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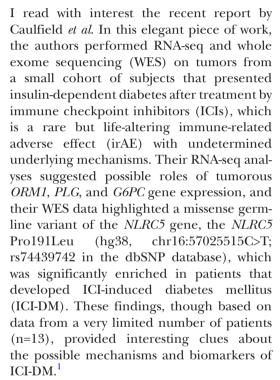
NLRC5 germline variants as potential pharmacogenomic markers for immune checkpoint inhibitors

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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



Despite the striking over-representation of the NLRC5 Pro191Leu variant in the ICI-DM patients compared with the general population (of European ancestry), this proteincoding 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 IFNa-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. 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=13100, Z-score=-5.1, p= 2.8×10^{-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 genomewide 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 allelefrequency 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. However, interestingly, summary statistics-based Mendelian randomization (SMR) analyses suggest a possible causeand-effect relationship between NLRC5 and T1DM, as provided in the eQTLGen database $(\beta_{SMR} = -0.40, P_{SMR} = 3.3 \times 10^{-2}).$

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



itc-2022-006570



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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, $p=2.2\times10^{-49}$; *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.³⁴ 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 immunerelated 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.

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