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Circling back to epigenetic regulation in osteosarcoma: Comment on 'Hsa_circ_0088212-mediated miR-520h/APOA1 axis inhibits the osteosarcoma progression' by ' Hao Peng'

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A B S T R A C T

Osteosarcoma is a genetically complex cancer, thus there are increasing efforts to identify biomarkers and regulators within the epigenome that can better predict patient outcomes and provide new therapeutic targets. In this commentary, we have evaluated the work of Peng and colleagues on the identification and function of the signaling axis circ_0088212/miR_520 h/APOA1 in osteosarcoma. We provide the context of how novel it is to demonstrate the anti-tumor functions of APOA1 and not just correlative gene expression with patient outcome. We further postulate why some studies involving circRNAs in osteosarcoma contradict one another. We conclude that the study performed by Peng and colleagues was performed with enough rigor to give confidence that circ_0088212 is a bona fide tumor suppressor in osteosarcoma.

Circular RNAs (circRNAs) are becoming increasingly useful as a biomarkers and therapeutic targets to treat various cancers. These gene expression regulators share similar molecular functions as micro RNAs and can exhibit both antitumor and pro-tumorigenic effects depending on the context. Thus, circRNAs can be classified as tumor suppressors or oncogenes. CircRNAs are covalently closed/looped single-stranded RNA molecules, created by back-splicing of the pre-mRNA and commonly considered as splicing errors. But recently a large number of circRNAs have been identified to be associated with the progression of several cancers, including osteosarcoma [1–3].

In the article by Hao Peng and colleagues, they recently studied a novel circRNA, circ_0088212, that was identified by bioinformatic analysis to have putative biological functions as a tumor suppressor in osteosarcoma [4]. Furthermore, through bioinformatic analysis an interacting miR and a target gene were implicated in a signaling axis that could regulate osteosarcomagenesis. The in-depth characterization of the circ_0088212/miR-520 h/APOA1 axis confirmed the bioinformatic assumptions that in osteosarcoma circ_0088212 is down-regulated, which results in a lack of inhibition of miR-520 h. The overexpression of miR-520 h in osteosarcoma allows for transcriptional silencing of the cell adhesion gene APOA1.

The APOA1 is the major protein of high density lipoprotein with an unknown mechanism regarding cancer, but numerous studies have shown that APOA1 expression is down regulated in several cancers and that low expression portends a worse prognosis [5]. It is hypothesized that APOA1 dampens the cancer hallmark of tissue inflammation, thus supporting the finding by Peng et al. that APOA1 inversely correlates with osteosarcoma progression [4]. The overexpression experiments of APOA1 highlighted that APOA1 expression not only associates with osteosarcoma, but it functions as a tumor suppressor. The decrease in cell migration and invasion and the increase in apoptosis in the presence of oe-APOA1 (overexpression) support these conclusions. These results should encourage others to look beyond the correlative data to the tumor suppressor functions of APOA1 in other cancers.

CircRNAs are not novel regulatory elements in osteosarcoma. The following table highlights known circRNAs and their target miR (Table 1).

The circRNAs are molecular sponges that generally inhibit the oncogenic actions of the miRs; however, there are some examples where binding can enhance the transcriptional regulation of miRs. While circRNAs and miRs have been studied for more than a decade in osteosarcoma, they are no less enigmatic after a decade of research. This can partly be attributed to the genomic complexity seen in osteosarcoma samples making it difficult to find consistent patterns across multiple samples. However, general trends should be ascertained regardless of the cohort origination and variations seen in genomic instability. It is when results completely contradict each other in the field of biomarkers in osteosarcoma that leaves the scientific community scratching their heads.

