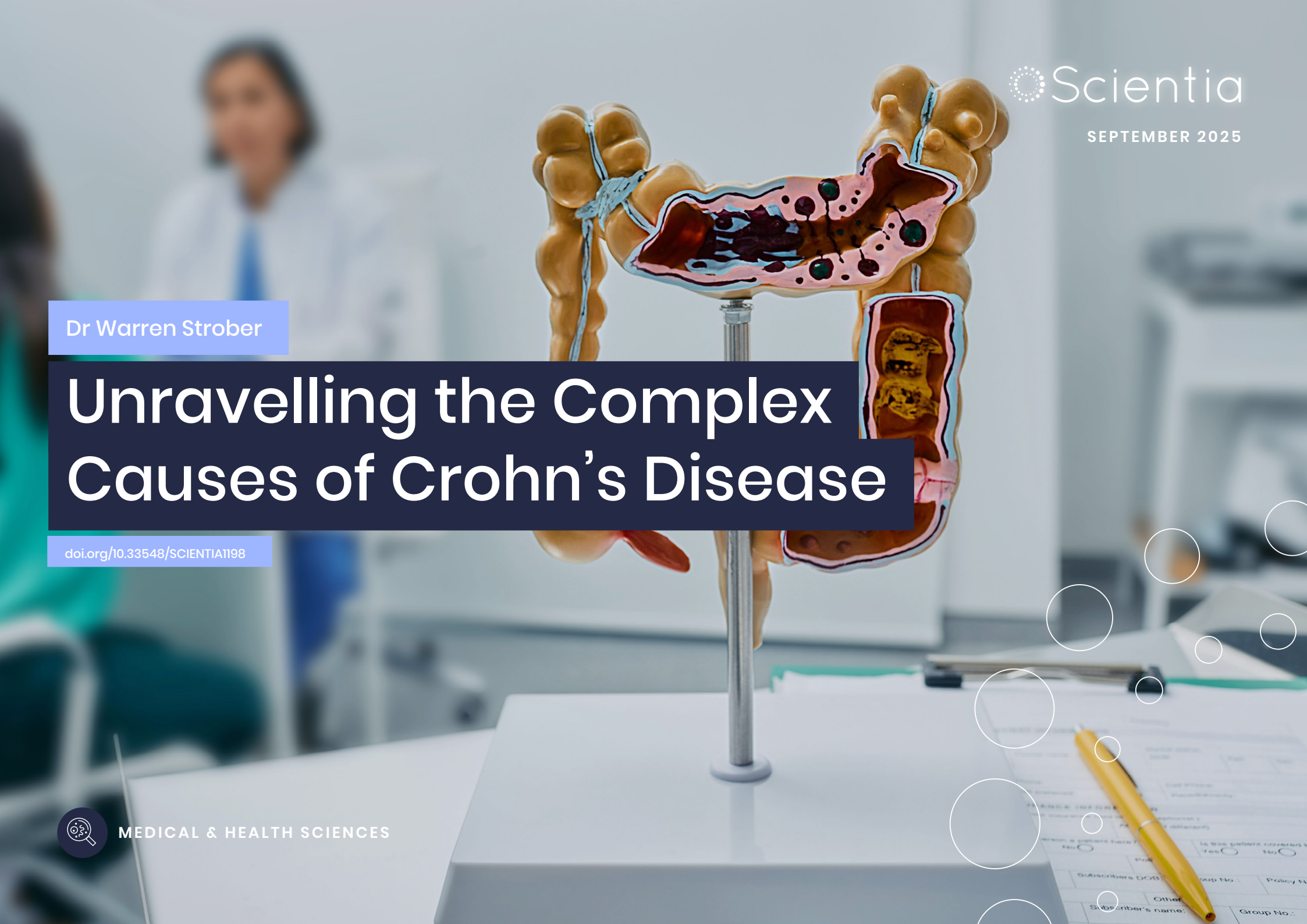

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Dr Warren Strober

Unravelling the Complex Causes of Crohn's Disease

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MEDICAL & HEALTH SCIENCES

Crohn's Disease (CD) is a type of inflammatory bowel disease that is due to abnormalities of the gastrointestinal (GI) immune system that result in immunologic hyper-responsiveness to normal GI constituents. It causes severe and recurrent GI symptoms that can be managed but not cured, except in rare cases where histocompatible bone marrow transplantation can be applied to replace the errant immune system.

Dr Warren Strober from the National Institutes of Health (NIH) in the USA, specialises in the study of the GI immune system, both when it operates normally to maintain homeostasis, as well as when it operates abnormally causing health issues such as CD.

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A Closer Look at Crohn's Disease

The myriad unpleasant GI symptoms caused by CD, including but not limited to diarrhoea, stomach cramps, fatigue, weight loss, and rectal bleeding, are usually treated by medications such as steroids, immunosuppressants, and anti-cytokine biologics that act in various ways to calm the inflamed gut. In rare cases, usually in children, CD is caused by a discrete genetic defect (a mutation) that shifts the GI immune system into overdrive and chronic inflammation. However, in most cases, CD is caused by a complex and usually undefined mixure of genetic and environmental factors that together drive the GI immune system into a similar hyperactive state.

