Cell Genomics

CellPress
OPEN ACCESS

Preview

Rare-variant association study unveils the Achilles' heel for HCC

Yin Wang[1] and Ying Wai Chan[1,*]
[1]School of Biological Sciences, The University of Hong Kong, Pokfulam, Hong Kong SAR, China
*Correspondence: gywchan@hku.hk
https://doi.org/10.1016/j.xgen.2024.100558

In this issue of *Cell Genomics*, Wang, Liu, Zuo, Wang, et al.[1] investigate rare variants in hepatocellular carcinoma (HCC) by performing the first rare-variant association study (RVAS) in a Chinese population cohort. It uncovers BRCAness phenotypes associated with the NRDE2-p.N377I variant, suggesting PARP inhibitors as a promising therapeutic approach for certain HCC patients.

The significant role of rare variants in disease susceptibility has become increasingly recognized. Genome-wide association studies (GWASs) have successfully identified numerous single-nucleotide polymorphisms (SNPs) associated with common human diseases and traits[2]; however, these account for only approximately 20%–30% of the total heritability, suggesting the presence of missing heritability.[3] The GWAS approach is based on the "common disease, common variant" assumption, focusing on allele variations present in more than 1% of the population while potentially overlooking rare variants.[4] Nevertheless, an inverse relationship exists between minor allele frequency (MAF) and SNP effect size. For instance, harmful rare variants often undergo natural selection, resulting in low frequencies within populations.[4,5] As a result, rare variants are proposed as significant contributors to the missing heritability phenomenon and offer valuable insights into disease susceptibility. Moreover, large-effect rare variants have demonstrated a higher potential for clinical translation compared to common variants in monogenic disorders.[6] Given the complex pathogenesis of hepatocellular carcinoma (HCC) and the limited explanatory power of current GWAS findings for heritability factors, exploring rare variants is essential for elucidating the underlying susceptibility mechanisms of HCC.

Deficient DNA damage response (DDR) contributes to the genomic instability of cancer cells, which can be exploited for therapeutic strategies. The poly(ADP-ribose) polymerase (PARP) inhibitors (PARPis) have been successfully employed in the clinic for breast and ovarian cancer deficient in either *BRCA1* or *BRCA2*. These inhibitors exert a synthetic lethality effect on cancer cells with homologous recombination (HR) deficiency.[7] Although *BRCA* mutations are infrequent in HCC,[8] emerging evidence suggests that not all cancer cells require mutations in classic HR genes to respond to PARPis. For example, DDX-Q238H mutation in Huh7 cells attenuates HR and induces PARPi sensitivity.[9] Moreover, combination therapy by inhibiting both PARP1 and DNA-PK exhibits promising therapeutic effects in HCC.[10] Therefore, exploring BRCAness in HCC opens new treatment possibilities. In this issue of *Cell Genomics*, a rare-variant association study (RVAS) of HCC in a Chinese population identified the NRDE2-p.N377I variant, which confers a loss-of-function effect and sensitizes cells to PARPis.[1] This discovery holds potential implications for expanding the application of PARPis to HCCs that display BRCAness.

In this paper, the authors identified four HCC-associated genes and their corresponding variants, with NRDE2-N337I emerging as the leading variant in single-variant-based analyses. They demonstrated that NRDE2 suppresses cancerous behaviors in HCC, while the NRDE2-N337I variant exhibits loss-of-function effects. Further investigation revealed that NRDE2 is involved in the repair of double-strand breaks (DSBs) by promoting the HR pathway. The team discovered an interaction between NRDE2 and casein kinase 2 (CK2), providing evidence of the role of NRDE2 in CK2-dependent regulation of DSB repair. Notably, NRDE2 facilitates the assembly and kinase activity of CK2 holoenzyme (composed of 2 CK2α and 2 CK2β subunits), while the N337I mutation, located within the tetratricopeptide repeat (TPR) domain of NRDE2, disrupts its interaction with CK2. To investigate the regulatory role of NRDE2 in CK2 kinase activity, the researchers conducted mass-spectrometry-based phosphoproteomics assays and identified DNA damage checkpoint 1 (MDC1) as a potential CK2 substrate. Phosphorylation of MDC1 at S329/T331/T378 by CK2 is crucial for recruiting the MRN complex, consisting of MRE11, RAD50, and NBS1, to DSB sites and thus promoting HR-mediated repair. Therefore, NRDE2-CK2 axis induces the phosphorylation of MDC1 to promote HR repair, a process that is compromised in the presence of the NRDE2-N337I mutant (Figure 1).

