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REGULAR ARTICLE

Gliadin is an uncatalogued Toll-like receptor ligand

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Abstract Coeliac disease is a chronic intestinal inflammatory condition, which is caused by an inappropriate immune response to components of wheat family cereals in a genetically susceptible host. Gliadins are the major pathogenic constituent of wheat; their toxicity and immunogenicity depend on their amino acid sequence. They are known to initiate the innate and the adaptive immune response. Nevertheless, it is not yet known how they are recognised by the intestinal epithelium and immune cells. Toll-like receptors (TLRs) are the best-studied group of pattern recognition receptors, which play a critical role in the initiation of innate immunity through the recognition of pathogen- and damage-associated molecular patterns. Exogenous food-derived proteins are not yet recognised as TLR ligands. Gliadin can activate TLR signalling pathway *in vitro*. The existing evidence is suggestive of the direct contribution of gliadin and/or other wheat components to activating TLR signalling. However, the data available so far are controversial and are mainly focussed on TLR 2 and TLR4. It is hypothesised that gliadin is a direct ligand for one of the TLRs. If indeed gliadin is proven to be a direct ligand of TLRs, our understanding of the pathogenesis of gastrointestinal diseases, such as colorectal cancer, will also be greatly influenced. In order to fully appreciate the role of gliadin as a direct TLR ligand, it should be proven to interact physically with and bind to one or more of the TLR molecules. Furthermore, it should be documented that TLR pathway activation is the downstream effect of gliadin/TLR binding.

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Introduction

Coeliac disease (CD) is a chronic intestinal inflammatory condition which is caused by an inappropriate immune response to proline and glutamine-rich proteins of wheat family cereals in a genetically susceptible host. It predominantly affects the proximal segment of the small intestine and results in disruption of the regular epithelial dynamic. The main histological

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presentation of the disease is atrophy of the villi and thus, reduced villous-to-crypt length ratio [1]. Gluten has been identified as the main toxic component of wheat family cereals and, as such, has been compared to pathogens in terms of eliciting an immune reaction [2]. Gliadins are a diverse group of proteins whose toxicity and immunogenicity are highly dependent on their amino acid sequence. Their contribution to the immune response has been studied extensively. However, their recognition by the intestinal epithelium has not yet been addressed [3].

Toll-like receptors

Toll-like receptors (TLRs) are the best-studied group of pattern recognition receptors (PRRs). TLRs play a critical role in the initiation of innate immunity through the recognition of pathogen- and damage-associated molecular patterns (PAMPs and DAMPs, respectively). To date, 10 human and 13 mouse TLRs have been identified. TLR1, TLR2, TLR4, TLR5 and TLR6 reside on the plasma membrane whereas TLR3, TLR7, TLR8 and TLR9 are localised to the endolysosomal compartment. Engagement of TLRs by their ligands results in homo- or heterodimerisation of TLRs; as a consequence, adaptor proteins, including myeloid differentiation primary response protein 88 (MyD88) and TIRAP inducing interferon β (TRIF), are recruited. All TLRs, except TLR3, signal *via* the MyD88-dependent pathway ultimately leading to activation and nuclear translocation of the transcription factors nuclear factor (NF)-κB, activating protein-1 (AP-1), or both. TLR3 function is exclusively mediated *via* a TRIF-dependent pathway. TLR4 can signal *via* both MyD88- and TRIF-dependent mechanisms. TRIF-dependent TLR signalling results in activation of interferon-regulatory factor 3 (IRF3) and NF-κB in a MyD88-independent manner. TLR pathway activity culminates in the expression of pro-inflammatory cytokines, type I interferon (IFN) and chemokines [4].

Thus far, the TLR ligands are classified as PAMPS, conserved structural motifs of bacteria, fungi and viruses; or DAMPs, endogenous proteins which are released upon tissue injury. However, other classes of molecules are being identified which can activate the TLR signalling pathway including but not limited to morphine [5,6], glucuronic acid and the ethanol metabolite ethyl-glucuronide [7], green tea polyphenol epigallocatechin-3-gallate [8], phenethyl isothiocyanate [9] and parthenolide [10]. It is highly plausible that the whole repertoire of TLR ligands has not been discovered yet.