One focus of Dr Strober's work is the investigation of the genes controlling immune responses and how these genes cause the kind of inflammation seen in CD. In many cases, the genes of interest were first identified in Genome-Wide Association Studies (GWAS) —a methodology that identifies small gene variations (called polymorphisms) more frequently occurring in individuals with a particular disease. Thus, these polymorphisms identify genes causing disease.

Among the several hundred CD-associated polymorphisms that have been found so far, those with the strongest association with CD are in a gene encoding NOD2 —a protein present in intestinal cells that triggers immune responses to components of the cell wall of bacteria present in the GI tract. Dr Strober and his associates discovered that cells bearing abnormal NOD2 protein as a result of these polymorphisms have an impairment in their ability to down-regulate the innate immune responses elicited by organisms in the normal gut microflora. This discovery provided a molecular explanation of how CD can be caused by an overly active intestinal immune response.

The ATG16L1 Gene

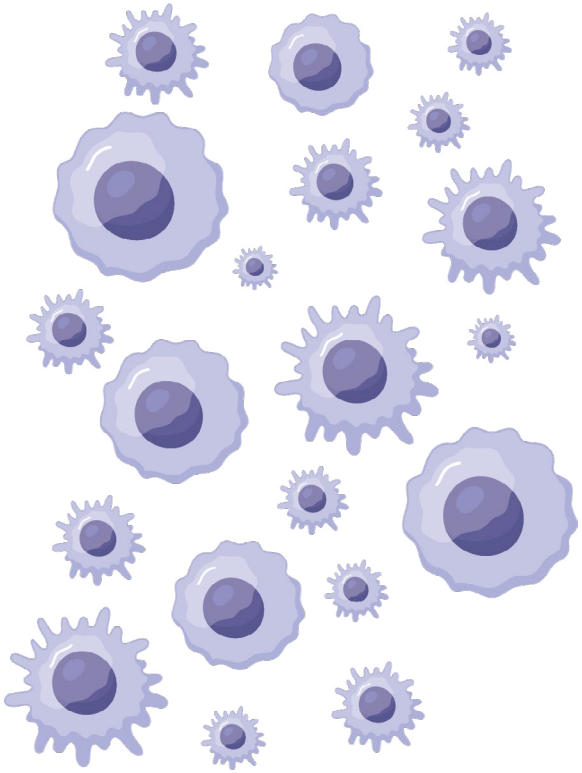
Recently, Dr Strober explored the immunologic consequences of a polymorphism affecting the ATG16L1 gene. The protein encoded by this gene is essential to a cellular function called autophagy, which had also been identified by GWAS to be more frequently disrupted in patients with Crohn's disease.

For this study, Dr Strober collaborated with Dr Fuping Zhang, a long-standing colleague who heads the group of scientists at the CAS Key Laboratory of Pathologic Microbiology and Immunology, in Beijing, China, who performed the majority of the work.

Autophagy is a process that facilitates the disposal of unwanted proteins within cells. The CD-associated polymorphism in the ATG16L1 gene (designated ATG16L1^{T300A}) is characterized by a change in a single nucleotide; this results in a form of ATG16L1 that is susceptible to cleavage and loss of function when exposed to cleaving proteins called caspases, which become activated during cell stimulation and inflammation.

Dr Strober says that, even though the ATG16L1 gene has been well-studied, the mechanisms by which the ATG16L1^{T300A} polymorphism serves as a contributor to CD is not yet fully understood. One possibility is based on the finding that autophagy is necessary for cellular clearance of damaging protein clusters that arise in gut epithelial cells subject to excessive stress caused by loss-of-function mutations or polymorphisms in genes encoding stress-regulating proteins; as a result, epithelial cells with the ATG16L1^{T300A} polymorphism are more subject to cell death. This is of particular relevance to specialised epithelial cells of the small intestine known as Paneth cells, cells that ordinarily secrete proteins that regulate bacterial growth and prevent inflammation; if these cells have the ATG16L1^{T300A} polymorphism and thus undergo cell death, the way is open to intestinal inflammation and CD. A major problem with this possibility is that inactivating mutations or polymorphisms in stress-related genes are rare; thus, they cannot yet explain the vast majority of cases of CD in which the ATG16L1^{T300A} polymorphism may have a contributory role.

A second possibility as to the origin of the increased CD susceptibility in people carrying the ATG16L1T300A polymorphism is that it causes an increase in the production of pro-inflammatory cytokines; these signaling proteins are used by cells to communicate and regulate the inflammatory process.



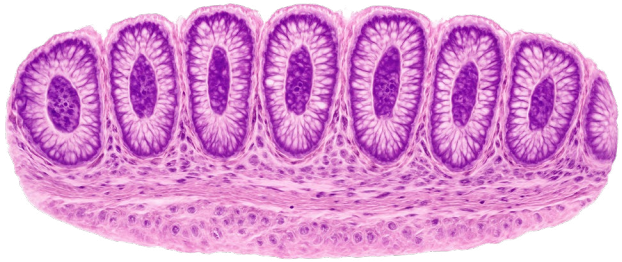
Investigating the Polymorphism

Dr Strober and Dr Zhang reasoned that the ATG16L1^{T300A} polymorphism causing CD might be related to the the effect of autophagy on the function of particular cell receptors called toll-like receptors (TLR) and NOD-like receptors (NLR). When stimulated by their respective ligands, these receptors signal cells to activate nuclear factor kappa B (NF-ϰB), a protein that plays an essential role in the synthesis (transcription) of immunologic pro-infammatory cytokine responses.

