Stony Brook University
The Graduate School

Doctoral Defense Announcement

Abstract

Role of truncating alleles of *TP53* in tumorigenesis

By

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TP53 is the most mutated gene in human cancers and known as “guardian of genome”. The truncating mutations in *TP53* are common in human tumors and are thought to give rise to p53-null alleles. Here, we show that *TP53* exon-6 truncating mutations occur at higher than expected frequencies and produce proteins that lack canonical p53 tumor suppressor activities but promote cancer cell proliferation, survival, and metastasis. In this study, we have shown that inactivation of p53 exon-6 truncating mutants either by RNAi or CRISPR/Cas9 leads to reversion of mesenchymal features and reduction in cell survival in-vitro and in-vivo. In addition to this, we have developed a chemically stabilized Cas9 which was employed to shown the dependency of p53 exon-6 truncating mutants on cell survival in xenograft mouse model. Functionally and molecularly, these p53 mutants resemble the naturally occurring alternative p53 splice variant, p53-psi. Accordingly, these mutants can localize to the mitochondria where they promote tumor phenotypes by binding and activating the mitochondria inner pore permeability regulator, Cyclophilin D (CypD). The opening of mitochondrial transition permeability pore by p53 exon-6 truncation leads to increase in mitochondrial reactive oxygen species (mROS). This increase in mROS alters the mitochondrial metabolism and causes epigenetic reprogramming of cells into mesenchymal state via change in DNA and histone methylation. Moreover, p53 exon-6 truncating cells are dependent on CypD activity and mROS production for cell survival. Together, our studies reveal that *TP53* exon-6 truncating mutations, contrary to current beliefs, act beyond p53 loss to promote tumorigenesis, and could inform the development of strategies to target cancers driven by these prevalent mutations by inhibiting CypD activity and production of mROS dependent changes in cells.

Date: April 24, 2017 **Program**: Genetics
Time: 10:00 am **Dissertation Advisor**: Raffaella Sordella
Place: Bush Auditorium, Cold Spring Harbor Laboratory