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LETTER

Comment On: "Integrating Single-Cell and Microarray Data to Explore the Role of Autophagy-Related Gene Atg7 in Osteoporosis" [Letter]

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Dear editor

We read with great interest the recent article by Lin et al, who integrated single-cell and microarray datasets to identify ATG7 as an autophagy-related gene associated with osteoporosis and further suggested its role in mesenchymal stem cell differentiation[1] The study is timely, and the effort to combine multi-omics analysis with experimental validation is commendable. We would, however, like to respectfully raise several points that may help further contextualize the strength of the mechanistic and translational conclusions.

First, the discovery framework may be somewhat sensitive to cohort structure and prior feature restriction. The single-cell analysis included only 4 osteoporosis and 4 control samples, and the bulk training and validation cohorts were also relatively small. In addition, ATG7 was not identified from an unrestricted disease-wide screen, but from the overlap between differential expression results and a predefined panel of 30 core autophagy genes.[1] While this is a reasonable candidate-selection strategy, it may also increase sensitivity to donor composition, normalization choices, and prior gene-list restriction. Recent methodological studies have suggested that donor effects and analytic bias can materially influence single-cell differential expression results when not explicitly modeled.[2]

Second, the proposed EYA1-ATG7 axis may currently be better viewed as an informative hypothesis than as a fully established mechanism. In the present study, this axis is supported primarily by pseudotime analysis and CellChat-based ligand-receptor inference. These approaches are valuable for generating biologically meaningful hypotheses; however, recent reviews have emphasized that cell-cell communication tools differ substantially in assumptions, scoring frameworks, and database design, and that important limitations remain unresolved.[3] Likewise, newer work has noted that conventional pseudotime is fundamentally a descriptive ordering rather than a direct representation of biological time.[4] Additional orthogonal evidence, such as spatial validation, EYA1-high cell isolation, lineage-resolved perturbation, or bidirectional functional testing of EYA1 and ATG7, would likely strengthen this mechanistic interpretation.

Finally, the translational implications may merit somewhat more cautious framing. Although ATG7 overexpression in OVX-derived BMSCs restored autophagy- and osteogenesis-related markers, these findings do not yet establish necessity, pathway specificity, or therapeutic efficacy in vivo. Human data have also suggested that osteoporosis may involve a broader reduction in autophagy activity rather than a single immediately actionable molecular node.[5] In this context, the current evidence may more securely support ATG7 as a promising associated candidate than as a validated critical regulator or therapeutic target.

Overall, this study provides an interesting and potentially important direction for future work. We believe that modest tempering of the causal and translational language, together with additional donor-aware analyses and orthogonal validation, would further strengthen the reliability and clinical interpretability of the conclusions.

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Author Contributions

JL: Methodology, Writing – original draft, Writing – review & editing, Supervision. CW: Methodology, Supervision, Writing – review & editing. Both authors gave final approval of the version to be published, agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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