To explore this possibility they studied human macrophages (a type of immune cell in the blood and tisues that expresses the ATG16L1 gene) isolated from individuals with and without the ATG16L1^{T300A} polymorphism. In addition, they studied normal and "knock-in" mouse macrophages—cells in which a normal ATG16L1 gene had been replaced by an ATG16L1^{T300A} gene. They found that, when appropriately stimulated by TLR or NLR ligands, cells expressing the CD-associated ATG16L1^{T300A} polymorphism exhibited enhanced pro-inflammatory responses compared to cells expressing normal ATG16L1 because of increased activation of NF-ϰB. These findings established that autophagy was acting as a rheostat for NF-ϰB activation and that impaired autophagy (such as that due to the CD-associated ATG16L1 polymorphism) is accompanied by increased NF-ϰB activation.

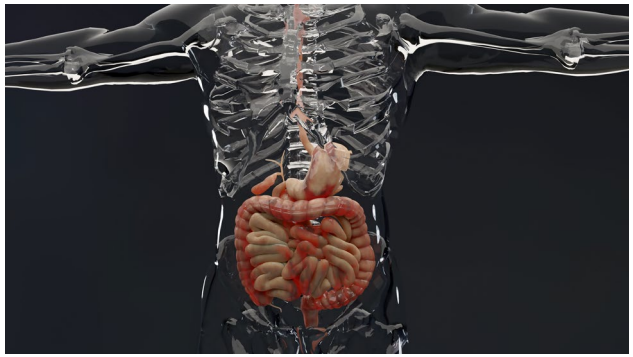
Strong Explanatory Evidence

In studies examining the molecular mechanisms undergirding these findings, Drs Strober and Zhang found that the ATG16L1^{T300A} polymorphism and its accompanying autophagy clearance defect led to accumulation of a ubiquitinating molecule called SQSTM1/p62 that, in turn, caused enhanced ubiquitination of essential NF-ϰB-activating molecules. Ubiquitination is a process during which a small protein called ubiquitin is added on to a target protein and thus facilitates its interactions with other proteins. The SQSTM1/p62 accumulation or possible accumulation of other ubiquitinating molecules therefore emerged as a likely cause of increased NF-ϰB-activation. Since removal of SQSTM1/p62 from cells normalized NF-ϰB-activaton, this proved to be the case.



The Key to Understanding Crohn's Disease

Along with the team in Beijing, Drs Strober and Zhang have obtained strong evidence showing how and why a disruption of autophagy due to the ATG16L1^{T300A} polymorphism leads to enhanced TLR- or NLR-mediated signalling and NF-ϰB-mediated inflammatory responses. They thereby established that this polymorphism is a risk-factor or cause of CD, at least in part, because it causes increased NF-ϰB-driven inflammation. These studies thus provide a further molecular explanation of how CD may be due to immune over-drive. Interestingly, since they also found that the ATG16L1^{T300A} polymorphism causes increased inflammatory responses of cells from individuals bearing this polymorphism who do not have CD, it is possible that, while functioning as a risk factor for CD, this polymorphism also serves as a factor that protects normal individuals from infection.



MEET THE RESEARCHER

Dr Warren Strober
National Institute of Allergy and Infectious Diseases, National Institutes of Health, Maryland, MD, USA

Dr Warren Strober obtained his MD from the University of Rochester in 1962 and completed his internship and residency at the Strong Memorial Hospital, New York. He has occupied various scientific and administrative positions at the National Institutes of Health (NIH) and is currently Chief of the Mucosal Immunity Section at the National Institute of Allergy and Infectious Diseases. Outside of NIH he has served as Chair of the American Board of Allergy and Immunology, President of the Mucosal Immunity Society and Chair of the Advisory Board for the Harvard Digestive Diseases Center. He has held numerous editorships, including those at the *Journal of Immunology*, the *Journal of Clinical Investigation* and *Mucosal Immunity*. Throughout his well-published career, Dr Strober has received multiple honours and awards, including the William Beaumont Prize from the American Gastroenterological Association, the Lifetime Achievement Award from the Society of Mucosal Immunology and Ismar Boas Medal of the German Society of Digestive Diseases. His areas of research interest are mucosal immunity, immunological abnormalities of the gastrointestinal system and immunological deficiency states.

CONTACT

wstrober@niaid.nih.gov

FURTHER READING

P Gao, H Liu, H Huang, *et al*., The Crohn Disease-associated ATG16L1T300A polymorphism regulates inflammatory responses by modulating TLR- and NLR-mediated signaling, *Autophagy*, 2022, 18(11), 2561–2575, DOI: https://doi.org/10.1080/15548627.2022.2039991