Molecular Therapy
Nucleic Acids
Commentary

Circular RNA in liquid biopsy as biomarkers toward precision medicine

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Circular RNA (circRNA), a group of single-stranded RNA with circular configurations produced by backsplicing, have been widely identified for both diagnostic and prognostic applications in various human diseases. In this study, Zheng et al. applied comprehensive transcriptomic analyses on the adjacent non-tumorous tissues and tumorous tissues from patients with intrahepatic cholangiocarcinoma (ICC) and plasma-derived exosomes from both patients with ICC and healthy individuals.[1] The study revealed that circRNAs in exosomal fractions well distinguished healthy individuals and patients with ICC. Moreover, the authors highlighted novel subgroups of ICC defined by using transcriptomic profiling. This information consolidated and exemplified the great clinical potential for the application of circRNA in better classification of ICC and also for the development of better strategies targeting distinct groups of ICC (Figure 1).

The diagnostics of a given disease are attributed to the convenience and reachability of diagnostic tools. The development of ICC at early stages is typically asymptomatic and difficult for diagnosis. In this study, the authors set out to develop a non-invasive tool for early detection of ICC and demonstrated a potentially game-changing tool for the early diagnosis of ICC by using comprehensive and unbiased characterization of circRNA profiles on both solid and liquid biopsies. Adjacent non-tumorous tissues and tumorous tissues were first collected and analyzed. The authors not only confirmed the previous known biomarkers—ciRS-7/CDR1as and circ-0000284—but also acquired an additional panel of differentially expressed circRNA. These results are promising and showed that circRNA profiling is fairly applicable to serve as a diagnostic tool to distinguish non-tumorous and tumorous tissues.

Nevertheless, to include a broader spectrum of patients with ICC, the authors integrated additional transcriptomic profiles collected in The Cancer Genome Atlas (TCGA) and identified 3 distinct groups of patients with ICC, suggesting that ICC is a disease with heterogonous origins and/or composition. This discovery is consistent to the not-yet-consensual classification of ICC, which includes at least 4 subtypes of ICC according to anatomic/cellular origins of disease and histological characteristics.[2,3] It was reported that molecular profiling using genomic mutation can distinguish ICC originating from a small or large duct.[2,4] The results of this study further push the limit for a finer classification of ICC using transcriptomic profiling. Of special note, there were no genetic profiles or histological or pathological details provided for the ICC tissues analyzed in this study, and thus the link between these three newly classified subgroups and pre-existing classified subtypes remains to be established in the future. Despite this missing link, the authors indeed made a novel discovery that one of the subgroups associated with the feature of T cell exhaustion and neutrophil extracellular trap (NET) and thus coined the term "immunogenic ICC." The idea of T cell exhaustion is a currently evolving concept referred to a state of differentiated T cells with a declined capacity to secrete cytokines and elevated expression of inhibitory receptors (such as PD-1) in response to persistent exposure of antigen and/or chronic T cell receptor (TCR) stimulation. Knowing the properties of the T cells infiltrated in tumorous tissues is an important prior task for the success of immunotherapy. Thus, the authors provided a novel insight into how circRNA can be a novel diagnostic biomarker for identifying patients with ICC suitable for PD-1 blockade treatment. A recent study has shown that pembrolizumab, a full-length monoclonal antibody against the immune checkpoint PD-1, restored the activity of exhausted T cells,[5] providing a piece of supporting evidence that this particular ICC type with exhausted T cell infiltration may be a good candidate for immunotherapy (Figure 1). In addition to T cell exhaustion, genes related to NET were upregulated in the immunogenic ICC tissues. NET is an emerging player implicated in many human diseases. In the field of cancer biology, it has been reported that systematic stimuli of NET causes circulating tumor cells trapped at remote organs. It should be noted that such NET stimuli usually come from inflammatory stimulation. It will be worthwhile to further clarify whether the patients with immunogenic ICC in this study suffered such NET stimuli.

The authors further characterized the top differentially expressed circRNAs in tumorous and adjacent non-tumor tissues from patients with immunogenic ICC and showed that the circRNA profile is a practical tool for distinguishing immunogenic ICC tissues. To further maximize its flexibility in clinical application for routine examination,

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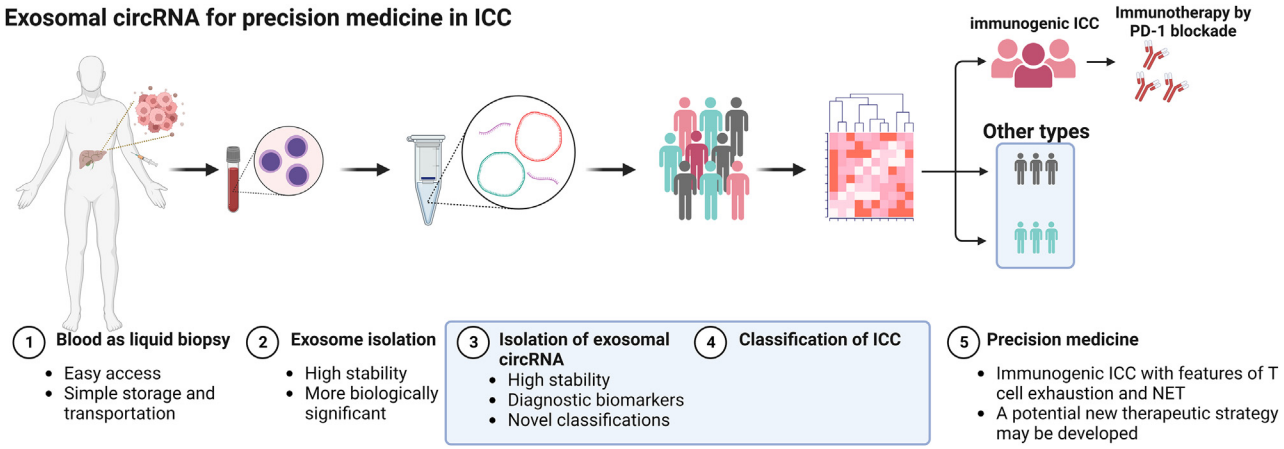

Figure 1. Exosomal circRNA as biomarkers for better diagnostics and novel classification of ICC.

the authors used the circRNA collected from exosomes and revealed that circRNAs in exosomes have even better power to distinguish patients with immunogenic ICC from healthy individuals. The application of circRNA in exosomes shows significant superiority over other types of molecules and liquid biopsy. For example, exosomes exist in almost all body fluids, and both circRNAs and exosomes harbor high stability. The high biological stability reduces the cost of sample storage and relieves the difficulty of transportation, both of which greatly improve the clinical applicability. Nevertheless, the information from circRNAs encapsulated in exosomes are more biologically relevant than cell-free nucleic acids, which are mainly released from necrotic or apoptotic cells. Thus, both circ-PTPN22 and circ-ADAMTS6 will be convenient diagnostic biomarkers for patients with ICC. It will certainly be worthwhile to further investigate the biological functions of circ-PTPN22 and circ-ADAMTS6 during the development of ICC to evaluate whether they can serve as prognostic markers or therapeutic targets as well.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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