RESTORING DRUG SENSITIVITY IN COLORECTAL CANCER THROUGH CDC42 INHIBITION

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Background: Colorectal cancer (CRC) remains a leading cause of cancer mortality, and therapeutic failure is often driven by resistance to chemotherapy. Cdc42-a is a small Rho GTPase that regulates cell survival, cytoskeletal dynamics, and stress responses and has emerged as a plausible target for reversing chemoresistance in CRC.

Materials and methods: Non-resistant (NR) and doxorubicin-resistant (DOX-R) LoVo cells were generated by stepwise doxorubicin escalation and validated by IC50 determination (NR: 0.1398 μM; DOX-R: 0.5281 μM). Cells were treated for 48 h with CASIN (a Cdc42 inhibitor; 5 μM), doxorubicin (at each line's IC50), or the combination. Cell viability was measured by Alamar Blue. Cdc42 activity was quantified using a G-LISA assay, and intracellular doxorubicin was assessed fluorometrically.

Results: CASIN alone did not significantly alter viability in either NR or DOX-R cells. In contrast, CASIN plus doxorubicin markedly reduced viability in both models, lowering DOX-R cell survival to <10% of control-consistent with restored drug sensitivity. Basal Cdc42 activity was comparable between NR and DOX-R cells, indicating resistance was not driven by elevated Cdc42 activation. CASIN did not increase intracellular doxorubicin, suggesting the chemosensitizing effect occurs independently of altered drug uptake or efflux.

Conclusion: Pharmacologic Cdc42 inhibition with CASIN substantially restores doxorubicin responsiveness in resistant CRC cells through mechanisms unrelated to drug transport. These findings support Cdc42 targeting as a promising approach to overcome chemoresistance in CRC.

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Key words: colorectal cancer, chemoresistance, cdc42, CASIN, Doxorubicin, IC50

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