Letter to the Editor

Response to the hunt for the perfect biomarker in nasopharyngeal carcinoma—the RRAS "race" beyond Epstein-barr virus?

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Response to: Tan MTL, Wee JTS, Chua MLK. The hunt for the perfect biomarker in nasopharyngeal carcinoma—the RRAS "race" beyond Epstein-Barr virus? Transl Cancer Res 2019;8:1659-62.

Submitted Sep 23, 2018. Accepted for publication Sep 29, 2019.
doi: 10.21037/tcr.2019.10.01
View this article at: http://dx.doi.org/10.21037/tcr.2019.10.01

We sincerely appreciate Mark T. L. TAN and his co-workers for their comments "The Hunt for the Perfect Biomarker in Nasopharyngeal Carcinoma—the RRAS "race" beyond Epstein-Barr virus?" on our study titled "Identification of RRAS gene related to nasopharyngeal carcinoma based on pathway and network-based analyses". Nasopharyngeal carcinoma (NPC) is an endemic tumor closely associated with Epstein barr virus (EBV) (1). EBV infection is detected in almost 100% of non-keratinizing nasopharyngeal carcinomas (NPCs) (2,3). Recent studies have suggested that EBV DNA level in the plasma is correlated to the prognosis of patients with NPC (4). Despite the continuing identification of NPC related biomarkers, EBV-associated antigens and cfEBV DNA (cell free EBV DNA) tests remain to be the optimal choice for NPC patients. Nevertheless, because of the prevalence of EBV infection in the population, it makes sense to look for more specific biomarkers to improve the assessment of prognosis.

In our study, we introduced a bioinformatics strategy to find new potential biomarkers for NPC. We found that PI3K-Akt signaling pathway plays an important role in our pathway crosstalk analysis, and one of the hub genes PIK3CA had been reported to be amplified in NPC. Our findings are consistent with previous studies, which indicated the reliability of our strategy (2). Ultimately, we found RRAS may be associated with PIK3CA. Although putative homologs have been found interacting in other species, the interaction between RRAS and PIK3CA in human needs experimental verification.

We found that RRAS was down-regulated in NPC and associated with advanced clinical stages of NPC patients. However, the expression of RRAS showed no significant correlation with distant metastasis and regional recurrence. The combination of RRAS and cfEBV DNA might be helpful in predicting the prognosis of NPC patients, but more powerful biomarkers are needed to complement the existing tools. Considering the feasibility of the tests, detection of circulating tumor DNA or non-coding RNA in plasma might be a promising direction (5-7).

As Tan *et al.* mentioned, R-Ras was originally identified as an oncogene, however, accumulated evidence has suggested a tumor suppressor role for R-Ras (8). Recent study showed that RRAS is downregulated in tumor vasculature and could inhibit VEGFR activation (8-10). Besides, as lymphocyte infiltration is extensive in NPC, altered expression of R-Ras may affect the functions of immune cells associated with tumor and exert their antitumor effect (11,12). Although the role of RRAS in NPC remains to be elucidated, the strategy of our research is helpful to find more potential genes associated with NPC and reveal its pathogenesis.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Editorial Office, *Translational Cancer Research*. This article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.10.01). RX reports grants from National Natural Science Foundation of China, outside the submitted work; SM reports grants from National Natural Science Foundation of China, outside the submitted work.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Xiao R, Mai S. Response to The Hunt for the Perfect Biomarker in Nasopharyngeal Carcinoma—the RRAS "race" beyond Epstein-barr virus? Transl Cancer Res 2019;8(6):2506-2507. doi: 10.21037/tcr.2019.10.01