Recently two studies were published independently from similar

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Table 1
CircRNAs and known miR targets.

circRNA	Target miR
circ_0001564	miR-29c-3p
circ-0016347	miR-214
circGLI2	miR-125b-5p
circ-03955	miR-3662
circ-0001785	miR-1200
circPVT1	miR-52b
circ_NT5C2	miR-448
circ_0009910	miR-449a

geographic areas and similar demographic patient cohorts on circRNAs and their regulation on osteosarcoma cells. Both groups identified the circRNA through human clinical samples and validated their claims with benchtop science. Alarmingly, the two separate groups shared contrasting data for the same circRNA in the same disease state. In the study by Wu et al., they presented their findings that circCRIM1 was downregulated, similar to circ_0088212, thus acting as a tumor suppressor in osteosarcoma [6]. In juxtaposition to this study, Liu et al., demonstrated one year earlier that circCRIM1 was overexpressed in osteosarcoma, drawing the conclusion that circCRIM1 acts an oncogene to facilitate osteosarcomagenesis [7].

Despite using very similar approaches between the two studies, one slight difference is that the Liu et al. study confirmed that they were indeed measuring circRNA by performing RNase R degradation experiments [7]. One possible explanation is that these circRNAs undergo isoform switching between their linear form and the circular form [8]. While yet unproven, it would be fascinating if a linear RNA and a closed loop of the same sequence had opposing molecular functions. In the current study by Peng and colleagues, they performed the requisite RNase R treatments on their isolated samples to confirm that they indeed were measuring and testing the effects of the circular isoform of circ_0088212 [4].

Osteosarcoma is a complicated cancer with rampant genomic instability. Markers that can be consistently associated with outcomes could prove beneficial in the detection and management of this disease. Even more advantageous is the identification of a signaling axis with known contributions to the progression of the disease. Peng and colleagues have identified such a signaling axis in osteosarcoma with respect to circ_0088212/miR-520h/APOA1 [4]. Understanding that miR-520h is the overexpressed driver in this axis promoting osteosarcoma progression, it is feasible to provide circ_0088212 mimetics to exert an anticancer effect on these cells.

CRediT authorship contribution statement

Kaniz Fatema: Writing – original draft, Writing – review & editing. **Jared J. Barrott:** Writing – original draft, Writing – review & editing.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Reference

[1] D.-.H. Bach, S.K. Lee, A.K. Sood, Circular RNAs in Cancer, Mol. Ther. - Nucleic Acids 16 (2019) 118–129, https://doi.org/10.1016/j.omtn.2019.02.005.
[2] H. Jin, X. Jin, H. Zhang, W. Wang, Circular RNA hsa-circ-0016347 promotes proliferation, invasion and metastasis of osteosarcoma cells, Oncotarget 8 (2017) 25571–25581, https://doi.org/10.18632/oncotarget.16104.
[3] B. Chen, S. Huang, Circular RNA: an emerging non-coding RNA as a regulator and biomarker in cancer, Cancer Lett. 418 (2018) 41–50, https://doi.org/10.1016/j.canlet.2018.01.011.
[4] F. Liu, X. Zhang, F. Wu, H. Peng, Hsa_circ_0088212-mediated miR-520h/APOA1 axis inhibits osteosarcoma progression, Transl. Oncol. 14 (2021), 101219, https://doi.org/10.1016/j.tranon.2021.101219.
[5] K. Georgila, D. Vyrla, E. Drakos, Apolipoprotein A-I (ApoA-I), Immunity, Inflammation and Cancer, Cancers (Basel) 11 (2019) 1097, https://doi.org/10.3390/cancers11081097.
[6] Wu, P.; Kong, Y.; Dai, Z.; Liu, W.; Zhao, Z. The circular RNA circCRIM1 inhibits osteosarcoma progression through sponging miR-513. Mamm. Genome2021, 10.1007/s00335-021-09903-2, doi:10.1007/s00335-021-09903-2.
[7] J. Liu, G. Feng, Z. Li, R. Li, P. Xia, Knockdown of CircCRIM1 Inhibits HDAC4 to Impede Osteosarcoma Proliferation, Migration, and Invasion and Facilitate Autophagy by Targeting miR-432-5p, Cancer Manag. Res. 12 (2020) 10199–10210, https://doi.org/10.2147/cmar.S253130.
[8] J. Zhang, S. Chen, J. Yang, F. Zhao, Accurate quantification of circular RNAs identifies extensive circular isoform switching events, Nat. Commun. 11 (2020) 90, https://doi.org/10.1038/s41467-019-13840-9.