All Roads Lead to Rome

The Relevance of Lipid Rafts in the Pathogenesis of Metabolopathies

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The plasma membrane is the physical boundary of the cell. It plays fundamental roles on multiple cellular processes, including the regulation of signals in and out of the cell, the endocytosis and exocytosis of material and pathogens, the formation and stability of synapses and the myelination of axons. Many of these processes rely upon the existence of specialized plasma membrane microdomains, also known as lipid rafts. These membrane realms are highly fluid, dynamic and heterogeneous in size, composition and degree of lateral diffusion (movement) within the plasma membrane. Lipid rafts appear to form by the coalescence of molecules with specific physicochemical properties, including certain sterols (cholesterol), sphingolipids (gangliosides; sphingosines; ceramides) and a collection of associated proteins (Lingwood et al., 2010). Their planar architecture makes them “invisible” to traditional microscopic techniques, contributing to the controversy of an elusive existence.

As integral components of the membrane, lipid rafts appear to participate in multiple cellular processes that require specific architectural conformations of receptors (i.e., Patched receptor, Karpen et al. 2001), integral proteins (myelin proteolipid, Simons et al. 2000) and specific enzymatic activities (gamma secretase, Kapoor et al. 2010). Many if not all of the raft-associated functions are highly influenced by their biochemical composition. Too much or too little of any of the associated raft components will inevitably impact on the ability of these domains to convey correct signals and appropriate biophysical architecture of the membrane. It is with this idea in mind that rafts are seen as converging dynamic platforms that may be affected in multiple, unrelated metabolic diseases, triggering multiple defects.

Psychosine is a toxic sphingolipid that is thought to cause the death of oligodendrocytes in Krabbe disease (see Chapter 43). The pathogenic mechanism/s of psychosine are only partially characterized but appear to involve several pathways including phospholipases, peroxisomal function, mobilization of stored calcium, caspases, PKC and even mitochondrial function. One interpretation of the involvement of such a diverse array of pathways is that psychosine targets a "master" function and/or structure, which in turn can alter the function of multiple downstream effectors. Because of its sphingolipidic nature, psychosine was an ideal candidate molecule to study raft function in Krabbe disease. Not surprisingly, psychosine was found to accumulate and disrupt rafts in the nervous system of animal models of Krabbe disease as well as in affected patients, suggesting a consequent disruption of downstream signaling (see Ch. 43). Growing numbers of examples of raft dysfunction in unrelated inborn metabolic diseases are being reported (Walkley et al., 2000; Kosicek et al. 2010; Rakheja et al., 2004), so this may be a more common component of pathogenesis that previously suspected. Further, lipid rafts may have a role in the pathogenesis of other unrelated diseases such as viral entry infection, Parkinson disease, Alzheimer's disease and others. The growing interest in understanding the biology and behavior of lipid rafts in disease will undoubtedly reveal more relevant mechanistic functions and therapeutic targets. It is likely that further studies of these membrane conundrums will deliver radical therapies for the treatment of an array of neurological diseases.

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