The loss-of-function of NRDE2 in HCC, resulting in a BRCAness phenotype, has significant implications for translational applications. NRDE2 displayed a negative correlation with PARPi sensitivity in various cancer cells, including those derived from HCC. Notably, NRDE2 deficiency led to increased sensitivity to PARPis in both HCC cell lines and patient-derived xenograft (PDX) models. These effects were found to be dependent on MDC1 phosphorylation mediated by CK2.

This study provides several noteworthy findings that enhance our understanding of HCC and its treatment. Firstly, it identified rare variants in the Chinese HCC population, including NRDE2, RANBP17, RTEL1, and STEAP3, thus broadening our knowledge of HCC predisposition factors. Secondly, the authors conducted an

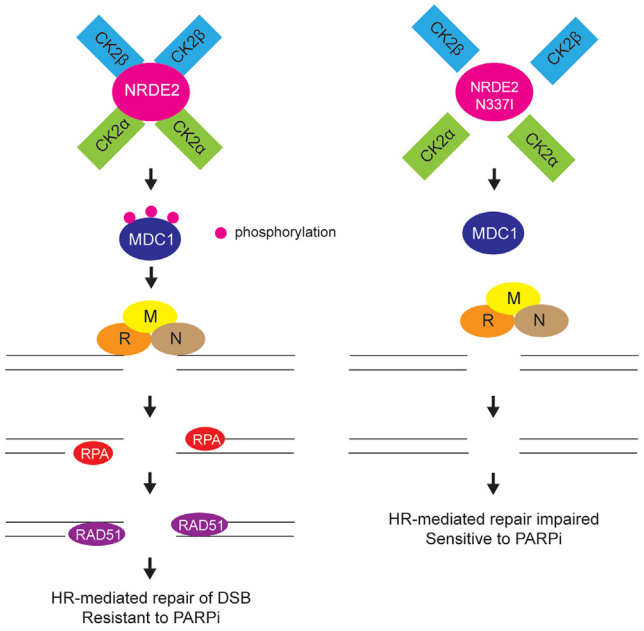

Figure 1. Model of the function and mechanism of how NRDE2 promotes HR

Wild-type NRDE2 promotes the assembly and kinase activity of the CK2 holoenzyme, which in turn phosphorylates MDC1 and facilitates the recruitment of the MRN (MRE11-R-RAD50-NBS1) complex to the DSB sites, promoting end resection. Single-stranded DNA is initially coated with RPA, which is subsequently replaced by RAD51 to form the RAD51 filament, mediating HR repair. As a result, cells are HR proficient and resistant to PARPis. However, when cells express NRDE2-N337I, which is unable to interact with and activate CK2, MDC1 is not phosphorylated at S329/T331/T378, preventing the recruitment of the MRN complex to DSB sites and hindering resection. Consequently, mutant cells are deficient in HR and exhibit increased sensitivity to PARPis.

in-depth examination of the NRDE2 gene and its rare variant NRDE2-N337I in HCC, unveiling a novel relationship between NRDE2 and BRCAness. Their findings indicate that NRDE2 deficiency increases PARPi sensitivity in HCC, suggesting a promising new therapeutic approach for HCC and broadening the potential use of PARPis beyond tumors with *BRCA1/2* mutations. Thirdly, this work offers insights into the role of NRDE2 in DDR regulation, expanding our knowledge of the DDR regulatory network. Finally, the study proposes that NRDE2 deficiency could serve as a potential biomarker for PARPi treatment in HCC. Considering that DDR-related genes constitute a significant group of cancer susceptibility genes, it is worth investigating the presence of NRDE2 mutations in other cancer types and its potential as a pan-cancer susceptibility gene for germline testing.

