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The role of animal models in unravelling therapeutic targets in coeliac disease

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A B S T R A C T

Coeliac disease is a complex small intestinal enteropathy that develops consequently to a breach of tolerance to gliadin, a storage protein abundantly found in cereals such as wheat, rye and barley. The understanding of the mechanisms underlying the development of coeliac disease in HLA-DQ2 and HLA-DQ8 genetically susceptible individuals has greatly improved during the last decades but so far did not allow to develop curative therapeutics, leaving a long-life gluten free diet as the only treatment option for the patients. In order to bring new therapeutic targets to light and to test the safety

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and efficacy of putative drugs, animal models recapitulating features of the disease are needed. Here, we will review the existing animal models and the clinical features of coeliac disease they reflect and discuss their relevance for modelling immune pathways that may lead to potential therapeutic approaches.

Introduction

Coeliac disease (CD) is an immune-mediated small intestinal enteropathy induced by dietary gluten in genetically predisposed individuals. CD incidence is estimated between 0.5 and 2% in Caucasian populations and in industrialised countries has increased two-to four fold over the past 40 years [1]. Its diagnosis relies on detection of serum antibodies directed against the enzyme tissue transglutaminase 2 (TG2) and on characteristic histological features in duodenal biopsies, combining villus atrophy, crypt elongation and accumulation of intraepithelial lymphocytes (IEL).

The gluten-dependent cascade of events leading to epithelial damage in CD has been partially elucidated. Gluten is the collective name given to the numerous hydro-insoluble proteins present in the storage grains of wheat, barley and rye. Compelling evidence indicates that CD depends on the activation of intestinal $CD4^+$ T cells by gluten peptides that are presented at the surface of antigen-presenting cells (APC) by HLA-DQ2 or -DQ8 molecules, the main genetic risk factor for CD [2]. Two properties of gluten proteins facilitate their presentation to $CD4^+$ T cells. First, gluten proteins, are very rich in proline residues and thereby much more resistant to digestive enzymes than most other dietary proteins. Consequently, their intraluminal digestion is incomplete and releases large immunogenic peptides that can translocate across the epithelial barrier and interact with intestinal HLA-DQ2 or -$DQ8^+$ APC [3–5]. Second, gluten peptides are excellent substrates for TG2, an endogenous tissue repair enzyme that is activated during intestinal injury. Upon activation, TG2 can deamidate glutamine residues in gluten peptides, introducing negative charges that enhance their avidity for HLA-DQ2 or -DQ8 and, thereby, their presentation to T cells [2,6]. This first series of events initiates the presentation of gluten peptides to intestinal $CD4^+$ T cells that, in CD patients, differentiate into activated T cells producing IFN-γ and IL-21. In most individuals, priming gluten specific $CD4^+$ T cells is however not sufficient to induce CD as potent regulatory mechanisms establish and maintain immune tolerance to gluten (reviewed in Ref. [7]). The onset of tissue damage in CD also requires the activation of $CD8^+$ cytotoxic IEL. This seems to depend on chronic intestinal up-regulation of IL-15, which can impair immune regulatory mechanisms and synergise with cytokines produced by $CD4^+$ T cells to stimulate the expansion of cytotoxic $CD8^+$ T cells [7–9].

The only treatment of CD remains the strict lifelong gluten-free diet (GFD) defined in the 1950s by W. Dicke [10]. It is efficacious and safe but does not cure the disease. Moreover, GFD is very constraining and strict adherence is a burden for many patients. Additionally, a small subset of severely affected patients can develop primary or secondary resistance to GFD (Reviewed in Ref. [11]). This calls for the development of therapies to replace or complete GFD. The development of animal models allowed substantial progress in the understanding of CD pathogenesis. As with all animal models for autoimmune disease, each model recapitulates particular features of CD. It is therefore critical to fully understand their specificities and limitations. Herein, we will review available *in vivo* models and consider whether and how they can be used to discover drug targets or test therapeutic strategies in CD.

Overview of existing animal models

Spontaneous models of gliadin-dependent enteropathy have been described in rhesus macaques [12–14] and Irish setters [15–17]. Both species develop hallmarks of CD such as partial villus atrophy, increased IEL and anti-TG2 antibodies (only in macaques). A recent study also described the occurrence of spontaneous inflammatory small bowel disease in horses with partial villus atrophy that was