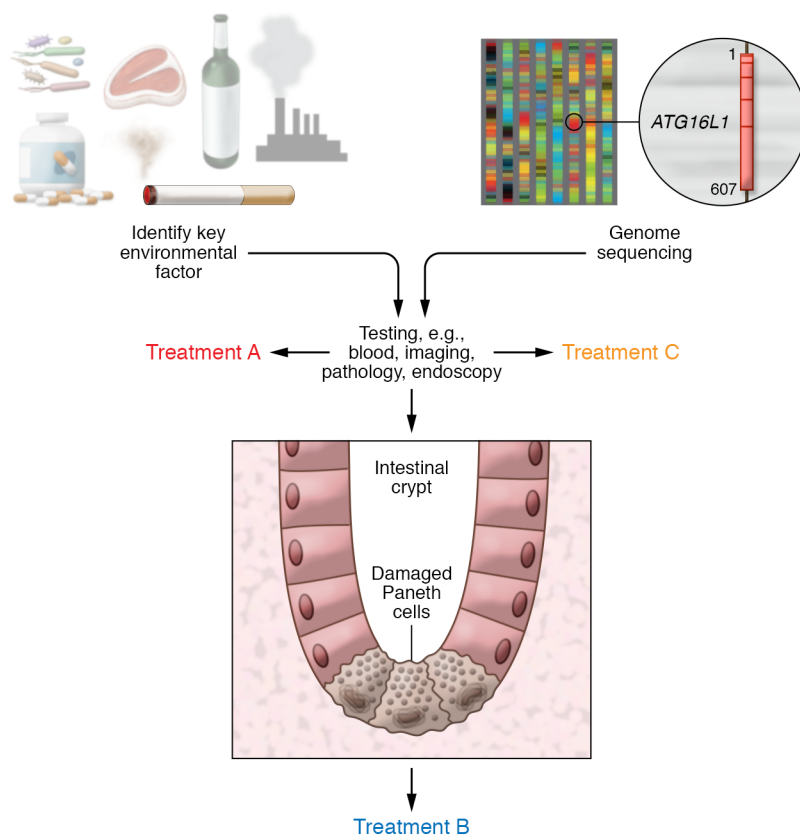
## Link between the risk of Crohn's disease and environmental factors

The key mechanism underlying the pathogenesis of Crohn's disease involves environmental factors triggering inflammation in genetically susceptible patients. There are several well-defined or putative environmental risk factors, including use of tobacco (13), dietary factors (14), and some kind of drug use (e.g., antibiotic and non-steroidal antiinflammatory drugs) (15, 16). Recent studies have suggested potential interactions between genetic and environmental factors. An increased n-6/n-3 polyunsaturated fatty acid (PUFA) ratio is associated with an increased risk of Crohn's disease in children who are carriers of specific variants of the monooxygenases *CYP4F3* and *FADS2*, genes involved in the regulation of PUFA metabolism (17). In established Crohn's disease, use of tobacco has been clinically associated with greater disease activity and early postop-

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**Figure 1. The approach of personalized medicine for Crohn's disease.** After screening of environmental factors and the genetic background, confirmation of appropriate biomarkers determines therapeutic strategies.

erative recurrence. Studies have demonstrated a significant link between the risk of Crohn's disease and factors such as tobacco smoking, genetic variants in the cytochrome CYP2A6/Egl nine homolog 2 (EGLN 2) locus, and glutathione transferase enzymes (GSTP1) (18).

### Targeting Paneth cells in Crohn's disease

In this issue, Liu et al. (19) show that the smoking status and Paneth cell phenotype may be prognosticators of recurrence in patients with Crohn's disease who received ileocolonic anastomosis and postoperative immunomodulatory and/or biologic prophylactic therapy. The combination of these factors further stratified patients into prognostically distinct subgroups. In addition, patients with Crohn's disease carrying the *ATG16L1*<sup>T300A</sup> genotype who were also smokers (T300A-smoking group) showed a significantly shorter time to recurrence after surgery. Recent studies have suggested that necroptosis modulates Paneth cell function (20, 21). How-

ever, smoking-induced Paneth cell defects in T300A mice were rescued only by inhibition of apoptosis, but not through inhibition of necroptosis. Liu et al. show that apoptosis was a central mechanism behind smoking-associated Paneth cell defects in patients with Crohn's disease and mice with the *ATG16L1*<sup>T300A</sup> genotype. Importantly, apoptosis and Paneth cell defects were regulated by PPAR $\gamma$  signaling, which may be a potential target for treatment.

Personalized medicine involves the determination of patients at high risk of disease progression and occurrence of complications. Moreover, it includes the characterization of patients who may respond preferentially to specific therapies (Figure 1). In addition to drug discovery based on personalized medicine, the comprehensive exploration of biomarkers is necessary for the optimization of treatment using currently available therapeutic agents. The development of personalized medicine for patients with Crohn's disease is not only possible, but is an attractive prospect. The identification of biomarkers able to predict

the efficacy of molecular-targeted drugs prior to their administration reduces time to remission and increases the efficacy of the drugs. In addition, this process may contribute greatly to the medical economy. Recent studies have been aimed at identifying factors predictive of drug response (corresponding to a specific signaling pathway) for the improved management of patients with Crohn's disease. Furthermore, imaging techniques applicable in personalized medicine have advanced considerably in recent years. Ultrasonography, computed tomography, and magnetic resonance enterography (22, 23) are widely used for the evaluation of inflammation in the gut. Prognostic and therapeutic subgroups in Crohn's disease are determined based on clinical characteristics and genetic-environmental factor interactions for the selection of the most appropriate treatment. Liu et al. investigated the link between a genetic susceptibility allele (*ATG16L1*<sup>T300A</sup>) and an environmental factor (smoking) and the development of a morphological change (Paneth cell defects) that ultimately results in a distinct phenotype. The investigation of environmental and genetic factors, coupled with the evaluation of morphological changes through endoscopy and/or pathological biopsy, permits the use of personalized medicine for the treatment of Crohn's disease.

### Concluding remarks

In conclusion, Crohn's disease is considered the result of interplay between genetic susceptibility and environmental factors. Based on the relationship between the mutation on the susceptibility gene and the smoking status of patients, the Paneth cell phenotype may define the therapeutic effect. In the future, the selection of therapeutic strategies may be determined through the combination of various environmental factors and genetic mutations. The use of personalized medicine based on this approach may provide more effective and safer therapies for Crohn's disease.

Address correspondence to: Mamoru Watanabe, Department of Gastroenterology and Hepatology, Graduate School, Tokyo Medical and Dental University (TMDU), 1-5-45, Yushima, Bunkyo-ku, Tokyo 113-8519, Japan. Phone: 81.3.5803.5877; Email: mamoru.gast@tmd.ac.jp.

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