Back to the Future: HLA in Gastroenterology

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Celiac disease (CD) and inflammatory bowel diseases (IBD) are among the most common gastrointestinal disorders and share strong genetic risks that may predict their diagnosis or even guide their management, particularly the Human Leukocyte Antigen (HLA) system.

Historically, various associations between the HLA and autoimmune diseases were reported since the 1970s, and the HLA is now incriminated in a myriad of diseases including CD and IBD [1,2].

This HLA complex is a genomic region located at the short arm of chromosome 6 (6p21) and involves more than 200 genes, most of are a mandatory requisite for the immune system. In particular, the HLA class II genomic region encodes proteins (namely HLA DR, DQ, and DP) that mediates the adaptive immunity [3,4].

Celiac disease (CD) is probably the best-recognized disease related to HLA genes: more than 95% of patients with CD share the HLA-DQ2 heterodimer, and the remainder present the HLA-DQ8 heterodimer. Present in nearly all patients with CD, these risk-haplotypes have a negative predictive value of CD approaching 100% [5,6]. This aspect is backing the recommendations from several societies (notably the ESPGHAN) that suggest HLA typing to rule out CD [7].

Regarding IBD, data is increasingly converging on the crucial role of the HLA system. In fact, this HLA complex is associated with multiple risk/protective alleles for IBD and most HLA genes harbor IBD-associated genotypes; while the HLA-DRB1*03:01 is the most associated risk allele in Crohn's disease and ulcerative colitis [8].

As a cherry on the cake, studies focusing on HLA in IBD are shedding the light, at least partly, on the obscure pathophysiology of these long-term gastrointestinal disabling conditions: in a recent genome-wide association study performed in a cohort of 1240 patients with Crohn's disease, Sazonovs., *et al.* revealed that the HLA-DQA1*05 allele, carried by approximately 40% of Europeans, significantly increased the rate of immunogenicity to anti-tumor necrosis factor (anti-TNF) therapies in Crohn's patients (up to 92% at 1 year in those who carried HLA-DQA1*05 versus as low as 10% in those without this gene) [9].

Thus, the HLA system appears more and more as a genetic model of a personalized and predictive medicine, incorporating the gastroenterology field [10].

In our modern context of dramatic increase in prevalence of autoinflammatory/autoimmune gastrointestinal diseases, predictive medicine through HLA typing emerges as an interesting, low-cost tool to discriminate individuals genetically susceptible either to develop such conditions (like in CD) or to resist to treatment (like anti-TNF in IBD).

Genomics are merely the future of medicine!

Bibliography

1. Rahmoune H., *et al*. "HLA and Celiac Disease". *Moroccan Health Journal* 18 (2017): 14-15.

2. Pallav K., *et al*. "Clinical utility of celiac disease-associated HLA testing". *Digestive Diseases and Sciences* 59 (2014): 2199-206.

3. Cruz-Tapias P., *et al*. "Major histocompatibility complex: Antigen processing and presentation". In: Anaya JM, Shoenfeld Y, Rojas-Villarraga A, et al., editors. Autoimmunity: From Bench to Bedside [Internet]. Bogota (Colombia): El Rosario University Press (2013).

4. Martina S., *et al*. "Genetic susceptibilty and celiac disease: what role do HLA haplotypes play?". *Acta Bio Medica: Atenei Parmensis* 89 (2018): 17.

5. Rahmoune H., *et al*. "Celiac Disease, Diabetes and Crohn Disease: An Autoimmune Implosion?". *International Journal of Celiac Disease* 6.2 (2018): 62-63.

6. Rahmoune H., *et al*. "HLA genes as a predictive screening tool for celiac disease". *Turkish Archives of Pediatrics* 52 (2017): 182-184.

7. G Husby S., *et al*. "European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease". *Journal of Pediatric Gastroenterology and Nutrition* 54 (2012): 136-160.

8. Ashton JJ., *et al*. "Review article: the genetics of the human leucocyte antigen region in inflammatory bowel disease". *Alimentary Pharmacology and Therapeutics* 50.8 (2019): 885-900.

9. Sazonovs A., *et al*. "HLA-DQA1* 05 carriage associated with development of anti-drug antibodies to infliximab and adalimumab in patients with Crohn's disease". *Gastroenterology* 158.1 (2020): 189-199.

10. Charron D. "HLA, immunogenetics, pharmacogenetics and personalized medicine". *Vox Sang* 100.1 (2011): 163-166.