TIME LAB
TUMOR IMMUNE MICRO-ENVIRONEMENT LABORATORY

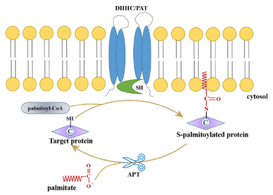
Targeting APT-2 against therapy resistance in Breast Cancer

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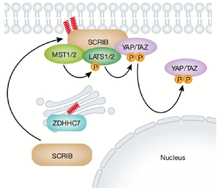
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BACKGROUND

Breast cancer accounts for more than one million new cases each year and is the most prevalent malignant neoplasm among women. Multidrug resistance to chemotherapy and targeted therapy is still a significant issue in the treatment of breast cancer. Drug resistance involves numerous unique mechanisms. Among them, the over expression of ATP-binding cassette (ABC) transporter proteins in the membranes of cancer cells is one of the ways for conferring chemoresistance (Noguchi et al. 2013). Protein s-palmitoylationMore than 100 cancer-associated proteins require; a kind of post translational modifications for their membrane attachment and oncogenic properties. Palmitoyl S-acyltransferases (PATs) catalyze the palmitoylation process (Rocks et al., 2010). The cytosolic acyl protein thioesterases (APTs) 1/2 catalyzedeacylation, which is the reverse of protein s-palmitoylation (Lin and Conibear 2015). The tumor suppressor scaffold protein SCRIB, transcription factor STAT3,TNFR1 have all been depalmitoylated by APT2. Depalmitolyation of SCRIB affects membrane localization and reduce tumorgenicity(Hernandez et al., 2017).

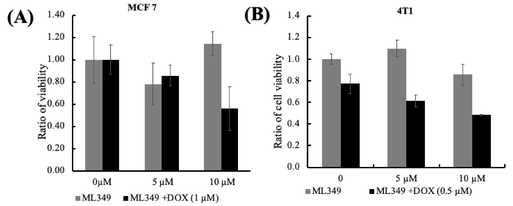


Reversible protein palmitoylation depalmitoylation cycle (Li et al. 2022)

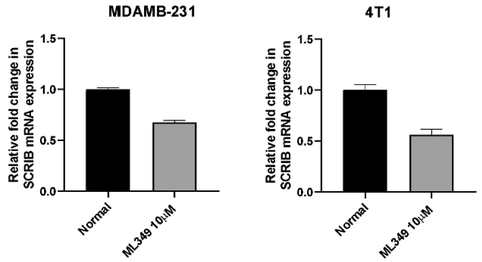


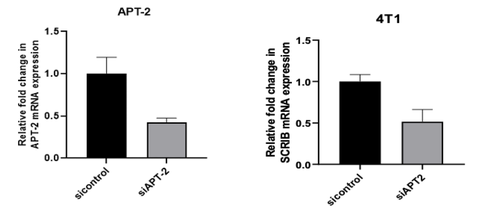
Protein S palmitoylation of SCRIB (Ko and Dixon 2018)

APT-2 specific inhibitor ML349 sensitize breast cancer cells towards Doxorubicin

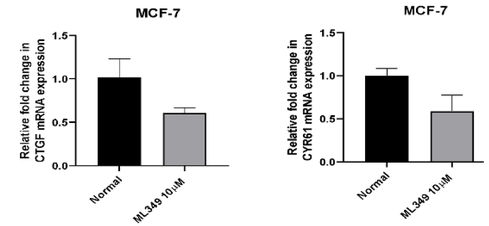


APT-2 inhibitor ML349 and APT2 knockdown suppressed SCRIB mRNA expression

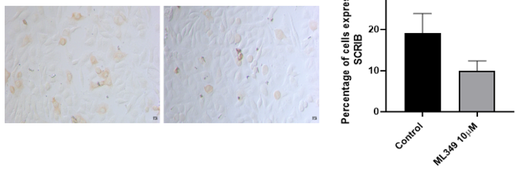




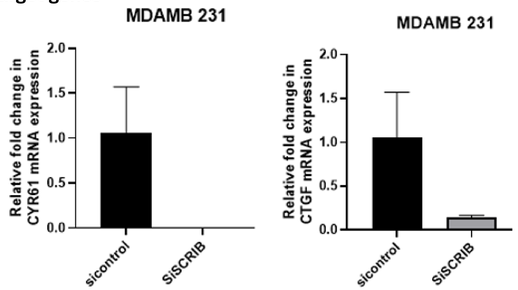
APT-2 inhibitor ML349 downregulates expressions of YAP/TAZ target genes



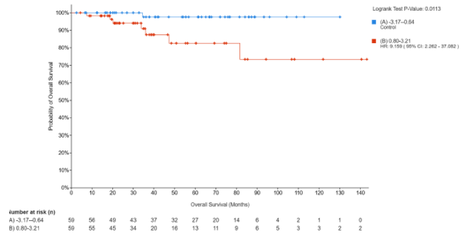
APT-2 inhibitor ML349 suppressed SCRIB protein expression



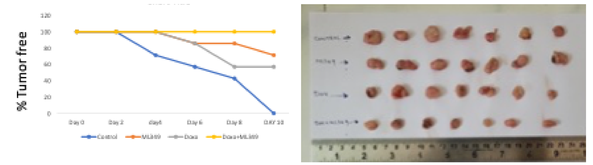
SCRIB Knockdown inhibited mRNA expression of YAP/TAZ target genes

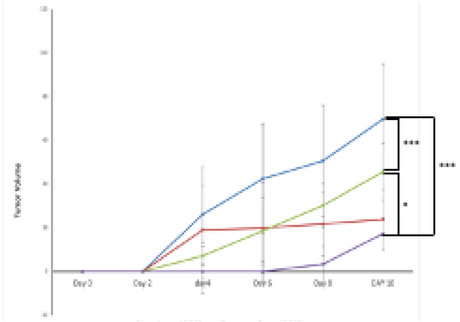


Lower SCRIB expression correlated with increased Overall survival of Breast Invasive Ductal Carcinoma, Doxorubicin patients. (Kaplan-Meier plot)-cBioPortal



APT-2 inhibiitor ML349 inhibted Doxorubicin therapy resistance invivo





Observations and Conclusion

APT-2 inhibitor ML349 treatment sensitized breast cancer cells towards Doxorubicin. APT2 inhibition or knockdown (via ML349 or SiAPT2) suppresses SCRIB, leading to downregulation of YAP/TAZ targets genes(CTGF, CYR61). Consistently, SCRIB knock down by siRNA also reduces YAP/TAZ expression. Low SCRIB expression correlates with better patient survival. ML349 combined with Doxorubicin shows synergistic tumor suppression in In-vivo.

These results reveal the APT2–SCRIB–YAP/TAZ–ABCB1 axis as a key mediator of therapy resistance.

ACKNOWLEDGEMENT

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