



The driving role of cancer-testis genes: a new perspective for cancer researches

Cheng Wang^{1,2}, Hongbing Shen^{1,2}, Zhibin Hu^{1,2}

¹State Key Laboratory of Reproductive Medicine, ²Department of Epidemiology and Biostatistics, Jiangsu Key Lab of Cancer Biomarkers, Prevention and Treatment, Collaborative Innovation Center for Cancer Personalized Medicine, School of Public Health, Nanjing Medical University, Nanjing 210029, China

Correspondence to: Zhibin Hu. State Key Laboratory of Reproductive Medicine, Nanjing Medical University, No. 818 East Tianyuan Road, Nanjing 210029, China. Email: zhibin_hu@njmu.edu.cn.

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We appreciate the attention Kaczkowski *et al.* paid to our previous work (1), in which we provided a source of candidate epi-driver genes by studying the cancer-testis (CT) gene expression pattern in normal and tumor tissues. The identification of CT genes and the link between CT genes and cancer epi-drivers are attractive but less-studied topics. We believe that the study of CT genes with special expression patterns provides new perspectives for the identification of cancer epi-drivers.

One of the major points raised by Kaczkowski and his colleagues was that aberrantly expressed genes should not be proposed to be epi-drivers without supporting epigenetic data. They firstly mentioned that several other mechanisms such as mutations in regulatory regions/factors and copy number alterations might also contribute to the expression changes of genes in cancer cells. We don't think that these mechanisms prevent us from identifying driver genes by investigating aberrantly expression patterns, because epigenetic regulation is widely accepted as one of the major regulation mechanisms of gene expression (2). In addition, previous studies have showed that epigenetic regulators contribute greatly to restricted expression pattern of genes involved in the development of germ cells (3). Being testis-restrictedly expressed genes, it is highly possible that many CT genes can be activated in cancer cells through similar epigenetic modifications in germ cells. We also noticed that CT genes shared several characters with epi-drivers: (I) they were activated aberrantly in tumor tissues; (II) their activation in cancer cells may provide malignant phenotype and selective advantage (gametic recapitulation theory) (4).

Thus, we proposed our hypothesis that CT genes might act as epi-driver genes.

Additional evidence further supports the hypothesis. We found that CT genes were more likely to show aberrant activated expression patterns in cancer than other genes. In addition, although there was no known epigenetic evidence, we observed that *MEIOB* expression was not associated with genomic alterations (including mutations and copy number changes) near *MEIOB*, but was associated with global copy number aberration level, suggesting that the activation of meiosis-specific protein *MEIOB* may result in genome instability in cancer cells. The driving role of another extremely-high expressed CT gene (EECTG) *LIN28B* in multiple cancers has been clearly stated (5,6), but its CT expression pattern was first reported. More importantly, the *LIN28B* and *let-7* regulation loop have been extensively explored (5-7), which evidently suggested that *LIN28B* was an epi-driver gene.

With these evidences, we think that CT genes are a source (but not the only source) of epi-driver candidates. In our previous study, we aimed to provide a comprehensive landscape of CT genes and to suggest their potential to be epi-drivers rather than to tell all CT genes should be epi-driver genes of cancer. Actually, even for significantly-mutated genes, which are candidates of mut-drivers, additional mechanism studies are warranted to clarify their driving role. Thus, we agree that further epigenetic evidence is necessary to elucidate the activation mechanisms of CT genes in the next stage investigation.

Unlike many cancer studies, we did not use adjacent

cancer tissues as control, because they are not equal to normal tissues and may induce unnecessary bias (8,9). They are widely applied simply because a paired normal tissue can hardly be obtained from a tumor patient. As we have showed that CT genes are not expressed or very little expressed in a large number of normal tissues, we believe that it is an advantage of our study to avoid using adjacent cancer tissues as controls. However, we recommend to use adjacent cancer tissues as controls when studying CT genes with low expression level in tumor tissues.

