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Identification of lysine-specific demethylase 1 as a therapeutic target of triple negative breast cancer

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Statement of the Problem: Triple-negative breast cancer (TNBC) refers to any breast cancer that does not express the genes for estrogen receptor (ER), progesterone receptor (PR) and Her2/neu. Therefore, triple-negative breast cancer does not respond to hormonal therapy (such as tamoxifen or aromatase inhibitors) or therapies that target HER2 receptors, and it often requires combination therapies clinically. TNBC is highly resistant to available therapies and contains a high ratio of breast cancer stem cells (BCSCs). The lysine-specific demethylase LSD1 is a key regulator of stem cell potential in cancer progression.

Findings: We found that BCSCs were more resistant to radiotherapy due to higher DNA repair capability and LSD1 contributes to this radiotherapy resistance of BCSCs. Overexpression of LSD1 promoted cell proliferation and enhanced DNA repair capability after ionization radiation by increasing the activation of ATM and the phosphorylation level of its substrate. ORY-1001 is a highly potent and selective LSD1 inhibitor that combined with paclitaxel had a significant inhibitory effect on TNBC *in vitro*, as well as in orthotopic xenograft and in PDX (patient-derived tumor xenograft) mice. Mechanically, ORY-1001 enhanced the cytotoxic effect of paclitaxel partially through arresting cell cycle G1 phase. Furthermore, we designed the new LSD1 inhibitor- DC551042 and found that DC551042 strongly prohibited TNBC cell proliferation and tumor growth in vivo.

Conclusion & Significance: We identified LSD1 as a significant therapeutic target of TNBC. ORY-1001 and another LSD1 inhibitor may be selective LSD1 inhibitors in preclinical trials and is potentially being evaluated in patients TNBC

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