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Commentary

Regulatory RNA Editing Sites in Cancer: Prediction and Beyond

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The major form of post-transcriptional RNA editing in mammalian animals, Adenosine to Inosine (A-to-I) RNA editing, is catalyzed by the *ADAR* gene family. The potential oncogenic role and clinical relevance of individual RNA editing sites in cancer have been extensively studied in recent studies, especially those characterizing the landscape of RNA editing across various cancer types via The Cancer Genome Atlas (TCGA) (Xu et al., 2018). For example, Han et al. systematically characterized the A-to-I RNA editing profiles of thousands of patients and revealed a diverse pattern of RNA-editing patterns in different cancer types (Han et al., 2015). They identified appreciable numbers of clinically relevant editing sites, and further demonstrated the functional effects of several nonsynonymous RNA editing sites through cell viability assay and drug sensitivity assay. Furthermore, Wang et al. systematically characterized the miRNA editing landscape across various cancer types and identified several A-to-I miRNA editing hotspots (Wang et al., 2017). They further showed the functional switch of miR-200b by targeting a new target to activate tumor invasion instead of suppression. Similar to this, Pinto et al. used the same dataset from TCGA and demonstrated that edited versions of miRNAs tend to suppress expression of oncogenes, and many miRNA binding sites are differentially edited (Pinto et al., 2017). Gong et al. recently characterized the functional effects of RNA editing on long noncoding RNA (lncRNA) by potentially altering the lncRNA secondary structure and miRNA-lncRNA interactions (Gong et al., 2017).

Beyond the individual editing sites, the genome-wide editing level may also contribute to transcriptomic diversity in human cancer. For example, Paz-Yaacov et al. developed an approach to estimate a global editing index (EI), and showed that this EI could actually predict the patient survival in several cancer types (Paz-Yaacov et al., 2015). In this issue, Sharpnack et al. developed a novel computational pipeline to identify RNA editing sites with significant correlation between its editing level and gene expression level, which differs from previous strategies. They defined these editing sites as regulatory editing sites (Sharpnack et al., 2017). Through analysis of TCGA lung adenocarcinoma data, they prioritized genes based on number of regulatory editing sites, and identified a potentially novel cancer-related gene, *APOL1*. The editing sites on 3′-UTR of *APOL1* may alter the RNA secondary structure, the binding of RNA binding proteins (RBPs) and miRNAs. Interestingly, RNA editing sites on *APOL1* is associated with the overexpression of *APOL1* itself, and lead to worse survival. Moreover, those genes with the largest number of regulatory editing sites are enriched in apoptosis pathway and innate immune related pathways, which may imply a novel connection between known regulatory functions of *ADAR* and its role in lung adenocarcinoma.

The *ADAR* gene family plays significant roles in regulating the dynamic landscape of RNA editing. A recent study demonstrated that *ADAR1* primarily edits the repetitive sites, *ADAR2* mainly edits the nonrepetitive coding sites, while the catalytically inactive *ADAR3* probably inhibits the editing process across a large number of normal tissues from the Genotype-Tissue Expression (GTEx) project (Tan et al., 2017). However, it is not clear whether this principle of regulation is maintained in disease, e.g., cancer. Particularly in cancer, *ADAR1* is often overexpressed to act as an oncogene, while *ADAR2* is usually downregulated to act as a tumor suppressor gene (Chan et al., 2016). More interestingly, the disrupted equilibrium between *ADAR*s may play key roles in interfering with the balance of RNA editing, such that patients with *ADAR1* overexpression and *ADAR2* downregulation exhibit increased risk of cancer (Chan et al., 2014). In this study, Sharpnack et al. presented consistent pattern with previous studies that *ADAR1* is amplified in lung adenocarcinoma. Remarkably, they showed that *ADAR1* amplification is associated with decreased immune cell concentrations; patients with *ADAR1* amplification had significantly fewer CD8 + T cells, CD4 + T cells and other immune cells. Despite the fact that the authors could not distinguish two *ADAR1* isoforms, including *ADAR1* p110 and p150, this result highlighted the potential utility of RNA editing and/or the *ADAR* gene family in cancer immunotherapy.

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Recent studies detected millions of RNA editing sites through next-generation sequencing (NGS), while the vast majority of these RNA editing sites have unknown functions (Gong et al., 2017). RNA editing sites could have pivotal functions on protein-coding genes, including introns and 3′-UTRs, miRNAs, as well as lncRNAs (Xu et al., 2018). They could also be evaluated at the whole transcriptome level (e.g., as EI). Particularly in this study, the functional impact of RNA editing sites is estimated at the gene level as the number of regulatory editing sites per gene. This method can be applied to any dataset with matched RNA editing level and gene expression. Nevertheless, further studies are necessary to better utilize RNA editing, at individual sites, gene level, and the whole transcriptome level, in precision medicine as diagnostic, prognostic, and therapeutic markers.

Disclosure

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