A small molecular glue that increases P53 level and suppresses tumor growth in vivo

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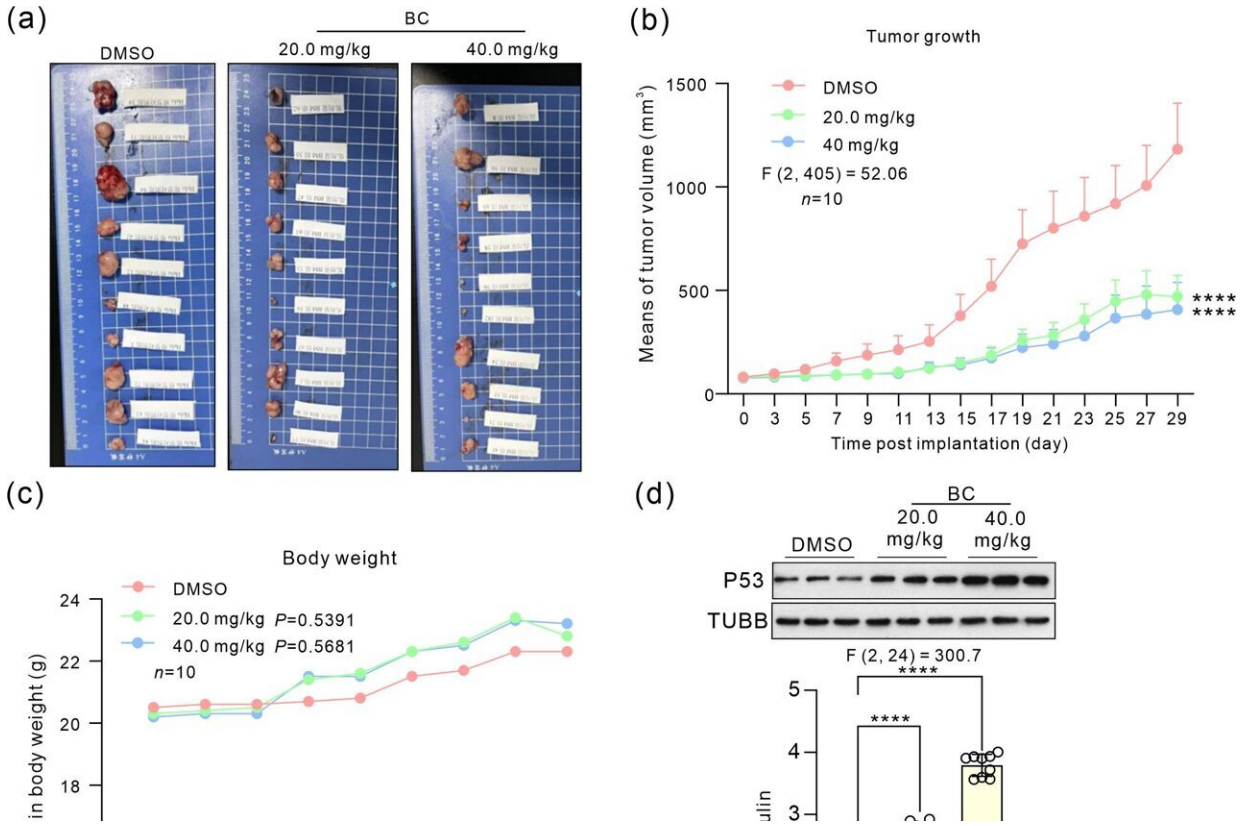

Anti-tumor effects of molecular glue BC. (a) Representative images of tumors in different treatment groups after 28 days. (b) Quantifications of anti-tumor activity of compound BC in the xenograft. (c) Body weight changes in the xenograft nude mouse model during the BC treatment period. (d) Representative western blots and quantifications of the P53 level in tumor tissues after BC treatment after 28 days. (e) Schematic model showing that BC mediated P53 upregulation nude mouse model by measuring the tumor volume. Credit: Science China Press

Molecular glues are typically small chemical molecules that act on the interface between the target protein and the degradation machinery to trigger ternary complex formation. Identification of molecular glues is challenging, and there has been a lack of target-upregulating molecular glues, which are desired for many targets such as tumor suppressor proteins (TSPs).

TSPs are usually degraded by the proteasome through polyubiquitination (poly-ub) by specific E3 ligases, whereas deubiquitinases (DUBs) can remove poly-ub conjugates to counteract these E3 ligases. Thus, small molecular glues that enhance the anchoring of TSPs to DUBs may stabilize them through deubiquitination.

Here, through small-molecule microarray-based technology and unbiased screening, the researchers identified three potential molecular glues that may tether P53 to the DUB USP7 and elevate the P53 level. Among them, bromocriptine (BC) is an FDA-approved drug showing the most robust effects. They further demonstrated that BC increased P53 stability via the predicted molecular glue mechanism engaging USP7.

To confirm the generality of the screening platform, they identified another USP7-engaging molecular glue that upregulates PTEN, which is another well-known TSP.

Taken together, the researchers established a potential screening platform that may facilitate the discovery of novel molecular glues stabilizing TSPs via engaging the DUB USP7. Similar strategies could be applied to the identification of other types of molecular glues that may benefit drug discovery and chemical biology studies.

The work is published in the journal *Science Bulletin*.

This study was led by Boxun Lu (State Key Laboratory of Medical Neurobiology and MOE Frontiers Center for Brain Science, Huashan Hospital, School of Life Sciences, Fudan University).

More information: Zhaoyang Li et al, P53 upregulation by USP7-engaging molecular glues, *Science Bulletin* (2024). DOI: 10.1016/j.scib.2024.04.017

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