

Editorial: Celiac Disease: progress towards diagnosis and definition of pathogenic mechanisms

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The current issue of the International Reviews of Immunology is dedicated entirely to Celiac Disease (CD). Recent development of additional biomarkers and diagnostics resulted in a sharp revision of the prevalence of this condition, with a previously unrecognized subclinical occurrence in the adult population. This was paralleled by groundbreaking progress in understanding its molecular pathogenesis: while gluten-derived peptides activate the innate immunity, post-translationally modified gluten elicits an adaptive immunity. These arms amplify each other, resulting in a self-perpetuating autoimmune condition, influenced by disturbances of the gut flora and mucus chemistry. The process evolves dramatically in a subset of patients with vulnerable immune homeostasis (eg. Treg cells) explaining the progressive, aggravating syndrome in the clinically overt version of CD. In depth understanding of the pathogenesis of CD thus creates the premises of developing novel, more accurate animal models that should support a rationale development of new prophylactic and therapeutic interventions.

In the current issue of the International Reviews of Immunology, we are pleased to host a special topic dedicated to recent advances on Celiac Disease (CD).

CD is an inflammatory disorder of the small intestine triggered by gluten in genetically sensitive individuals. CD occurs in about 1% of the Western population and is associated with significant complications and comorbidity. In recent years, the view of CD has undergone a profound revision due to a significant progress in the understanding of genetic and immunologic components of this disease. From a translational research standpoint, CD represents a food-related hypersensitivity as well as an autoimmune condition; accordingly, various potential non-dietary therapies are under consideration as alternatives to a lifelong gluten-free diet.

This issue encompasses a compilation of informative, state of the art and opinion reviews on this topic.

In the study by Lionetti and Catassi, the authors discuss how the development of highly sensitive and specific serological tools revealed the true prevalence of CD in recent years, showing an unsuspected frequency of clinically atypical or even silent forms encountered also in the adults. This is noteworthy because only twenty years ago this pathology was just considered a rare pediatric condition. In particular, the authors focus on the epidemiology of CD, now efficiently conceptualized by the iceberg model where typical clinical cases represent the visible peak, but atypical, silent and potential forms altogether represent the main components of the iceberg. Moreover, the study points out crucial aspects of CD pathogenesis, in particular the central role of adaptive immunity and of post-translational modifications in the gluten molecules, as well as

the quite tantalizing contribution of innate immune mechanisms triggered by distinct gluten peptides.

Recent research on CD has addressed the role of environmental factors, other than gluten, in the onset of this pathology. Sanz and colleagues discuss one of these factors, the intestinal dysbiosis. Newly discovered bacteria-mediated mechanisms influencing the CD pathogenesis are examined. Starting from the observation of a different distribution of Gram-positive and Gram-negative strains occurring in the gut of CD patients, the authors underscore the involvement of a bacteria-driven, altered intestinal composition of short-chain fatty acids and of changes in the glycosylation pattern of the mucous layer. Finally, Sanz and colleagues acknowledge the possible benefits of probiotic strains in this disorder, while providing a complete overview on this specific topic.

As underlined above, the incidence of CD in the world population has been recently revised up dramatically, following identification of new serological markers. The study by Lindfors and colleagues addresses this issue by providing a detailed overview on current diagnostic tools for CD diagnosis. CD is still heavily underdiagnosed, as 75-90% of the celiac population in Western countries remains unrecognized, presumably due to the absence, or the atypical nature of symptoms. Accordingly, the importance of serum anti-endomysial (EMA) and anti-tissue transglutaminase (TG2) antibodies assessment is highlighted by the authors, in the quest to uncover this condition; the authors also discuss possible drawbacks related to the use of these biomarkers. The study underlines possible pitfalls of histology when used for diagnosis. Finally, the recent focus on mucosal anti-TG2 antibody deposits as a diagnostic tool is underscored: they appear early in the disease process, before overt mucosal lesions and most importantly, before the very same antibodies are detectable in the circulation.

On the other hand, full knowledge of the immunopathogenic aspects of CD as well as identification of new therapeutic strategies has been delayed to date by the lack of adequate *in vivo* models of CD. This is essentially related to the difficulty of breaking oral tolerance *in vivo* and inducing a gluten-specific enteropathy characterised by a Th1 phenotype, as reported in CD. Marietta and colleagues review in their study the current knowledge of established animal models for CD. In particular, cited work points out to a new paradigm for CD pathogenesis, consisting of three components: an aberrant innate immune response to gliadin, adaptive immunity that occurs in the context of a DQ2/DQ8 restricted response, and perturbations to the regulatory arm of the immune system, resulting in autoimmunity. Therefore, authors indicate the next approach to make the models more representative for the natural disease, through the use of multiple genetic manipulations encompassing these three features likely involved in the pathogenesis of CD. This key achievement would likely expedite the testing and development of new prophylactic and therapeutic means for CD.

In conclusion, together, the different yet complementary aspects reported in the present issue underline an emerging yet still incomplete picture of CD pathogenesis. On this basis, we anticipate that the near future of CD research holds great translational promise.