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COELIAC DISEASE

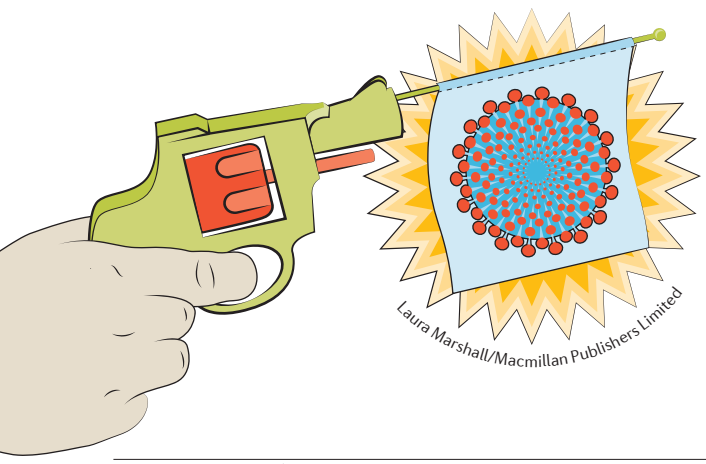
A viral trigger of food insensitivity and coeliac disease?

> "T1L … infection promoted a pro-inflammatory phenotype … in response to dietary antigens…"

A new study published in *Science* provides evidence that reovirus infection can disrupt intestinal immunohomeostasis and instigate a harmful immune reaction to dietary antigens (such as gluten) in mouse models. The findings point to a possible role for reovirus infection as a trigger contributing to the development of coeliac disease.

Previous epidemiological evidence has indicated a role for environmental factors in the pathogenesis of coeliac disease, with studies showing an association with viruses from the *Reoviridae* family and initiation of disease. However, experimental data supporting this link were lacking.

The researchers first established a viral infection model in mice using genetically engineered *Orthoreovirus* strains (herein, named reovirus), which are double-stranded RNA viruses. Two human reovirus isolates — type 1 Lang (T1L) and type 3 Dearing (T3D) — that differed in terms of replication biology, cellular tropism, pathogenesis, innate immune response activation and intestinal effects were examined; T1L is capable of intestinal infection and also perturbs intestinal immune homeostasis, whereas T3D cannot infect the intestine. By engineering a T3D reassortant virus (T3D-RV) that can infect the gut, the investigators established infection models with two reoviruses with potentially different immunopathological effects. Both T1L and T3D-RV infected the intestine, replicated, induced type 1 T helper (T_H1) immune responses in Peyer's patches and were ultimately cleared without causing intestinal damage.



T1L, but not T3D-RV, infection promoted a pro-inflammatory phenotype in mesenteric lymph node dendritic cells (DCs) in response to dietary antigens (ovalbumin, a model antigen). Crucially, the tolerogenic phenotype was altered: differentiation of $CD4^+$ T cells into peripheral regulatory T (T_{reg}) cells was blocked and a T_H1 immune response to dietary antigens was promoted instead. This process was dependent on interferon regulatory factor 1 (IRF1).

Crucially, T1L infection induced the same switch to T_H1 immunity in response to gluten in transgenic mice expressing HLA-DQ8 (a key determinant of coeliac disease). Transglutaminase 2 activation, which has been linked to coeliac disease pathogenesis, was also observed after T1L infection. Moreover, patients with coeliac disease tended to have higher anti-reovirus antibody titres ($P = 0.06$) than those without the condition. Indeed, a subset of patients with coeliac disease on a gluten-free diet with high anti-reovirus antibody titres had markedly increased *IRF1* levels in small intestinal biopsy samples.

"We provide evidence that reovirus can trigger loss of oral tolerance and invoke inflammatory immune responses to gluten," explains author Bana Jabri. "A virus that is apparently innocuous … can alter in the background, in absence of overt disease, the way the intestinal immune system sees a dietary antigen," she adds.

"The most significant finding … is the elucidation of a mechanism for how a virus can shape the immune response to oral antigens to become harmful," notes Ludvig Sollid, University of Oslo, who was not involved in the research. "It has been suspected that environmental factors other than gluten, in particular infectious agents, can affect the risk of contracting coeliac disease; this paper presents in an elegant way a mechanism for how this can be". However, Sollid emphasizes that more work is needed to verify that the findings observed in mice can be translated to a clinical scenario and that reovirus is truly involved in the aetiology of coeliac disease in humans.

The researchers plan further work to define the specific host–viral interactions required for virus-induced loss of oral tolerance. They also hope to investigate whether other viruses could have similar immunopathological properties.

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ORIGINAL ARTICLE Bouziat, R. *et al.* Reovirus infection triggers inflammatory responses to dietary antigens. *Science* **356**, 44–50 (2017)
FURTHER READING Verdu, E. F. *et al.* Novel players in coeliac disease pathogenesis: role of the gut microbiota. *Nat. Rev. Gastroenterol. Hepatol.* **12**, 497–506 (2015)