Letter to the Editor

The important role of the eccDNA in tumors

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Response to: Qian L, Xia X, Liu J, *et al.* Characterization of extrachromosomal circular DNA in patients with acute myeloid leukemia. Proof-of-concept report using a cohort from Beijing and Shanghai. Ann Transl Med;10:843.

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We would like to thank Qian *et al.* for their interest in our published work about the potential function of extrachromosomal circular DNA (eccDNA) in esophageal squamous cell carcinoma (ESCC) (1). We have read their article revealing the characterization of the eccDNA in acute myeloid leukemia (AML) with great interest (2).

In the article, the authors did not mention the total amount of detected eccDNAs in their samples and showed only 298 up-regulated and 71 down-regulated eccDNAs in AML patients compared to healthy controls, which is far less than the number in our work (1,2). Maybe it is due to tumor specificity or different sequencing methods. The authors identified a cluster of up-regulated eccDNAs derived from the mitochondrial genome, however, our work detected no such eccDNAs. Additionally, the study observed altered biological processes related to up-regulated eccDNAs and no process or network related to down-regulated eccDNAs. Nevertheless, our work demonstrated various biological processes playing key roles in ESCC progression by analysis of either up-regulated or down-regulated eccDNAs (1,2). These differences may be caused by less amount of differently expressed eccDNAs. We think maybe the optimized methods in eccDNA extraction and amplification or sequencing with higher sensitivity and specificity is possible to have more conclusive results in AML study.

Since the discovery, eccDNAs have been reported to contribute to many malignancies (3). As far as we know, there are several mechanisms for their potential function in tumors. Firstly, long-size eccDNAs containing the sequence of oncogenes can lead to oncogene amplification and participate in tumors. Oncogene transcription is more efficient in eccDNA amplification compared to matched linear DNA (4). Secondly, Zhu *et al.* (5) recently demonstrated that eccDNAs can contact with specific chromosomal genes through RNA polymerase II—mediated chromatin interaction and function as a mobile enhancer to activate the expression of genes relevant to oncogenesis pathways. Thirdly, eccDNAs with limited size rarely carrying full length of protein-coding sequence can encode regulatory short RNAs, such as microRNA and siRNA, to modulate gene expression and participate in tumor biology (6). Fourthly, eccDNAs with limited size possibly function as sponges for transcription factors to regulate gene expression indirectly (7). Of course, other possible mechanisms, such as immune response to naked DNA from eccDNAs, remain to be elucidated. To be noted, our work and previous reports have shown that the length of differently expressed eccDNAs in tumors varies and they are unevenly distributed in different genomic regions, such as 5'- and 3'-untranslated regions (UTRs), CpG island regions, exons etc. (1,8). Maybe different categories of eccDNAs function by different mechanisms. The important role of eccDNAs in tumors still needs to be investigated in further studies.

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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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