Journal for ImmunoTherapy of Cancer

NLRC5 germline variants as potential pharmacogenomic markers for immune checkpoint inhibitors

Xiang-Yu Meng

To cite: Meng X-Y. *NLRC5* germline variants as potential pharmacogenomic markers for immune checkpoint inhibitors. *Journal for ImmunoTherapy of Cancer* 2023;**11**:e007255. doi:10.1136/jitc-2023-007255

Accepted 17 May 2023

► http://dx.doi.org/10.1136/jitc-2022-006570

Department of Pharmacology, College of Basic Medical Sciences, Medical School, Hubei Minzu University, Enshi, China

Correspondence to
Dr Xiang-Yu Meng;
mengxy_whu@163.com

I read with interest the recent report by Caulfield *et al*. In this elegant piece of work, the authors performed RNA-seq and whole exome sequencing (WES) on tumors from a small cohort of subjects that presented insulin-dependent diabetes after treatment by immune checkpoint inhibitors (ICIs), which is a rare but life-altering immune-related adverse effect (irAE) with undetermined underlying mechanisms. Their RNA-seq analyses suggested possible roles of tumorous *ORM1*, *PLG*, and *G6PC* gene expression, and their WES data highlighted a missense germline variant of the *NLRC5* gene, the *NLRC5* Pro191Leu (hg38, chr16:57025515C>T; rs74439742 in the dbSNP database), which was significantly enriched in patients that developed ICI-induced diabetes mellitus (ICI-DM). These findings, though based on data from a very limited number of patients (n=13), provided interesting clues about the possible mechanisms and biomarkers of ICI-DM.[1]

Despite the striking over-representation of the *NLRC5* Pro191Leu variant in the ICI-DM patients compared with the general population (of European ancestry), this protein-coding mutation itself is more likely to be a non-causal marker given its predicted benign effect by multiple tools including Polyphen and SIFT, as shown in the gnomAD database (https://www.gnomad-sg.org). Nevertheless, this does not necessarily mean no causal role of the *NLRC5* gene in ICI-DM, for the following reasons. First, as also discussed in Caulfield *et al*, the *NLRC5* gene has been experimentally shown to play an important role in the development of IFNα-induced autoimmunity against pancreatic β cells, through not only transcriptional activation of HLA class I and antigen presentation-related genes, but also generation of β cell neoantigens by cross-talk with alternative splicing.[1] Second, although the *NLRC5* Pro191Leu amino acid change may confer non-significant impact on the function of *NLRC5* protein, this variant is indeed significantly associated with the *NLRC5* gene expression level in blood, as shown in the eQTLGen database (https://eqtlgen.org; rs74439742 T vs C, n=13 100, Z-score=−5.1, $p=2.8\times10^{-7}$, FDR=8.6×10^{-4}). This cis-eQTL relationship suggest a potential causal role of *NLRC5* gene in the development of ICI-DM, though further studies are needed for validation. On the other hand, no *NLRC5* genetic variants have been linked with type I diabetes (T1DM) at genome-wide significance in GWAS studies so far, per queries in the GWAS Catalog (https://www.ebi.ac.uk/gwas) and IEU-GWAS (https://gwas.mrcieu.ac.uk) databases, which is consistent with the report by Caulfield *et al* that no significant difference in the allele-frequency of *NLRC5* Pro191Leu was noted between the T1DM subjects and the controls in previously published T1DM datasets and the Type 1 Diabetes Genetics Consortium database.[1] However, interestingly, summary statistics-based Mendelian randomization (SMR) analyses suggest a possible cause-and-effect relationship between *NLRC5* and T1DM, as provided in the eQTLGen database ($\beta_{SMR}=-0.40$, $P_{SMR}=3.3\times10^{-2}$).

NLRC5, also known as MHC class I transactivator, has been widely recognized as a key transcriptional activator of MHC class I and antigen presentation genes. It has recently been shown to play crucial roles in cancer immune surveillance, and a recent study by the Kobayashi lab suggested the translational significance of *NLRC5* gene expression in ICI-based immunotherapy in melanoma patients.[2] Interestingly, strong coexpression is observed between *NLRC5* and *PDCD1*/*CD274*/*CTLA4* in tumors of a number of ICI-relevant cancer types, including melanoma, lung cancer, bladder cancer, breast cancer, colorectal cancer, and head-and-neck cancer, among others, per queries for TCGA

data in the cBioPortal database (https://www.cbioportal.org; eg, TCGA BLCA, n=404: *NLRC5* with *PDCD1*, Spearman's r=0.78, p=2.9×10^{-84}; *NLRC5* with *CD274*, Spearman's r=0.65, p=2.2×10^{-49}; *NLRC5* with *CTLA4*, Spearman's r=0.76, p=6.1×10^{-84}). Considering the contributing effects exerted by genetic variants in anticancer immunity and ICI-response, *NLRC5* variants could be potential biomarkers for ICI responsiveness and efficacy, similar as the previously identified marker SNPs associated with *CTLA4*, *PDCD1*, and *CD274* genes.[3 4] On the other hand, per query in the GTEx database (https://www.gtexportal.org/), although immune-related tissue types present the highest expression level of *NLRC5* (ie, spleen and whole blood, median TPM, 63.98 and 35.93, respectively), it is also widely expressed in many other tissue types, and at a high level in lung, small intestine, and skin (median TPM, 24.63, 22.05, and 19.15, respectively). Therefore, if *NLRC5* does play a role in irAE and with possible effects conferred by its germline variants, presumably ICI-DM is not the only form of manifestation. Indeed, as reviewed by Wang *et al*, *NLRC5* is also implicated in a number of immune-related disorders, such as rheumatoid arthritis, inflammatory liver injury, and fibrosis in the liver, heart, and kidney.[5]

Taken together, current data by Caulfield *et al* and others suggest possible implications of *NLRC5* in ICI-based cancer immunotherapy, with regard to both clinical efficacy and adverse effects. Further studies are warranted to test and validate the clinical utility of *NLRC5* variants as potential pharmacogenomic markers for ICI-treatment efficacy and safety. Common germline polymorphisms located in *NLRC5*-related regulatory regions and/or demonstrate significant correlation with *NLRC5* gene expression or methylation could be candidates of interest.

Contributors X-YM is the single author of this work.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD

Xiang-Yu Meng http://orcid.org/0000-0001-5669-3502

REFERENCES

1 Caulfield JI, Aizenbud L, Perdigoto AL, *et al*. Germline genetic variants are associated with development of insulin-dependent diabetes in cancer patients treated with immune Checkpoint inhibitors. *J Immunother Cancer* 2023;11:e006570.
2 Yoshihama S, Cho SX, Yeung J, *et al*. Nlrc5/CITA expression correlates with efficient response to Checkpoint blockade Immunotherapy. *Sci Rep* 2021;11:3258.
3 Sayaman RW, Saad M, Thorsson V, *et al*. Germline genetic contribution to the immune landscape of cancer. *Immunity* 2021;54:367–86.
4 Khan Z, Di Nucci F, Kwan A, *et al*. Polygenic risk for skin Autoimmunity impacts immune Checkpoint blockade in bladder cancer. *Proc Natl Acad Sci U S A* 2020;117:12288–94.
5 Wang J-Q, Liu Y-R, Xia Q, *et al*. Emerging roles for Nlrc5 in immune diseases. *Front Pharmacol* 2019;10:1352.