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Abrogation of LBH589-induced autolysosome maturation by Mevastatin promotes cell death in triple-negative breast cancer cells

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There is a growing interest in the synergy of histone deacetylase inhibitors (HDACi) with other promising agents to achieve attractive therapeutic effects. We found that Mevastatin, a HMGCR reductase inhibitor, augments the antitumor efficacy of the HDACi LBH589 in triple-negative breast cancer (TNBC). The combination treatment with Mevastatin and LBH589 enhanced cell death of TNBC cells relying on a caspase-8 dependent apoptosis. Accompanied with the increased cell death, Mevastatin abrogated the autophagic flux triggered by LBH589, through activating LKB1-AMPK signaling and subsequently suppressing of mTOR, resulting in the blockade of VPS34/Beclin-1 complex formation and the inhibition of Rab7 prenylation, an active form of the small GTPase needed for autophagosome-lysosome fusion. In addition, our results indicate that disruption of autophagosome-lysosome fusion likely underlies Mevastatin-LBH589 synergistic anti-tumor effects. Furthermore, combinatorial treatment of metastatic TNBC with Mevastatin/LBH589 provoked a strong synergistic inhibition of tumor growth in MDA-MB-231 xenograft mice. These findings provide a potential therapeutic strategy for further clinical study and suggest that screening for novel autophagy modulators could be an efficient approach to strengthen the efficacy of HDACi in solid tumors.

Biography

Xiaoxiao Jiang is a PhD student in the Department of Biochemistry & Pharmacology. She has received her Bachelor's degree in Pharmacy from Shandong University and a Master's degree in Tumor Pharmacology from Fudan University. Currently, her research project is on post-translational modification and development of anti-cancer drug screening assay. Her research interests include cancer immunotherapy and high-throughput genome sequencing.

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