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rticc
Rappaport
Technion Integrated Cancer Center

Cancer
Cure is
Born Here



D. DAN AND BETTY KAHN
HUMAN HEALTH BUILDING

THE RUTH AND BRUCE RAPPAPORT
FACULTY OF MEDICINE
BEATING TIME



Host

Asst. Prof. Ori Green
Schulich Faculty of
Chemistry

RTICC
**INTERNATIONAL GUEST
SEMINAR**

4th November
13:30-14:30



**4th Floor seminar Room, The Ruth and
Bruce Rappaport Faculty of Medicine**

- Light refreshments will be served

"Identification of Druggable and Redox Vulnerabilities in Cancer"

Reactive oxygen species (ROS) are required for normal cellular function, but at high concentrations can lead to human pathologies including cancer and neurodegeneration. While the electron transport chain within the mitochondria is widely appreciated as one of the main physiological generators of ROS within cells, the pathways which sense ROS and regulate its production remain poorly understood. Using comprehensive base-editing screens, we identify VPS35 as a cytosolic ROS sensor, which regulates mitochondrial translation to control intracellular ROS levels. Mechanistically, we find that oxidation of VPS35 disrupts its function within the Retromer protein trafficking complex, leading to mislocalization of the arginine transporter SLC7A1 and a subsequent decrease in mitochondrial translation. Mitochondrial ROS synergizes with the activity of some chemotherapies to induce tumor killing, and we identify that oxidation or depletion of VPS35 leads to cisplatin resistance in ovarian cancer models. Collectively, these findings demonstrate a mechanism by which cytosolic ROS sensing impinges on mitochondrial function to control ROS levels.