Stony Brook University
The Graduate School

Doctoral Defense Announcement

Abstract

Acid Sphingomyelinase Generates Plasma Membrane Ceramide via Lysosomal Exocytosis During Cellular Stress

By

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Plasma membrane ceramide (PMCer) plays a pivotal role in diverse cellular processes, including apoptosis, pathogen infection, plasma membrane repair, and the regulation of cell adhesion and migration. Two enzymes have been reported to generate PMCer in response to signaling events: neutral sphingomyelinase 2 (nSMase2) and acid sphingomyelinase (ASM). Whereas nSMase2 has been implicated in maintaining steady-state PMCer levels and mediating physiological inputs, ASM is more commonly associated with cellular stress responses. In this study we demonstrate that stress-induced plasma membrane ceramide generation does require ASM, not by acting on the plasma membrane, but by delivering ASM-generated lysosomal ceramide to the plasma membrane via lysosomal exocytosis. To investigate its intracellular processing and further study ASM interaction with other proteins, we developed an internal HA tag. ASM containing one of the seven designed tags exhibited enzymatic activity, and further studies will validate subcellular localization under basal and stress conditions. Lastly, we investigated whether different pools of ceramides might dictate their function. Unlike nSMase2, which directly acts on the plasma membrane and promotes migration, ASM-derived ceramide originating in the lysosome did not increase PMCer. On the contrary, knockout of ASM enhanced migration in MCF7 cells, suggesting a distinct role of lysosomal-derived ceramide. Taken together, this dissertation highlights a paradigm changing mechanism of ASM induced PMCer under stress and suggests that PMCer is tightly regulated by distinct enzymes under different conditions, which may guide its function.

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