ACKNOWLEDGMENTS

The work is supported by the Guangdong Natural Science Fund General Program from the Guangdong Provincial Department of Science and Technology (project no. 2021A1515010437), Hong Kong Research Grant Council General Research Fund (project no. 17119421), and the University of Hong Kong.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

1. Wang, Y., Liu, X., Zuo, X., Wang, C., Zhang, Z., Zhang, H., Zeng, T., Chen, S., Liu, M., Chen, H., et al. (2024). NRDE2 deficiency impairs homologous recombination repair and sensitizes hepatocellular carcinoma to PARP inhibitor. Cell Genom. *4*, 100550. https://doi.org/10.1016/j.xgen.2024.100550.
2. Buniello, A., MacArthur, J.A.L., Cerezo, M., Harris, L.W., Hayhurst, J., Malangone, C., McMahon, A., Morales, J., Mountjoy, E., Sollis, E., et al. (2019). The NHGRI-EBI GWAS Catalog of published genome-wide association studies, targeted arrays and summary statistics 2019. Nucleic Acids Res. *47*, D1005–D1012. https://doi.org/10.1093/nar/gky1120.
3. Zuk, O., Hechter, E., Sunyaev, S.R., and Lander, E.S. (2012). The mystery of missing heritability: Genetic interactions create phantom heritability. Proc. Natl. Acad. Sci. USA *109*, 1193–1198. https://doi.org/10.1073/pnas.1119675109.
4. Manolio, T.A., Collins, F.S., Cox, N.J., Goldstein, D.B., Hindorff, L.A., Hunter, D.J., McCarthy, M.I., Ramos, E.M., Cardon, L.R., Chakravarti, A., et al. (2009). Finding the missing heritability of complex diseases. Nature *461*, 747–753. https://doi.org/10.1038/nature08494.
5. Zeng, J., de Vlaming, R., Wu, Y., Robinson, M.R., Lloyd-Jones, L.R., Yengo, L., Yap, C.X., Xue, A., Sidorenko, J., McRae, A.F., et al. (2018). Signatures of negative selection in the genetic architecture of human complex traits. Nat. Genet. *50*, 746–753. https://doi.org/10.1038/s41588-018-0101-4.
6. Abdellaoui, A., Yengo, L., Verweij, K.J.H., and Visscher, P.M. (2023). 15 years of GWAS discovery: Realizing the promise. Am. J. Hum. Genet. *110*, 179–194. https://doi.org/10.1016/j.ajhg.2022.12.011.
7. Lord, C.J., and Ashworth, A. (2017). PARP inhibitors: Synthetic lethality in the clinic. Science *355*, 1152–1158. https://doi.org/10.1126/science.aam7344.
8. Katagiri, T., Nakamura, Y., and Miki, Y. (1996). Mutations in the BRCA2 gene in hepatocellular carcinomas. Cancer Res. *56*, 4575–4577.
9. Cao, K., Wang, R., Li, L., Liao, Y., Hu, X., Li, R., Liu, X., Xiong, X.D., Wang, Y., and Liu, X. (2024). Targeting DDX11 promotes PARP inhibitor sensitivity in hepatocellular carcinoma by attenuating BRCA2-RAD51 mediated homologous recombination. Oncogene *43*, 35–46. https://doi.org/10.1038/s41388-023-02898-x.
10. Wang, C., Tang, H., Geng, A., Dai, B., Zhang, H., Sun, X., Chen, Y., Qiao, Z., Zhu, H., Yang, J., et al. (2020). Rational combination therapy for hepatocellular carcinoma with PARP1 and DNA-PK inhibitors. Proc. Natl. Acad. Sci. USA *117*, 26356–26365. https://doi.org/10.1073/pnas.2002917117.