TLR signalling in CD

The contribution of TLR signalling to CD is definitely far from being understood. Endogenous damage-associated proteins are known to initiate an immune response *via* activating TLR signalling. Hence, it is not surprising to postulate a similar mechanism of action for gluten in the pathogenesis of CD. In fact, in an analogy to intestinal microbiota, normal intestinal epithelium is hypo-responsive to food ingredients including gliadins, the best-studied constituents of gluten. However, the intestinal tolerance to gliadin is lost in CD [11]. In the first-generation genome-wide association study (GWAS) of CD, PRRs are not identified to be significantly associated with the disease [12–14]. However, in the second-generation GWAS in 4533 cases and 10,750 controls, TLR7 and TLR8 loci were found to have a suggestive (less than significant yet important) association to the disease; both loci showed a positive correlation with the gene expression levels [15]. TLR7 and TLR8 are among the nucleotide-sensing TLRs which detect single-stranded RNA. It has been shown that coeliac patients' sera contain antibodies against a peptide which was highly similar to a viral component [16]. Furthermore, it has been previously suggested that gliadin has sequence homology to a gastrointestinal adenovirus [17,18]. However, the contribution of TLR7 and TLR8 to the pathogenesis of CD is not yet understood.

If indeed TLR signalling contributes to the pathogenesis of CD, it has been hypothesised that the gene expression pattern as well as genetic variants might give a clue as to the underlying mechanism. TLR 3, 4 and 7 gene expressions were assessed in duodenal biopsies in adult and paediatric CD. The expression levels were not different between affected children and adults. However, TLR4 gene expression was found to be significantly increased in CD patients (both adult and children) compared to controls. In the immunohistochemistry analysis of TLRs, TLR3, 4 and 7 were present in 37.8%, 85.5% and 9.52% of cases, respectively. TLR4 staining was positive in both epithelial and mononuclear cells. There was no significant association between TLR4 expression and clinical features of the disease [19]. In another report, TLR3, 4 and 5 gene expressions were not different in small intestinal biopsy of controls, untreated coeliac and treated coeliac patients. However, TLR9 was found to be increased in coeliac patients compared to controls, whereas TLR2 was decreased in coeliac patients compared to controls [20]. In the next study, TLR2, TLR3 and TLR4 gene expression and protein levels were measured in duodenal biopsies of coeliac children (treated and untreated) and healthy controls. In contrast to the previous report, TLR2, TLR3 and TLR4 gene expression and protein levels were increased in coeliac patients compared to controls. The TLR2 level was also different in untreated patients versus patients on a gluten-free diet (GFD) [21]. TLR 2 and TLR4 gene expressions were also increased in dendritic cells (DCs) and monocytes in CD in children [22]. A few reports also exist on genetic variation of TLRs in CD. TLR 2 and TLR4 copy number variation was assessed in CD patients; no copy number variation was detected [23]. No significant association between TLR4 Ala896Gly, Asp299Gly and Thr399Ile single-nucleotide polymorphisms (SNPs) was detected in CD patients versus controls [24,25].

The hypotheses/ideas

TLRs along with other members of PRRs are responsible for maintaining a hypo-responsive state to the luminal content in the gastrointestinal tract. Intestinal luminal content is composed of the resident bacteria and the food ingredients and metabolites. Exogenous food-derived proteins are not yet recognised as TLR ligands. Given the potential role of TLR signalling and innate immunity in the pathogenesis of CD, it is hypothesised that gliadin is a direct ligand for one of the TLRs. If indeed gliadin is proven to be a direct ligand of TLRs, our understanding of the pathogenesis of gastrointestinal diseases, such as colorectal cancer (CRC), will also be greatly influenced.

Evaluation of the hypotheses/ideas

There are only a few published functional analyses of TLR signalling in CD. Catalogued TLR ligands are either PAMPs or DAMPs. However, it has been shown that pathogenic wheat com-

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