M^{6}A Demethylase ALKBH5 Regulates FOXO1 mRNA Stability and Chemoresistance in Triple-Negative Breast Cancer

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Abstract: Resistance to chemotherapy is the main reason for treatment failure and poor prognosis in patients with triple-negative breast cancer (TNBC). Although the association of RNA N6-methyladenosine (m6A) modifications with therapy resistance is noticed, its role in the development of therapeutic resistance in TNBC is not well documented. This study aimed to investigate the potential mechanisms underlying reactive oxygen species (ROS) regulation in doxorubicin (DOX)-resistant TNBC. Here, we found that DOX-resistant TNBC cells displayed low ROS levels because of increased expression of superoxide dismutase (SOD2), thus maintaining cancer stem cells (CSCs) characteristics and DOX resistance. FOXO1 is a master regulator that reduces cellular ROS in DOX-resistant TNBC cells, and knockdown of FOXO1 significantly increased ROS levels by inhibiting SOD2 expression. Moreover, the m6A demethylase ALKBH5 promoted m6A demethylation of FOXO1 mRNA and increased FOXO1 mRNA stability in DOX-resistant TNBC cells. The analysis of clinical samples revealed that the increased expression levels of ALKBH5, FOXO1, and SOD2 were significantly positively correlated with chemoresistance and poor prognosis in

patients with TNBC. To our knowledge, this is the first study to highlight that ALKBH5-mediated FOXO1 mRNA demethylation contributes to CSCs characteristics and DOX resistance in TNBC cells. Furthermore, pharmacological targeting of FOXO1 profoundly restored the response of DOX-resistant TNBC cells, both in vitro and in vivo. In conclusion, we demonstrated a critical function of ALKBH5-mediated m6A demethylation of FOXO1 mRNA in restoring redox balance, which in turn promoting CSCs characteristics and DOX resistance in TNBC, and suggested that targeting the ALKBH5/FOXO1 axis has therapeutic potential for patients with TNBC refractory to chemotherapy.

What will audience learn from your presentation?

- This study could potentially be used for explaining tumor chemoresistance from an epigenetic perspective.
- All methods used in this study could help others for their research.
- This research could expand other faculties' research in particularly of small molecule targeting ALKBH5/FOXO1.

Biography of presenting author (should not exceed 100 words)

Dr. Xi Liu received her master's degree of obstetrics and gynecology in 2010 at Kunming Medical University. She has been worked as a physician in Gynecological Oncology Department between 2010 to 2017. In 2018 she entered in MD Anderson Cancer Center and started research of treatment tolerance of breast cancer in Prof. Qiang Shen's lab. In 2019 she worked as a Trainee Fellow at Stanley S.Scott Cancer Center of Louisiana State University Health Sciences Center. Xi Liu received PhD degree in 2020 at Kunming Medical University. Xi Liu focus on research related to therapy resistance of tumor and is currently engaged in molecular diagnosis of tumors.

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