18th International Conference on
CANCER AND CANCER THERAPY
June 13-14, 2022 | Webinar

Received date: 18-04-2022 | Accepted date: 20-04-2022 | Published date: 24-06-2022

Targeting mutant p53 degradation for cancer therapy

Shengliang Zhang
Brown University, USA

The tumor suppressor TP53 is mutated in over 50% of human tumors. Most of the p53 mutations are missense mutations. Mutant p53 protein not only loses the wild-type functions but also gains new oncogenic properties that contribute to tumorigenesis, tumor progression, and drug resistance. Targeting mutant p53 by either restoring the p53 pathway and/or depleting its gain-of-function is a promising strategy for cancer therapy. We conducted a high-throughput screening using multiple chemical libraries and identified a small molecule NSC59984 as a promising lead compound with the dual capability to restore p53 pathway signaling and destabilize mutant p53 in cancer cells. NSC59984 induces mutant p53 degradation via the MDM2-mediated Ubiquitin-proteasome pathway. A reactive oxygen species (ROS)-ERK2 axis is required for NSC59984 to induce the MDM2-dependent mutant p53 degradation. These discoveries propose that an inducible ROS-ERK2-MDM2 axis exposes a vulnerability in mutant p53 stabilization and can be exploited by small-molecule compounds to induce mutant p53 degradation for cancer therapy. Tumor suppressor p73, a member p53 family can transcriptionally activate many p53-targets, therefore, p73 appears to be a promising target to reinforce p53 pathway signaling bypassing restoration of wild function to mutant p53. The mutant p53 degradation releases p73 from the mutant p53 inhibitory complex. Small molecule NSC59984 restores p53 pathway signaling via enhancing p73 transcriptional activity. Our xenograft tumor models demonstrate that NSC59984 suppresses tumor growth via p73, and the high cellular ROS increases the efficacy of NSC59984 antitumor effects. Overall, our studies provide a therapeutic strategy for activating and releasing p73 from a mutant p53 inhibitory complex by induction of mutant p53 degradation in cancer cells.

E: Shengliang_Zhang@brown.edu