REPLY TO HAN ET AL.:

On track for an IDO1-based personalized therapy in autoimmunity

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Advances in genome-wide association studies (GWASs) have highlighted the heterogeneous nature of autoimmune diseases (1), conditions whereby malfunctioning of molecular mechanisms underlying tolerance translates into the activation of autoreactive immune cells. Immune checkpoint molecules are regulators of the immune system that preserve self-tolerance and prevent autoimmunity. Indoleamine 2,3-dioxygenase 1 (IDO1) is a metabolic enzyme that acts as immune checkpoint molecule and is characterized by common single-nucleotide polymorphisms (SNPs), all detectable in noncoding regions of the *IDO1* gene (2). Among these, the CC genotype at *IDO1* rs7820268 is associated with impaired IDO1 activity in peripheral blood mononuclear cells (PBMCs) from children with autoimmune diabetes and with an enhanced risk of developing the disease (3). Full restoration of IDO1 activity can nevertheless be obtained in vitro by the use of an interleukin 6 receptor blocker, although only in one-third of patients (3). The same genotype increases the risk for developing multiple sclerosis (MS), particularly the relapsing-remitting form of the disease (RRMS) (4). Defective IDO1 activity in PBMCs from RRMS patients can be restored by a positive allosteric modulator of IDO1 (4). Therefore, the available data would suggest that rs7820268 may represent a critical SNP for IDO1-based personalized therapy in autoimmune diseases, although the biologic mechanism whereby this SNP influences IDO1 expression and activity has not been clarified yet.

Noncoding disease-associated SNPs may contribute to pathology by acting as expression quantitative trait loci (eQTL), i.e., genomic regions that regulate the expression of one or more transcripts (5). Therefore, eQTL mapping represents a powerful approach that allows regulatory variants to be identified and linked to specific genes, providing powerful insight into the human genomic landscape through the generation of expression maps key to interpreting of noncoding variants arising from GWAS datasets (6). This is particularly useful for non-Mendelian immune disease phenotypes where the interaction between polygenic variants and environmental factors may be required for the manifestation of the disease phenotype (as is the case for autoimmune diseases). Moreover, whereas many eQTLs affect gene expression only under specific conditions of cellular activation, a significant proportion of eQTLs present in homeostasis are instead lost after an inflammatory insult (7, 8).

By using large-scale deposited eQTL datasets, Han et al. confirm the impact of rs7820268 on IDO1 expression (9). In blood, they found that the T allele enhances IDO1 transcripts. Perhaps most interestingly, rs7820268 was found to be associated with a differential regulation of IDO1 expression across distinct brain regions. Therefore, these data provide further support to the heterogeneity in IDO1 expression and may represent an important initial step in unveiling the effects of regulatory variation on IDO1 expression in blood cells and brain regions. However, because the used eQTL datasets were derived from healthy individuals, it remains to be elucidated whether this holds true in a disease-relevant context. In this regard, the recent discovery of a coding variant (rs751360195) associated with a very low IDO1 function in a patient affected by multiple autoimmune disorders (10) may help pursuing effective IDO1-based personalized therapy in autoimmunity.

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The authors declare no competing interest.

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