SECTION I: GENETICS, GENOMICS, IMMUNOLOGY AND APPLICATION TO THERAPY

Preface Section I

Eduardo Arranz MD, PhD

Chapters 1 to 6

1. Genetics of Celiac Disease. HLA and non-HLA genes. Gene Expression Studies. Leticia Plaza-Izurieta, Nora Fernandez-Jimenez, Jose Ramon Bilbao.

2. Mechanisms of Intestinal Tolerance to Dietary Proteins. David Bernardo, Stella C. Knight.

3. Cereal Proteins. Immunomodulatory and Toxic Peptides. Fernando G. Chirdo, Eduardo Arranz.

4. Pathogenesis of Celiac Disease. C. Escudero-Hernández, José A. Garrote, Eduardo Arranz.

5. Intestinal Microbiota and Celiac Disease. Marta Olivares, Yolanda Sanz.

6. Celiac Treatments, Adjuvant Therapies and Alternatives to Gluten-Free Diet. Elena Justin L. McCarville, Alberto Caminero, Elena F. Verdú.

The scope of **Section I** is to review the current knowledge on environmental, genetic and immunological factors involved in celiac disease, as well as to describe alternative therapies, which are at different stages of development. Gluten is a complex mixture of storage proteins with a low nutritional value, but unique functional properties for the elaboration of a wide variety of food products. Gliadins and glutenins from wheat and their counterparts in barley and rye, also called prolamins, are partially digested in the human intestine and, as a result, different immunogenic peptides are generated with the ability to stimulate an immune response in individual with genetic susceptibility.

Chapter 1 describes genetic factors known to have a central role in the susceptibility to celiac disease, though the mode of inheritance is still unknown. The contribution of environmental and genetic factors has been estimated in studies on the prevalence of celiac disease in affected families and, especially, by comparing twin pairs. The genetic component of celiac disease is higher than the estimated contribution for other immunological complex diseases. The genetic risk is mainly based on the presence of certain Human Leucocyte Antigen (HLA) alleles, though their contribution to the heredity is modest, and other non-HLA susceptibility loci may contribute with of many small effects.

Chapter 2 describes the unique properties of the lymphoid tissue associated to the gastrointestinal tract for the maintenance of the immune homeostasis while dealing with an antigen rich environment. Here, the default response is oral tolerance, which controls the immune response against food antigens and the commensal flora. However, there are situations where the mechanisms of immune tolerance are not developed and/or maintained, leading to the activation of immune responses against gluten proteins (celiac disease), or the commensal

flora (Crohn's disease). The main role of dendritic cells in controlling the mechanisms of immune homeostasis in the gastrointestinal tract is also discussed.

Chapter 3 provides relevant information on cereal proteins which are toxic: gliadins and glutenins from wheat, and other prolamins from barley and rye. Adherence to a gluten-free diet is the actual treatment of celiac disease and, to this end, certified gluten-free products are mandatory. Immunochemical techniques for gluten analysis are based on polyclonal and monoclonal antibodies raised against prolamins. Luminal digestion generates different immune-modulatory and toxic peptides which are responsible for an exacerbated immune response in the intestinal mucosa of celiac disease patients, with a central role for the adaptive immunity and gluten-reactive T lymphocytes, though the innate immunity may be also involved, as it has been shown that some gliadin peptides may induce structural changes in the intestine as well as inflammatory reactions.

Chapter 4 discusses the most widely-accepted model of the pathogenesis of celiac disease which focuses on the stimulation of gluten-reactive CD4+ T cells by TG2-deamidated gluten peptides presented by HLA-DQ2/DQ8 molecules, and the production of inflammatory cytokines. Other gliadin peptides may have a direct effect on the epithelium, with interleukin (IL)-15 as the main mediator, and manifested by the expression of stress molecules and the activation of CD8+ intra-epithelial T-cell cytotoxic function. An abnormal immune response to gliadin peptides may lead leads to the development of intestinal lesions with intraepithelial lymphocytosis, epithelial destruction, mucosal re-modeling, and the production of auto-antibodies to tissue transglutaminase.

Chapter 5 reviews the reported association between celiac disease and changes in the composition of intestinal microbiota, which is not completely restored after a gluten-free diet, and may be associated with the HLA-DQ genotype, as shown in healthy infants at family risk of celiac disease. The gut microbiota composition may have a role in the pathogenesis of celiac disease, and its proteolytic activity may be responsible for the generation of immunogenic and toxic peptides, and microbiota is known to have the ability to regulate the epithelial barrier function. Further studies are necessary to confirm these effects and to learn how the administration of specific bacterial strains may modulate the immune homeostasis at the gastrointestinal level and to reducing the risk of celiac disease.

Chapter 6. To date, the only accepted therapy for celiac disease is a lifetime gluten-free diet, which is safe and effective in most patients, though some of its limitations and the growing understanding of celiac disease pathogenesis have led to the development of alternatives. These new therapies include: a) Gluten detoxification strategies in foods; b) Luminal therapies aiming to neutralize gluten peptides in intestine by enzymes, probiotics and gluten binders; c) Intestinal barrier enhancing therapies to inhibit the passage of peptides to the lamina propria; c) Immune targeted therapies, among them, those targeting T cells or inflammatory mediators, and vaccine therapy; and d) Experimental therapies using compounds or biological strategies in discovery phase, for example, the Elafin molecule studied by the authors in an animal model.