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LETTER TO THE EDITOR Open Access

Letter to the Editor: Single-cell multi-omics reveals DUSP9 as a key regulator of cancer stemness and a potential therapeutic target in hepatocellular carcinoma

Jingyang Zhang[1], Qin Zheng[2*] and Mulin Liu[1*]

To the Editor,

We read with great interest the recent study by Xu et al. [1], which elegantly integrates single-cell and spatial transcriptomics to delineate the landscape of DUSP9$^+$ hepatocellular carcinoma (HCC) cells. We particularly commend the authors for identifying the spatial co-localization of DUSP9$^+$ stem-like cells with cancer-associated fibroblasts (CAFs), proposing a "niche-dependent" mechanism of tumor maintenance. While the study offers compelling bioinformatic insights and identifies a potential inhibitor (AKOS000434153), we wish to offer two complementary methodological perspectives to support their planned future preclinical validations, thereby further bridging the gap between their computational predictions and translational applications.

The discrepancy between TME-centric insights and monoculture-based validation

A core finding of the study is the specific spatial localization of DUSP9$^+$ cells within CAF-rich immunosuppressive niches [1]. The authors' CellChat analysis further predicted specific ligand-receptor interactions (e.g. THBS2-SDC4) between CAFs and tumor cells that ostensibly support stemness. However, the subsequent functional validations: including siRNA knockdown and drug sensitivity assays, were conducted exclusively in 2D monocultures of HepG2 and Huh7 cells [1].

This experimental design disconnects the "seed" from its "soil". Since the authors hypothesize that the CAF-enriched niche is critical for maintaining the DUSP9$^+$ stem-like phenotype, testing DUSP9 inhibition in isolation potentially oversimplifies the therapeutic landscape. Stromal signals often confer resistance to therapy. Therefore, we suggest that validating the efficacy of AKOS000434153 in a co-culture system (with CAFs) or a 3D spheroid model would be essential to confirm that DUSP9 inhibition remains effective even in the presence of protective stromal signals. In the event that establishing these complex models is technically limited, utilizing CAF-conditioned media (CM) presents a highly practical and robust alternative to assess the paracrine influence of the stroma. This would robustly support the authors' claim of targeting the "immune barrier".

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*Correspondence:
Qin Zheng
zhengqin90@126.com
Mulin Liu
liumulin87@126.com
[1]Department of Clinical Laboratory, First Affiliated Hospital of Dalian Medical University, Dalian, Liaoning 116011, China
[2]Department of Biochemistry and Molecular Biology, Liaoning Provincial Core Lab of Glycobiology and Glycoengineering, College of Basic Medical Sciences, Dalian Medical University, Dalian, Liaoning 116044, China

Necessity for biophysical validation of target engagement

The identification of AKOS000434153 via virtual screening represents a promising translational step. However, the current validation relies primarily on phenotypic readouts (e.g. sphere formation, cell viability) and downstream signaling changes (p-ERK/p-FOXO3 levels) [1]. While these results are consistent with DUSP9 inhibition, they do not definitively prove direct target engagement.

Small molecules obtained from virtual screening can sometimes act through off-target mechanisms or general toxicity, which mimics the phenotypic effects of the target gene knockdown. We highly commend the authors for explicitly acknowledging the preliminary nature of their drug discovery and the need for rigorous future preclinical validation. Building upon this rigorous self-assessment, we recommend that these future validation efforts incorporate biophysical assays such as Surface Plasmon Resonance (SPR) or Cellular Thermal Shift Assay (CETSA). Demonstrating direct physical binding would elegantly complement their functional findings, significantly enhancing the drug's potential for clinical translation while mitigating the biological interpretive limitations of relying solely on either approach.

Conclusion

In conclusion, Xu et al. provide a robust multi-omics framework linking DUSP9 to HCC stemness. Bridging the gap between microenvironmental observations and functional models, such as utilizing co-culture or conditioned media systems, along with complementing their preliminary drug findings with biophysical target engagement assays, will highly enrich their planned preclinical validations. We believe these complementary approaches will further solidify the translational relevance of this inspiring work.

Abbreviations

HCC	Hepatocellular carcinoma
CSCs	Cancer stem cells
DUSP9	Dual-specificity phosphatase 9
ERK	Extracellular signal-regulated kinase
CAFs	Cancer-associated fibroblasts

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