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Targeting proteins for lung cancer treatment and cancer stem cell control

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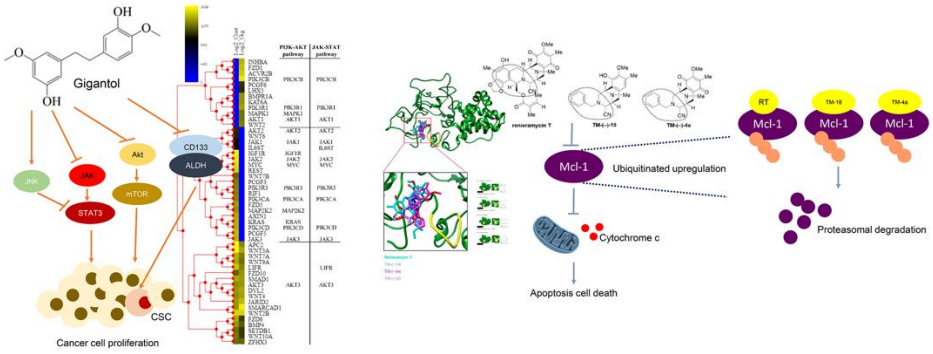
Abstract: Proteins are critical functioning molecules contribute cancer aggressiveness and chemotherapeutic failure. Our research covers the fields of protein function, and protein as an anti-cancer drug target, Structure-Activity Relationship (SAR) of compound targeting protein controlling cancer aggressiveness. We found that p21 when appearing in cytoplasmic part of the cells can cause pro-survival function and mediate anti-cancer drug resistance. The cytoplasmic p21 was up-regulated in the resistant cancer cells. Kinase array, immunoprecipitation, and computer modelling revealed that nuclear p21 interacted and shuttered p-Chk2 out of the nucleus to protect the cancer cells from its pro-apoptotic functions. For proteins as drug targets, Myeloid cell leukemia 1 (Mcl-1) and B-cell lymphoma 2 (Bcl-2) proteins are interesting. We investigated the SAR and performed molecular docking analysis of renieramycin T (RT) and its analogues and identified the critical functional groups of Mcl-1 targeting. Five analogues of RT were synthesized and tested for Mcl-1- and Bcl-2-targeting effects. Specific cyanide and benzene ring parts of RT's structure were critical for its Mcl-1-targeting activity which were confirmed by computational molecular docking. Regarding cancer stem cell (CSC) targeting research, we demonstrated that gigantol from orchid species, has a potent CSC suppression. Proteomics revealed that gigantol inhibited CSC signals through PI3K/AKT/mTOR and JAK/STAT. Interestingly, the cancer cells pretreated with gigantol at non-toxic dose prior to a tumor becoming established could form tumors *in vivo*, but the gigantol-treated group showed a dramatic tumor regression as compared with the well-grown tumor mass of the untreated control, indicating that the CSC-targeting compound was able to reduce CSC population and consequently the tumor destabilized.



Keywords: cancer stem cell; Lung cancer; p21; Mcl-1; SAR; Bcl-2.

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