Abstract

Title of the thesis: Studies on the molecular mechanism of mutant p53 mediated chemo-resistance and its related oncogenic gain of functions in human cancer

Cancer-associated p53 proteins with prevalent missense mutations confer gain-of-function (GOF) and promote several cancer phenotypes including enhanced chemo-resistance, increased cellular growth, invasion, metastasis and genomic instability. In this dissertation, we have reported Cdc7-dependent altered DNA replication as a crucial underlying mechanism of mutant p53 driven oncogenesis. Our analyses revealed DNA replication as the most significantly altered pathway in lung adenocarcinoma patients harboring GOF mutant p53 with significant up-regulation of replication initiation factor Cdc7 kinase. We demonstrated that mutant p53 cooperates with oncogenic transcription factor Myb in vivo and transactivates Cdc7 in cancer cells. Chromatin enrichment of replication initiation factors and subsequent increase in origin firing confirmed Cdc7-dependent increased replication initiation in mutant p53 cells. Further, CDC7 inhibition significantly abrogated mutant p53-driven cancer phenotypes including enhanced tumorigenicity and chemo-resistance. Importantly, in clinical lung adenocarcinoma patient’s cohort, CDC7 expression significantly correlates with p53 mutation and predicts poor patient outcome. Together, our results highlight a novel functional interaction between oncogenic mutant p53 and DNA replication pathway in cancer cells. In addition, using small RNA deep sequencing, we identified mutant p53 regulated cellular miRNAs in a genome wide scale in NSCLC cells. Furthermore, the differentially regulated miRNAs were validated in NSCLC patients harboring mutant p53. Most importantly, we discovered a hitherto unknown miRNA from our deep sequencing data and functionally validated its oncogenic role in NSCLC cells. Our data provides a comprehensive picture of the emerging role of mutant p53 in miRNA regulation, and presents specific miRNAs as therapeutic targets in NSCLC patients with p53 mutation. We also identified potential gene expression signatures for mutant p53 driven acquired chemo-resistance by transcriptome profiling of drug resistant colorectal cancer cell line SW480 upon floxuridine treatment. Our analyses suggest that in response to chemotherapeutic treatment, GOF mutant p53 might deregulate important signaling pathways to confer drug resistance in cancer cells. Collectively, the present study unraveled crucial underlying mechanisms of mutant p53 driven oncogenesis and identified specific genes and miRNAs as potential therapeutic targets in human cancer with p53 mutation.

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