Despite the importance of CT genes, we considered them as a supplement rather than a replacement of mut-drivers. Here, we want to point out that CT genes are aberrantly activated in cancer and should be classified as potential oncogenes. As we all know, a tumor suppressor such as TP53 or PTEN usually cannot be used as a target of molecular targeted therapy. Thus, cancer patients can hardly benefit from the identification of mut-driver genes, even though total mutation rates of the mut-driver genes sometimes reach 100%. It is worth noting that some important tumor suppressors are transcription factors and their mutation may be involved in the activation of CT driver genes. Thus, study on the activation of CT genes and high-frequency tumor suppressor mutations may help provide additional targets for patients with tumor suppressors' mutations in future precise medicine and may have important clinical implications.

However, as mentioned by Kaczkowski and his colleagues, clinical transformation is difficult, not only for CT genes, but for all known cancer driver genes, though comprehensive mutations spectrums have been fully described in many cancer types. Our study emphasized the driving role of a group of CT genes instead of focusing only on the immunogenicity of CT antigens, thus our results may have tremendous clinical value in both immunotherapy and molecular targeted therapy. Kaczkowski and his colleagues also mentioned neo-antigens, which was a source of mutated genes with products of tumor specific immunogenic protein. Unsurprisingly, we noticed that Li *et al.* had recently developed a computational method to infer potential immunogenic neo-antigens (10). SPAG5 and TSSK6 were predicted as putative immunogenic cancer/testis antigens in multiple cancers (10). This analysis successfully connected the neo-antigen and CT genes and indicated the importance of these genes in cancer therapy.

At last, we appreciate that the authors emphasize the importance of CT non-coding RNAs (CT-ncRNAs). We observed that CT-ncRNAs may contribute to the activation

of CT genes and serve as one of the epigenetic activations of CT genes. However, our bioinformatics analyses were largely limited because little information on ncRNAs was known in both cancer and germ cell development. We hope that more comprehensive studies can further decode the connection between CT-ncRNAs and CT genes and illuminate underlying mechanisms.

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Footnote

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References

1. Kaczkowski B, Hashimoto K, Carninci P. Epi-drivers and cancer-testis genes. *Transl Cancer Res* 2016;5:334-6.
2. Jaenisch R, Bird A. Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. *Nat Genet* 2003;33 Suppl:245-54.
3. Sasaki H, Matsui Y. Epigenetic events in mammalian germ-cell development: reprogramming and beyond. *Nat Rev Genet* 2008;9:129-40.
4. Simpson AJ, Caballero OL, Jungbluth A, et al. Cancer/testis antigens, gametogenesis and cancer. *Nat Rev Cancer* 2005;5:615-25.
5. Zhou J, Ng SB, Chng WJ. LIN28/LIN28B: an emerging oncogenic driver in cancer stem cells. *Int J Biochem Cell Biol* 2013;45:973-8.
6. Nguyen LH, Robinton DA, Seligson MT, et al. Lin28b is sufficient to drive liver cancer and necessary for its maintenance in murine models. *Cancer Cell* 2014;26:248-61.
7. Piskounova E, Polytarchou C, Thornton JE, et al. Lin28A and Lin28B inhibit let-7 microRNA biogenesis by distinct mechanisms. *Cell* 2011;147:1066-79.
8. Braakhuis BJ, Leemans CR, Brakenhoff RH. Using tissue adjacent to carcinoma as a normal control: an obvious but questionable practice. *J Pathol* 2004;203:620-1.
9. Huang X, Stern DF, Zhao H. Transcriptional Profiles from Paired Normal Samples Offer Complementary Information on Cancer Patient Survival--Evidence from TCGA Pan-Cancer Data. *Sci Rep* 2016;6:20567.
10. Li B, Li T, Pignon JC, et al. Landscape of tumor-infiltrating T cell repertoire of human cancers. *Nat Genet* 2016;48:725-32.

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