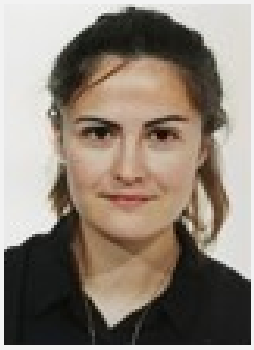
ImmunoTools *special* Award 2019



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Decoding how the gut microbiota in early life influences the risk to develop celiac disease

Background

Celiac disease (CeD) is a chronic inflammatory pathology caused by permanent intolerance to the gluten in genetically predisposed individuals. The development of CeD involves genetic and environmental factors. The HLA-DQ2 and HLA-DQ8 genes constitute the main genetic determinant and gluten the primary environmental factor. Still, the concurrence of these two factors does not explain by itself why some individuals develop the disease and others not. In fact, these genes are present in about 30% of the general population, but only a small percentage (approx. 3%) is diagnosed. Besides, in some cases, the disease debuts in childhood after the introduction of gluten, while in others, it does so in adulthood after long exposure to gluten.

The early life imprinting by the gut microbiota is critical to favor a good state of health later in adulthood. Focusing on CeD, the evidence accumulated so far indicates that certain perinatal events that alter the process of intestinal colonization are associated with an increase in the disease risk. These events are, for instance, formula-based feeding, cesarean births, antibiotic intake and, the incidence of intestinal infections. These observations are of the utmost importance since the gut microbiota is a highly modifiable factor and illustrates a unique opportunity to reduce the risk of a susceptible individual to develop CeD through gut-microbiota-based strategies. Accordingly, some experimental models have already shown the potential of the intestinal microbiota to induce tolerance towards dietary proteins and bacterial antigens.

Observational studies in CeD patients revealed imbalances in the intestinal microbiota, which could contribute to the pathogenesis of the disease. We propose that these imbalances are not only secondary consequences of the disease but could also be a predisposing factor. To test this hypothesis, we carried out the prospective PROFICEL study lead by Prof. Yolanda Sanz that recruited between 2006 and 2010 a cohort of about 200 newborns at risk of developing CeD due to their family history (all had at least one first-degree relative with CeD). With the follow-up of this cohort of children, we aim to decipher how genetic and environmental factors that influence the early intestinal colonization are associated with the later onset of CeD. To date, the main conclusions of the project are, firstly, that those healthy children with the risk genotype (HLA-DQ2) have higher proportions of Firmicutes, Proteobacteria, and Staphylococcus spp. and minors of Actinobacteria (Bifidobacterium spp.) compared to children without the genotype of risk (1). Besides, when looking at the prevalence of specific pathogenic bacteria, we found a higher prevalence of enterotoxigenic E. coli in the feces of healthy infants carriers of the high-risk genotype (2). Secondly, the PROFICEL study allowed us to describe for the first time the gut microbiota composition of children who later developed CeD (3). Accurately, these children presented an early maturation pattern characterized by an increase in bacterial diversity compared to children who did not develop CeD.

Objectives

We propose to take advantage of this unique collection of human samples to:

1. Analyze by cutting-edge technology the microbiome of the children from 6-month old to 36 months and assess their correlation with immune parameters in the feces
2. Study the immune response related to the microbiome in a murine model carrier of the HLA-DQ8 genotype in which the intestinal microbiota will be transplanted from the PROFICEL cases in which the CeD has debuted.

The **ImmunoTools** reagents include a set of ELISA kits for human and murine samples against cytokines involved in the Type 1 responses directed against threats such as virus and dietary antigens (p.e. IFN-γ, TNF-α, IL-1$\gamma\beta$), and in the Type 3 responses that are directed against extracellular microorganisms, such as intestinal bacteria (p.e., IL17A). These sets of antibodies will be used for the validation and the quantification of cytokines in feces from humans and mice.

The project here proposed raises ambitious objectives that, in turn, may have a high impact on public health. Its execution will mean an important advance in the knowledge of the relationship between the intestinal microbiota and CeD. It will allow its transformation into technologies and products that contribute to reduce the risk of suffering from the disease and to favor the maintenance of an active and healthy life.

References:

(1) Olivares M, Walker AW, Capilla A, Benítez-Páez A, Palau F, Parkhill J, Castillejo G, Sanz Y. Gut microbiota trajectory in early life may predict development of celiac disease. Microbiome. **2018**, 20;6(1):36**.**

(2) Olivares M, Benítez-Páez A, de Palma G, Capilla A, Nova E, Castillejo G, Varea V, Marcos A, Garrote JA, Polanco I, Donat E, Ribes-Koninckx C, Calvo C, Ortigosa L, Palau F, Sanz Y. Increased prevalence of pathogenic bacteria in the gut microbiota of infants at risk of developing celiac disease: The PROFICEL study. Gut Microbes.

(3) Olivares M, Neef A, Castillejo G, Palma GD, Varea V, Capilla A, Palau F, Nova E, Marcos A, Polanco I, Ribes-Koninckx C, Ortigosa L, Izquierdo L, Sanz Y. The HLA-DQ2 genotype selects for early intestinal microbiota composition in infants at high risk of developing coeliac disease. Gut. **2014**, 64:406-17.