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Response to "*NLRC5* germline variants and their potential role in eliciting an immune response in patients with cancer treated with immune checkpoint inhibitors" by Xiang-Yu Meng

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To the Editor:

We thank Dr Meng for the thoughtful letter further elaborating on the possible significance of NLRC5 polymorphisms in the development of immune checkpoint inhibitor-induced diabetes mellitus (ICI-DM) and other immune-related adverse events (irAEs). Dr Meng further highlights a potential role of NLRC5 expression or polymorphisms as a biomarker for predicting response to immunotherapy, based on work by Yoshihama *et al*.[1]

Despite several protein structure tools predicting a benign effect of the NLRC5 variant identified (Pro191Leu), as detailed in our study[2] and by Dr Meng, we agree that the mutant gene may still play a causal role in ICI-DM. We were encouraged by the significant association between the *NLRC5* gene variant and *NLRC5* expression in the blood identified in the eQTLGen database and highlighted by Dr Meng. While we did not see differences in *NLRC5* messenger RNA levels in tumors of patients with ICI-DM with the presence of the variant, we did not compare expression in other organs or the blood. As the identified *NLRC5* mutation was germline, other tissue-specific effects outside of the tumor, including on *NLRC5* transcription levels, could indeed be contributing to ICI-DM and should be explored further. We also think it is important for future efforts to remain cognizant of the fact that there are likely unique mechanisms leading to the development of ICI-DM that differ from type 1 diabetes mellitus (T1DM). It is unclear if the identified *NLRC5* mutation is relevant to T1DM as well, despite Dr Meng's thought-provoking summary statistics based on Mendelian randomization analyses, as our analysis and others performed by Dr Meng failed to show enrichment of NLRC5 Pro191Leu variants among individuals with T1DM. Ultimately, careful genotype–phenotype and functional studies are needed to establish the impact of the NLRC5 Pro191Leu variant, which our group has started to perform.

It is well established that *NLRC5* is expressed in various tissue types, including in other organ systems where irAEs typically manifest, raising the possibility that the identified *NLRC5* variant may contribute to the pathogenesis of other irAEs. We are currently exploring the incidence of *NLRC5* mutations in other irAEs in a larger cohort of patients undergoing treatment with ICIs. Of note, we have identified additional patients with ICI-DM with the *NLRC5* mutation, further supporting our initial findings.

Regarding the potential of *NLRC5* as a predictive biomarker of tumor response to ICIs, there are emerging reports connecting *NLRC5* to treatment response for various cancers,[3 4] with multiple studies suggesting that the mechanism is based on tumor evasion and mediated by human leukocyte antigens (HLA) expression.[5] Additionally, the correlation between irAEs and favorable response to ICIs has been widely demonstrated, and Jiang *et al* recently suggested that HLA alterations are the link between the two.[6] While our initial cohort size of 13 patients limited our ability to connect the *NLRC5* germline variant with response to ICIs, we are performing this analysis in the larger cohort of ICI-treated patients we are currently investigating.

In conclusion, we appreciate the additional analysis and comments provided by Dr Meng related to our study, and believe they support further efforts to better understand the role of NLRC5 in irAEs and response to ICIs, some of which are underway in our group.

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