ASHBi SEMINAR

Identification of Druggable and Redox Vulnerabilities in Cancer

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Date Thursday, 7 August 2025

Time 16:00 – 17:00 [JST]

Venue Conference Room Onsite Only*

B1F, Faculty of Medicine Bldg. B

Register here

Abstract

Reactive oxygen species (ROS) underlie human pathologies including cancer and neurodegeneration. However, the proteins which sense ROS levels and regulate their production through their cysteines remain ill defined. Systematic base-editor and computational screens revealed cysteines in VPS35–a Retromer trafficking complex member, when mutated phenocopy inhibition of mitochondrial translation. We find that VPS35 underlies a reactive metabolite-sensing pathway that lowers mitochondrial translation to decrease ROS levels. Intracellular H_2O_2 oxidizes cysteines within VPS35, resulting in Retromer dissociation from endosomal membranes and subsequent plasma membrane remodeling. We demonstrate that plasma membrane localization of Retromer substrate SLC7A1 is required to sustain mitochondrial translation. Furthermore, lowering VPS35 levels or oxidation of its ROS-sensing cysteines confers resistance to ROS-generating chemotherapies including cisplatin in ovarian cancer models. Thus, we identify that intracellular ROS levels are communicated to the plasma membrane through VPS35 to regulate mitochondrial translation, connecting cytosolic ROS sensing to mitochondrial ROS production.

Organizer : Institute for the Advanced Study of Human Biology (WPI-ASHBi), Kyoto University

Host: Prof. Yasuhiro Murakawa

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