The School of Informatics, Computing and Engineering (SICE)

INTELLIGENT SYSTEMS ENGINEERING COLLOQUIUM SERIES

Revolutionizing Precision Cancer Medicine Through Human Cancer Genomics

Xiongbin Lu

Xiongbin Lu is a professor of Medical and Molecular Genetics at IU School of Medicine. He was the first to identify a master inhibitory phosphatase, Wip1, in the ATM-p53 signaling pathway and explored the functions of Wip1 in mammary tumorigenesis. His recent studies uncovered the first functional link, KSRP, which connects the DNA damage response to microRNA biogenesis. He is currently the principle investigator for several NIH-funded projects with a focus on targeted cancer therapies. His current research, includes a development of genetic mouse models, state-of-art molecular biology/ genetics methodology and reagents, and bioinformatic analyses of human cancer genomics. In recent years, his team has developed a number of novel approaches to target human cancers harboring gene copy number variations. His major goal is to develop precision cancer therapies to treat human cancers with such genomic events. His laboratory has been collaborating with clinicians and pharmaceutical companies for translational and clinical development. As his laboratory is embedded at premier NCI-designated comprehensive cancer centers, which will facilitate translation of our findings into novel therapeutics.

Abstract

Genomic instability is one of the most pervasive characteristics of cancer cells. In my laboratory, we have been studying DNA damage response and cancer genomic alterations (translocation, amplification, and deletion). It is well known that the tumor suppressor p53 is frequently inactivated by mutation or deletion in a majority of human tumors. A tremendous effort has been made to restore p53 activity in cancer therapies. However, no effective p53-based therapy has been successfully translated into clinical cancer treatment due to the complexity of p53 signaling. Therefore, identification of vulnerabilities conferred by p53 deletion or mutation is a major challenge to target p53 aberrancy in human cancer. My recent work revealed that frequent hemizygous deletion of the p53 gene often encompasses a neighboring essential gene, POLR2A, rendering cancer cells vulnerable to further suppression of POLR2A (Liu Y et al., Nature 2015, Li Y et al., Nature Communications 2018). POLR2A encodes the catalytic subunit of RNA polymerase II complex, which can be specifically inhibited by α-amanitin. We showed that α-amanitin-based antibody drug conjugates (ADCs) are highly effective therapeutic agents in treating human cancers with hemizygous loss of p53 but have minimal systematic toxicity. In collaboration with physician scientists and pharmaceutical company, we are now developing precision medicine therapies for human cancers with such genomic defects.

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