FALL 2018

Biochemistry and Molecular Biology Brown Bag Series

Christian Garrido

Master Student

"Avicin Blocks K-Ras Plasma Membrane Interactions and Oncogenic Activity by Inhibiting Sphingomyelinases"

Tuesday, October 30, 2018

11:00 AM

129 Medical Sciences Building

Lab: Kwang-jin Cho

Boonshoft School of Medicine
WRIGHT STATE UNIVERSITY

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Avicin blocks K-Ras plasma membrane interactions and oncogenic activity by inhibiting sphingomyelinases

Ras are small GTPase proteins that cycles between a GTP- and GDP-bound state and consists of three main isoforms, H-, N-, and K-Ras. Constitutively active Ras mutations are found in ~15% of all human cancers and oncogenic K-Ras, the predominantly mutant Ras isoform, is found in ~95% of pancreatic, ~45% colorectal, and ~35% of lung cancers. In nearly 30 years since its discovery, there are still no anti-K-Ras drugs currently available for clinical use. Since K-Ras must be localized to the inner-leaflet of the PM for its full biological activity, targeting K-Ras plasma membrane (PM) interactions is a valid therapeutic approach for blocking its oncogenic activity. Our recent study identified that avicin, a family of natural plant-derived triterpenoid saponins from *A. victoriae*, could be an anti-K-Ras-specific drug. Avicin mislocalizes K-Ras from the PM to lysosomes and endomembranes, blocks its downstream signaling and reduces proliferation of K-Ras-positive cancer cells. In addition, avicin redistributes phosphatidylserine (PtdSer) from the inner-leaflet of the PM. We have elucidated the mechanism of avicin-mediated K-Ras and PtdSer PM mislocalization through inhibiting sphingomyelinases (SMases), which catalyzes the hydrolysis of sphingomyelin (SM) to ceramide. Avicin increases cellular SM levels by disrupting SMase activity and their cellular localization. Taken together, we have identified avicin as a new potent SMase inhibitor, which provides valuable insight to K-Ras PM interactions for the discovery and development of anti-K-Ras drugs.