Molecular mechanism revealing therapeutic opportunities of histone deacetylases inhibitors in triple-negative breast cancer

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With the support by the National Natural Science Foundation of China, Ministry of Science and Technology of China and Chinese Academy of Sciences, the research team led by Prof. Geng Meiyu (耿美玉) and Ding Jian (丁健) from Shanghai Institute of Materia Medica, Chinese Academy of Sciences, demonstrated the therapeutic opportunities of histone deacetylases (HDACs) inhibitors in triple-negative breast cancer, which was published in *Cancer Cell* (2016, 30: 459—73).

HDACs inhibitors represent the first success of epigenetic-based cancer therapy. Several HDACs inhibitors have been approved for the clinical treatment of subtypes of hematological malignancies. Since the first clinical approval, increasing efforts have been invested to expand the clinical benefits of HDACs inhibitors in solid tumors, with hundreds of trials still ongoing. Nevertheless, the efficacy of HDACs inhibitors in solid tumors remains uncertain. Clinical trials at the moment tend to combine HDACs inhibitors with chemotherapy or other targeted therapies to enhance the clinical efficacy, yet they have met with limited success in solid tumors due to lack of mechanism-based combination design.

To understand the molecular mechanisms conferring resistance to HDACs inhibitors in solid tumors, Profs. Geng and Ding's group took breast cancer as a representative and discovered a LIFR (leukemia inhibitory factor receptor) centered feedback loop that restrained the efficacy of HDACs inhibitors in breast cancer. The detailed mechanism involves the increased histone acetylation by HDACs inhibition at the LIFR gene promoter, which recruits BET family BRD4 and transcriptionally up-regulates LIFR. Up-regulated LIFR in turn activates Janus kinase/signal transducers and activators of the transcription (JAK/STAT) pathway and limits the response to HDACs inhibition. These results provide important mechanistic insights to explain clinically observed ineffectiveness of HDACs inhibitors in solid tumors.

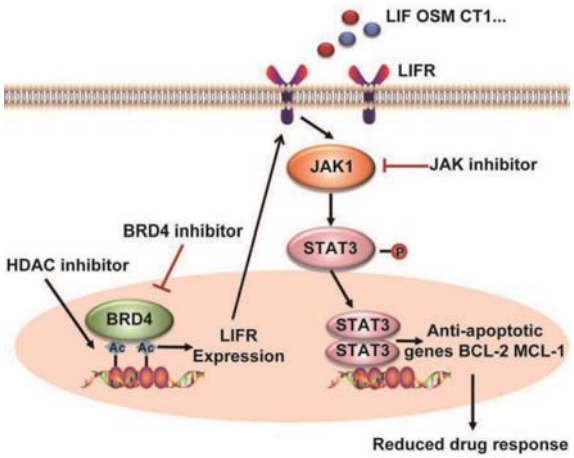

Figure A schematic model showing that LIFR upregulation conferred resistance to HDACs inhibitors.

Importantly, these findings also provide the evidence showing that the clinically available JAK or BRD4 inhibitor synergizes with HDACs inhibitors in treating triple-negative breast cancer, and hence identifies HDAC inhibitors-based therapeutic strategies that are ready to be tested in clinics. Moreover, the mechanism discovered in this study seems not limited to breast cancer, as the authors also observed feedback activation of STAT3 in a broad spectrum of solid tumor cells. To explore therapeutic opportunities of JAK/BRD4 inhibitors and HDACs inhibitors in other solid tumors could be promising.