Role of Ceramide-rich Membrane Macrodomains in Response to Stress

The interaction of sphingolipids, especially sphingomyelin (SM) and cholesterol, drives the formation of plasma membrane rafts [also known as glycosphingolipid-enriched microdomains (GEMs)]. These rafts, formed in the Golgi apparatus, are targeted to the plasma membrane, where they are thought to exist as floating islands within the sea of bulk membrane. Although there is substantial disagreement as to their content, these rafts are considered in most reports to comprise 3500 lipid molecules and about 30 proteins. A general consensus has developed over the last few years that plasma membrane rafts represent signaling microdomains. Rafts containing the protein caveolin manifest a unique flask-shaped structure by electron microscopy and may possess different properties than rafts lacking caveolin.

Numerous studies now show that SM hydrolysis to ceramide, usually via acid sphingomyelinase, occurs within rafts. Ceramide generated within rafts appears to alter raft structure in a manner consistent with the known physical properties of ceramide. Thus, patches of rafts enriched in ceramide become visible within seconds after translocation of acid sphingomyelinase onto the outer leaflet of the plasma membrane upon Fas activation of Jurkat cells and primary cultures of hepatocytes. These microdomains rapidly fuse into larger platforms forming caps on the cell surface. The functional significance of this reorganization of membrane structure would appear to allow for protein oligomerization. Indeed, preformed Fas trimers localize to these domains and appear to form higher order structures, allowing for the oligomerization of the downstream adaptors FADD/MORT-1 and caspase 8, a requirement for the initiation of apoptosis.

This mode of transmembrane signal transmission is not restricted to Fas but is activated by other cytokines of the TNF receptor superfamily and by numerous environmental stresses, most importantly by ionizing radiation during induction of endothelial cell death. In fact, it would appear that formation of ceramide-rich macrodomains are obligate for the wave of endothelial cell apoptosis that distinguishes single dose radiotherapy from fractionated radiotherapy (see section entitled Tumor Response to Stereotactic Radiosurgery). The extent that this mode of transmembrane signaling is required for signal transduction, the agents that utilize this system for signaling, and the proteins that translocate into or out of ceramide-rich platforms during signaling are topics of ongoing research in our laboratory.

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