CHINESE-AMERICAN LUNG ASSOCIATION

CALA Happy Friday Seminar

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Time: EST 10:30 am; PST: 7:30 am; Beijing time: 10:30pm

Zoom: 849 9682 9273 (Password: 654321)

Therapeutic targeting Mevalonate-Geranylgeranyl Diphosphate Pathway with Statins Overcomes Chemotherapy-resistance in Small Cell Lung Cancer

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Bio: Dr. Ji finished his PhD training in biological sciences at Shanghai Institute of Biochemistry, Chinese Academy of Science. He then moved to Harvard Medical School for postdoctoral training. After this, Dr. Ji join the Shanghai Institute of Biochemistry and Cell Biology, Chinese Academy of Sciences. The research interest in Dr. Ji's lab is to decipher the molecular mechanisms involved in lung cancer initiation, malignant progression, trans-differentiation and metastasis, with a long-term goal to identify effective biomarkers for diagnosis and therapeutic targets for personalized medicine. He has published many high impact papers including Nature Genetics, Nature Cancer, JCI, PNAS, Nature, Cancer Cell.

Abstract: Small cell lung cancer (SCLC) is a recalcitrant cancer that lacks effective treatments to tackle chemotherapy-resistance. Using human SCLC xenografts, we established multiple chemotherapy-resistant mouse models through long-term intermittent chemotherapy, mimicking clinical strategy. We discovered that chemotherapy-resistant SCLC has undergone metabolic reprogramming towards the Mevalonate (MVA)-Geranylgeranyl diphosphate (GGPP) pathway, which can be inhibited by clinically approved statins. Mechanistically, statins reduce chemotherapy-resistant SCLC growth through the GGPS1/RAB7A/autophagy axis via post-translational geranylgeranylation. Statins overcomes both intrinsic and acquired SCLC chemotherapy-resistance in multiple GGPS1 high SCLC PDX models, whereas GGPS1 expression is negatively associated with survival in SCLC patients. Strikingly, combining statins with chemotherapy resulted in durable responses in three patients who relapsed from first-line chemotherapy. Collectively, these data uncover the MVA-GGPP pathway as a metabolic vulnerability in chemotherapy-resistant SCLC and identify statins as a potentially effective treatment to overcome resistance.