LETTER

REPLY TO LIU ET AL.:

Haplotype matters: *CD226* polymorphism as a potential trigger for impaired immune regulation in multiple sclerosis

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Multiple sclerosis (MS) is an autoimmune disease of the central nervous system, which results from a breakdown in peripheral tolerance driven by genetic and environmental factors. The activating receptor DNAM-1 (DNAX accessory molecule-1, CD226) seems to be crucial in both NK-cell (1) and Foxp3$^+$ (forkhead box protein-3) regulatory T-cell (T_{reg}) (2) -mediated control of T-cell activity, suggesting that CD226-mediated immune regulation is conserved among innate and adaptive immune-regulatory networks. Concomitant with a disease-related impaired immune-regulatory function, NK cells (1) and T_{reg} (2) derived from MS patients exhibit a reduced cell surface expression of CD226. Thus, MS-related reduced CD226 expression likely decreases their suppressive capacity. Genome-wide association studies revealed susceptibility variants of polymorphisms in the *CD226* gene, namely rs727088^G and rs763361^T, in distinct autoimmune diseases, including MS (3–5).

Recently, Liu et al. investigated whether rs763361 effects CD226 expression (6). PhenoScanner (www.phenoscanner.medschl.cam.ac.uk/phenoscanner) database analysis revealed that rs763361 polymorphism controls expression of CD226 (6). Further analysis by this group demonstrates that rs763361^T resulted in reduced CD226 expression in different organs and tissues, including the brain (6). Moreover, expression quantitative trait locus (eQTL) meta-analysis of nontransformed peripheral blood samples from 5,311 individuals showed a correlation of the "MS risk" haplotype rs763361^T with reduced CD226 expression (7). Finally, a risk haplotype-dependent reduction of CD226 cell-surface expression was observed in distinct T-cell subsets, including T_{reg} derived from healthy individuals (2, 8). In MS, CD226 expression on T cells was reduced to levels comparable to the risk-haplotype carriers independent of the allele (2), proposing a general effect of the haplotype on protein expression and a more complex role with regard to disease predisposition.

Although CD226 seems to be important for immune regulatory function (1, 2), increased CD226 expression is associated with a proinflammatory Th1/Th17 cell response (9). In rodents, CD226 deficiency revealed contradictory results with either exacerbation (2) or amelioration (10) of experimental autoimmune encephalomyelitis, an animal model of MS. Thus, further studies are warranted to elucidate the beneficial versus detrimental effects of CD226 expression on distinct immune-cell subsets during the course of MS.

Overall, the rs763361^T allele is not only linked to an increased risk for MS (3–5), but also associated with reduced CD226 expression in healthy individuals (6). CD226 plays an important role in innate and adaptive immune regulatory networks and reduced CD226 expression seems to decrease the immune-regulatory capacity (1, 2). Thus, the rs763361^T allele might be one of the genetic driving forces contributing to MS susceptibility. However, this polymorphism cannot be regarded as "MS-specific" or even "autoimmune-specific." As with other disease polymorphisms, it contributes in concert with other factors. Longitudinal analysis of predisposed patients (i.e. comparison of clinically isolated syndrome to MS converters versus nonconverters) as well as genotype/phenotype correlations will shed light to what extent the *CD226* haplotype determines the susceptibility to

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develop MS, contributes to disease heterogeneity, or even therapeutic response profiles. Finally, further studies are required to elucidate the impact of rs763361^{T}, resulting in one amino acid substitution in the intracellular domain of CD226 (Gly307Ser/rs763361^{T}), on signaling and immune-regulatory function of NK cells and T_{reg}.

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