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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"

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Article Information

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

Authors: Laura Pilar Aguado Álvaro et al.

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Reviewer: [SJBG]

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Evaluation Rubric

Criterion	Brief Description	Score (0–5)
Scientific Relevance	Innovative topic with current biomedical impact	5
Originality	Novel contribution, unique combination of technologies, previously unreported findings	5
Clarity and Quality of Scientific Writing	Clear technical language, professional style, precise terminology	4.5
Structural Coherence (IMRaD)	Proper development of Introduction, Methods, Results, and Discussion	5
Methodological Rigor	Solid experimental design, replication, proper controls, detailed methods	5
Data Analysis and Result Validity	Modern bioinformatics, correct statistics, multi-layered evidence integration	5
Interpretation and Critical Discussion	Substantial discussion with bibliographic relation and therapeutic implications	5
Bias Identification and Control	Use of murine/human systems, negative controls, cross-validations	4.5
Currency and Relevance of References	Recent and relevant literature in the field	5
Clinical or Translational Applicability	Identification of KAT5 as potential anti-fibrotic pharmacological target	5

Total Score: 49 / 50

General Comments

This is a highly robust and original study employing cutting-edge functional genomics technologies. The identification of specific epigenetic regulators such as KAT5 opens new therapeutic opportunities for

targeted anti-fibrotic strategies.

The validation in human fibroblasts adds direct translational value. Methodological quality is excellent; however, the final version of the manuscript should correct character encoding errors (e.g., '�'). It is recommended that the authors pursue in vivo validations in animal models of chronic cardiac fibrosis to support the therapeutic claims.

Suggested In Vivo Validation Approach

To further strengthen the translational impact of this study, I recommend the use of a well-established in vivo model of cardiac fibrosis for validating the therapeutic potential of KAT5 inhibition. Specifically, the murine model of myocardial infarction (MI) induced by permanent ligation of the left anterior descending (LAD) coronary artery in C57BL/6 mice would be highly appropriate. This model reliably induces robust cardiac fibrosis, allowing for assessment of both preventive and therapeutic interventions. Treatment with KAT5 inhibitors (e.g., NU-9056 or TH1834) could be administered either prophylactically or therapeutically post-MI. Outcomes should include histological quantification of fibrosis, echocardiographic evaluation of cardiac function, and molecular analysis of fibrosis-related gene expression. Given that previous reports have shown beneficial effects of KAT5 inhibition on post-MI cardiac function, this in vivo validation would directly support the authors' claims and reinforce the therapeutic promise of targeting KAT5 in fibrotic heart disease.

Declarations

Potential competing interests: No potential competing interests to declare.