Cancer Biology

p53 Activation & Regulation

The Lu Lab: Activation and Regulation of p53

p53 is one of the key guardians of genomic integrity and metabolic homeostasis, responding to a variety of external stimuli to activate transcriptional programs involved in cell metabolism, senescence, cell cycle arrest, and programmed cell death. This response is necessary as a protective measure against carcinogenesis, and as a result p53 is the most frequently mutated gene in cancers.

While most work surrounding p53 centers on the activation and regulation in response to overt DNA damage, the Lab of **Hua Lu** examines the role of ribosomal stress in p53 activation and regulation. The focus includes the basic biology of ribosomal stress and p53 activation/regulation, as well as the potential for drug discovery by targeting the ribosomal stress-p53 axis.

Ribosomal Proteins & MDM2/X: Regulating Regulators

Normally, p53 is kept inactive by being marked for degradation by the MDM2 or MDMX proteins. Under conditions of ribosomal stress, the effect of MDM2 on p53 can be blocked, leading to an activation of the p53 response and transcriptional programs. Ribosomal stress can be caused by specific drugs, problems with ribosomal RNA processing, or genetic insults that adversely affect the ribosomal proteins or proteins involved in ribosomal synthesis.

Dr. Lu has shown that during ribosomal stress, the ribosomal proteins L5 and L11 bind directly to MDM2 – which disrupts the ability of MDM2 to mark p53 for degradation, stabilizing it and leading to the p53 response. Similarly, the lab has shown that the MDMX protein can be inactivated by the 14-3-3 chaperone protein. The research plan is to exploit these protein-protein interactions as a potentially druggable target in p53+ cancers. This could be in the context of their effects on metabolism, aging, and cancer development using various model systems (including a genetically-engineered mouse model). This is being pursued through a collaboration with a Tulane crystallographer, Dr. Hee-Won Park, focused on the co-crystallization of MDM2 and its partner ribosomal proteins.

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Small Molecule and Protein Regulators of p53

The Lu lab also explores the ability of existing drugs to regulate the behavior of p53, as well as the identification of novel cellular regulators and transcriptional targets. One example is Inauhzin, a drug that inhibits the activities of the proteins SIRT1, which deacetylates p53, and IMPH2, which is essential for GTP synthesis, leading to their inactivation.

Other work includes the novel p53 suppressor protein PHLDB3, which suppresses p53 activity by helping MDM2 mark p53 for degradation; the NGFR protein (which is normally found in neurons but is also overexpressed in cancers) which also suppresses p53 by stabilizing MDM2; and a novel target of the p53-related protein p63 called CCDC3, which is involved in lipid metabolism. With one lab studying several individual targets and regulators of p53, it is better positioned to ultimately understand how ribosomal stress and metabolism can influence p53 and its downstream transcriptional programs.

p53 Mutational Hotspots

p53 contains several amino acids which are frequently found mutated inhuman cancers – with one particular mutation found primarily in the developing world, either in HBV- or Afflotoxin-associated liver cancer. The Lu lab was the first to discover the importance of this mutation, which creates a novel phosphorylation site for the kinase CDK4.

This is the first mutation found in a protein that creates a functionally relevant new site of post-translational modification. The phosphorylated p53 can then bind to the Pin1 protein, which mediates the upregulation of the expression of the oncogene cMyc. These projects represent just a few of the ways that the Lu lab is pushing the p53 field forward through the study of its activation, regulation, and downstream targets, in addition to their roles in metabolism, aging, and cancer.

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