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Commentary

When Adherent-invasive *E. coli* plays with host glycosylation: Does it open new perspectives for therapeutic strategies in Crohn's disease?

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Inflammatory Bowel Diseases (IBD), including Ulcerative Colitis (UC) and Crohn's disease (CD) are worldwide spread diseases with higher incidences in western countries when compared to in-development countries. However, newly industrialised countries show an increase in the incidence of IBD [1]. Genetic factors, involving polymorphisms in more than 200 loci, including genes involved in the control of intra-cellular bacteria (autophagy genes *Nod2* and *Atg16l1*) and in glycosylation pathways of IgG [2], environmental factors, such as the western lifestyle, high-fat high-sugar low fibre diet and microbial factors have all been associated to an increased risk to develop CD. This multifactorial etiology of CD renders it difficult to identify a common therapeutic target for all the patients. In addition, the majority of current medications target the consequences and not the origin of the molecular deregulation leading to inflammation. In this article of *EBioMedicine* [3], the authors highlighted other mechanisms that could contribute to inflammation, such as modulation of glycosylation by *E. coli* pathobionts.

Glycobiology, which consists in the study of functional roles of sugar in the cell, has emerged as potentially interesting to better understand the etiology of CD and to identify new therapeutic targets. Glycans (sugars) are involved in many physiological pathways such as cell adhesion, protein folding, protein location, protein stability and in signal transduction, especially in inflammatory pathways [4]. In addition, interactions between bacterial pathogens and their hosts are highly specific binding events involving host or pathogen carbohydrate structures (glycans). Bacterial pathogens can also enzymatically alter host glycans to reveal binding targets, degrade the host cell glycans or alter the function of host glycoproteins [5]. Thus, by influencing gut glycosylation, the microbiota can further influence protection against pathogens and/or pathobionts. O-GlcNAcylation is one type of post-translational modification in which the O-GlcNAc transferase transfers GlcNAc from UDP-GlcNAc to selected serine and threonine residues on proteins.

In this article of *EBioMedicine*, Qian-Hui Sun and colleagues show that CD patients harbour a higher level of O-GlcNac in intestinal tissues in active phase of the disease when compared to patients with inactive disease. Among the various micro-organisms suspected of playing a role in the pathophysiology of IBD, a growing evidence indicates that Adherent-Invasive *E. coli* (AIEC) are involved in the pathogenesis of IBD, particularly in CD. Thus, the authors decided to investigate whether AIEC pathobionts could be involved in the up-regulation of O-GlcNac as they observed the same phenotype in mice infected by these specific bacteria. They found that AIEC infection strikingly increases the level of UDP-GlcNAc, a donor glucosamine for glycosylation, which was also associated to an increase in O-GlcNac in intestinal epithelial cells in mice and in human cell lines infected with the AIEC reference strain LF82. The authors also describe the consequences of AIEC infection on NF-kB activation and conclude that the infection mediated- O-GlcNAc of p65 facilitates its nuclear translocation and the trans-activation of NF-kB target inflammatory genes. It is likely that other inflammatory pathways are also modulated during the course of infection by AIEC bacteria, in a glycosylation-dependent manner. As an example, the intra-cellular innate immune receptor NOD2, for which specific polymorphisms have been associated to an increased risk to develop CD, is post-translationally modified by GlcNAc which increases the half-life of the protein and increase its ability to activate the NF-kB signaling pathway [6]. Now, it would be important to determine whether AIEC infection induces modifications in the glycosylation of NOD2 protein, and if the effects are the same on a WT or mutant form (harbouring one of the three CD-associated polymorphisms) of NOD2 protein. Based on the previously described roles of CEACAM6 and CHI3L1 molecules in the adhesion of AIEC pathobiont to epithelial cells, it would also be interesting to determine whether AIEC bacterial infection modifies and/or increases the glycosylation pattern of these molecules to favour their own interaction with the host cell, which could direct future studies on glycosylation to prevent AIEC colonisation. Indeed, AIEC pathobionts interact with [1] the abnormally over-expressed highly N-glycosylated CEACAM6 in CD patients, which could confer its ability to be bound by specific bacteria such as the AIEC pathobiont using its variant type-1 pili, and the [2] N-glycosylated asparagine in chitinase 3-like-1 through the chitin-binding domain of ChiA [7–9].

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One interesting therapeutic strategy for gastroenterologists to better manage CD patients could be to limit AIEC ileal colonisation, which could temper the inflammatory response. Another interesting data presented in this paper concerns the effects of DON, an agent that blocks the production of UDP-GlcNAc and inhibits O-GlcNAc, on autophagy pathway. The authors show that DON treatment, leading to depletion of O-GlcNAc in intestinal epithelial cells, leads to an over-activation of autophagy which in response to infection, and as a consequence, limits the number of intra-cellular bacteria. Autophagy deficiency has been clearly associated to CD and more particularly to a better ability of AIEC bacteria to replicate within intestinal epithelial cells and macrophages [10]. Over-activating autophagy in CD patients could represent a promising therapy to limit the growth of the AIEC bacteria. However further investigation are necessary to evaluate the beneficial/risk ratio of such a chemical treatment as DON molecule could have dramatic effects on the glycosylation of host cells impairing their function and altering intestinal homeostasis.

Finally, the authors nicely validated the pro-inflammatory effects of high level of O-GlcNac in a mouse model of infection with the pathobiont AIEC LF82 strain, and confirmed *in vivo* the anti-inflammatory effect of the O-glycosylation inhibitor DON. The data presented in this paper support the fact that AIEC infection increases the intra-cellular concentration of UDP-GlcNAc, which serves as a glucosamine donor for O-GlcNAc of intestinal proteins, leading to an inappropriate inflammatory response and defects in autophagy activation. Indirectly, AIEC bacteria are able to manipulate host glycosylation pathways to favour their encroachment in ileal mucosa and to induce an uncontrolled inflammatory response of the host cell. This study is therefore very promising, but it is now important to validate in a cohort of CD patients that a high level of O-GlcNac is correlated with a better ability of *E. coli* pathobiont to colonise the mucosa of the same patients, and if yes, it will be important to determine whether pharmacological treatment using DON or an equivalent shows a beneficial effect on intestinal inflammation in patients colonised by AIEC bacteria. This work opens the field to new therapeutic strategies, targeting glycosylation pathways and their enzymes, for a better management of CD patients harbouring AIEC bacteria.

Declaration of Competing Interest

The authors declare no conflict of interest.

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Authors' contribution

Jérémy Denizot and Nicolas Barnich performed the literature search and wrote the commentary.

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