ICR – IMPROMPTU

Institute of Cancer Research

Invitation

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Targeting intracellular P-glycoprotein in lysosomes to overcome drug resistance: The tumor microenvironment promotes anti-cancer activity of novel drugs

Prof. Des R. Richardson

Department of Pathology and Bosch Institute, University of Sydney, Sydney, New South Wales, Australia

Lecture Hall
Institute of Cancer Research (ICR)
Borschkegasse 8a
1090 Vienna

Host:
Gergely Szakacs

INSTITUTE OF CANCER RESEARCH
MEDICAL UNIVERSITY OF VIENNA

COMPREHENSIVE CANCER CENTER VIENNA
MEDICAL UNIVERSITY OF VIENNA
Vienna General Hospital

MEDICAL UNIVERSITY OF VIENNA

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Department of Pathology and Bosch Institute, University of Sydney, Sydney, New South Wales, Australia

Abstract
P-glycoprotein (Pgp) is functional on the plasma membrane and lysosomal membrane. Lysosomal-Pgp can pump substrates into the organelle, thereby trapping certain chemotherapeutics (e.g. doxorubicin; DOX). This mechanism serves as a "safe house" to protect cells against cytotoxic drugs. Interestingly, in contrast to DOX, lysosomal sequestration of the novel anti-tumor agent and Pgp substrate, di-2-pyridylketone-4,4-dimethyl-3-thiosemicarbazone (Dp44mT), induces lysosomal membrane permeabilization. This mechanism of lysosomal-Pgp utilization enhances cytotoxicity to multidrug-resistant cells. Consequently, Dp44mT has greater anti-tumor activity in drug-resistant relative to non-Pgp-expressing tumors.
Interestingly, stressors in the tumor microenvironment trigger endocytosis for cell signaling to assist cell survival. Hence, we examined how glucose variation-induced stress regulated early endosome and lysosome formation via endocytosis of the plasma membrane. Furthermore, the impact of glucose variation-induced stress on resistance to DOX was compared with Dp44mT and its structurally related analogue, di-2-pyridylketone 4-cyclohexyl-4-methyl-3-thiosemicarbazone (DpC). These studies showed that glucose variation-induced stress-stimulated formation of early endosomes and lysosomes. In fact, through the process of fluid-phase endocytosis, Pgp was redistributed from the plasma membrane to the lysosomal membrane via early endosome formation. This lysosomal-Pgp actively transported the Pgp substrate, DOX, into the lysosome where it became trapped as a result of protonation at pH 5. Due to increased lysosomal DOX trapping, Pgp-expressing cells became more resistant to DOX. In contrast, cytotoxicity of Dp44mT and DpC was potentiated due to more lysosomes containing functional Pgp under glucose-induced stress. These thiosemicarbazones increased lysosomal membrane permeabilization and cell death. This mechanism has critical implications for drug-targeting in multidrug-resistant tumors where a stressful micro-environment exists.