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Peer Review

Review of: "Identification of Epigenetic Regulators of Fibrotic Transformation in Cardiac Fibroblasts Through Bulk and Single-Cell CRISPR Screens"

Samiksha Mahapatra, PhD[1]

1. University of California, San Diego, United States

This paper provided key insights into the role of epigenetic regulation in cardiac fibrosis. The work was systematic and thorough; particularly, the Perturb Seq analysis was very well executed. The rescue with KAT5 inhibition on patient-derived fibroblasts was a good strategy to show clinical relevance to the findings presented here.

Critique regarding the manuscript:

1. The gating strategy in Extended Figure 1 should be explained in detail in the results section.
2. GO term analyses should be done on the three additional fibroblast subpopulations, and their identity should be further elucidated in the results section. You can use the Enrichr website and copy and paste the up- and downregulated genes in each population to further analyze these populations in terms of biological processes and molecular functions.
3. Since Wdrs82 and Scrap depletion showed the most profound effects on chromatin accessibility, why can't they be used as inhibitors just like KAT5 to see if they could have better effects than KAT5? You could potentially use them as a combination and see if you get an additive effect on fibrosis inhibition, which is adding both inhibitors at the same time to see if there is a better effect than adding single inhibitors.
4. Have you performed experiments to see the role of KAT5 inhibition in late-stage fibrosis? After the fibroblasts have turned into myofibroblasts and then added KAT5 inhibition, would it show a decrease in the fibrotic response? What you have shown here is that you add a KAT5 inhibitor to

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unstimulated fibroblasts and then add TGFb for 24 hours. What if you switch the sequence and add TGFb for 24 hours first and then add the KAT5 inhibitor?

5. Additional comments are added to the manuscript, which I have attached to my review. Overall, the work is very interesting and well thought out.

Attachments: available at https://doi.org/10.32388/9YF4FV

Declarations

Potential competing interests: No potential competing interests to declare.