Contribution ID: **37** Type: **Invited**

Unraveling the working mechanism of a tumor suppressor lipid

Wednesday, 15 March 2023 08:30 (40 minutes)

Ceramides attract wide attention as tumor suppressor lipids that can act directly on mitochondria to trigger Bax-mediated cell death. While ceramide engagement in mitochondrial apoptosis is clinically relevant, molecular details of the underlying mechanism are largely unknown. A chemical screen for ceramide binding proteins combined with molecular dynamics simulations and functional studies in cancer cells previously led us to identify the voltage-dependent anion channel VDAC2 as critical effector of ceramide-mediated apoptosis. VDAC residues involved in ceramide binding are also required for mobilizing hexokinase type-I to mitochondria, a potential checkpoint in apoptosis and glycolysis. Our data support a model in which ceramides serve as critical modulators of VDAC-based platforms to control mitochondrial recruitment of pro- and anti-apoptotic machinery. To challenge fundamental aspects of this model, we use molecular dynamics simulations and work towards reconstitution of ceramide-induced apoptotic pore formation in synthetic bilayers. In parallel, we exploit switchable ceramide transfer proteins and mitochondria-specific release of photocaged ceramides in combination with live cell imaging and functional studies. Understanding the molecular principles by which ceramides commit cells to death may facilitate the development of novel strategies to enhance their anti-tumor potential for therapeutic treatment.

Session

Interaction lipids/polymers/membrane proteins

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Session Classification: Interaction lipids/polymers/membrane proteins