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Mutant P53 depletion by Curcumin-Derived Compounds

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Describe role of Submitting/Presenting Trainee in this project (limit 150 words):
Under the supervision of my mentor, Dr. Tomoo Iwakuma, I have participated in the conceptual design of the research project, conducted the research assays, and contributed to the interpretation of data.

Background, Objectives/Goal, Methods/Design, Results, Conclusions limited to 500 words

Background: The protein p53 is a tumor suppressor that guards cells from becoming cancerous. Approximately 50% of human cancers carry mutations in the p53 gene, the majority of which are missense mutations, resulting in the expression of mutant form of p53 protein. Mutant p53 frequently promotes cancer progression via both loss of function as a tumor suppressor and gain of function as an oncogene. The presence of mutant p53 proteins in cancers is well correlated with poor patient's prognosis. Therefore, targeting mutant p53 is a promising approach for treatment of various types of cancer.

Objectives/Goal: Our preliminary docking study suggests that a derivative of a natural product curcumin, namely CDF, binds to DNAJA1, a member of HSP40 which is known to stabilize mutant p53. Indeed, CDF and another curcumin derivative, EF-24, reduced the levels of mutant p53, suggesting that these derivatives could inhibit DNAJA1’s activity stabilizing mutant p53. The goal of this research project is to characterize these curcumin derivatives as potential therapeutic agents that deplete mutant p53 in cancer cells.

Methods/Design: Various types of human cancer cell lines were treated with curcumin derivatives, CDF and EF-24, to examine their inhibitory effects on the viability/proliferation of human cancer cells with or without knockout for DNAJA1 or mutant p53.

Results: MTT viability/proliferation assay showed that these two curcumin derivatives inhibited viable cell proliferation of cancer cells in a dose-dependent manner. Immunoblotting assays showed that these two compounds induced a decrease in mutant p53 levels in a dose-dependent manner. Intriguingly, the observed inhibition of cancer cell proliferation was associated with the presence of mutant p53, since these derivatives had less effects on cells knocked out for mutant p53.
Conclusions: The curcumin-derived compounds, EF-24 and CDF, exert inhibitory effects on the human cancer cells, preferentially to mutant p53-expressing cells, accompanied with a decrease in mutant p53.

Significance: Delineating the mechanism through which curcumin derivatives mediate the anti-cancer effects would significantly accelerate development of a novel therapeutic strategy for cancer carrying mutant p53.