Celiac disease (CD) is an autoimmune disorder caused by an abnormal intestinal immune response to gluten proteins, present in wheat, barley and rye. Specifically, CD is associated with CD4 T lymphocyte-mediated immunity to gluten within the small intestinal mucosa that causes villous atrophy and crypts hyperplasia.

Human Leukocytes Antigens (HLA) class II genes represent the main genetic risk factor in many autoimmune disorders. The great majority of CD patients carry the HLA-DQA1*05 and HLA DQB1*02 genes, encoding the DQ2.5 molecules expressed on the surface of antigen-presenting cells (APCs). The density of DQ2.5 heterodimers influences the formation of HLA-gliadin complexes, needed to the achievement of gluten threshold for the activation of antigen-specific CD4 T lymphocytes, responsible for the intestinal damage.

Our findings supported the concept that not only the genotype carrying the predisposing HLA genes but also the expression of DQ2.5 alleles are important risk factors in celiac disease.

The CD risk alleles DQA1*05 and DQB1*02 encode the HLA DQ2.5 molecules either when they are in cis (DR3-DQ2 haplotype), or in trans configuration (DR5-DQ7/DR7-DQ2 genotype), the latest very frequent in Southern Europe. Both are associated to high risk for CD that is caused by the ability of DQ2.5 molecule to present full repertoire of gliadin-derived antigenic peptides to CD4 T cells. Our research demonstrated that the either homozygous and heterozygous APCs, carrying the risk genes in cis or trans, have the same stimulatory capability to activate gluten-specific CD4 T cells, because the amount of DQ2.5-gluten peptide complexes is comparable on different APCs. This result was explained by the high expression of DQA1*05 and DQB1*02 alleles in heterozygous genotypes causing the great density of DQ2.5 on APCs, that, regardless their homozygous or heterozygous genotypes induced comparable strength of antigen-specific CD4 T cells activation.

More interesting, a significant difference in the DQA1*05 and DQB1*02 risk allele expression was measured in APCs from celiacs with respect to healthy controls. This allows us to define the Δ value of the difference of risk alleles expression that will be used as early diagnostic tool. Actually, we are measuring the expression of DQA1*05 and DQB1*02 alleles in the blood cells from a cohort of patients in disease remission, at gluten free diet, and in a cohort of family member of affected subjects. The aim is to verify if this Δ value of the difference of risk alleles expression might be predictive of celiac disease in these subjects.

In conclusion we demonstrated that the autoimmune response in CD is determined either by the predisposing genotype and risk alleles expression. Significantly, the magnitude of the anti-gluten CD4 T cell response is strictly dependent by the antigen concentration, consequence of the gluten amount in the diet.
References:

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