Cardiolipin and Energy Metabolism in Normal Brain, Neurodegeneration and Gliomas

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Cardiolipin (Pdt_2Gro or 1,3-diphosphatidyl-s*n*-glycerol, CL) is a complex mitochondrial-specifc phospholipid that regulates numerous enzyme activities, especially those related to oxidative phosphorylation and coupled respiration. CL is essential for effcient oxidative energy production and mitochondrial function. CL contains two phosphate head groups, three glycerol moieties, and four fatty acyl chains and is primarily enriched in the inner mitochondrial membrane (Box Fig. 5-1). CL binds complexes I, III, IV and V and stabilizes the supercomplexes (I/III/IV, I/III and III/IV), demonstrating an absolute requirement of CL for catalytic activity of these respiratory enzyme complexes (Kiebish et al., 2008). CL restricts pumped protons within its head group domain, thus providing the structural basis for mitochondrial membrane potential and supplying protons to the ATP synthase. Respiratory-complex proteins that interact with CL have evolved to form hydrophobic grooves on their surface. These grooves accommodate the fatty acid chains of CL. While the amino acid sequence of electron transport proteins is highly conserved, considerable variability occurs in the acyl chain composition of CL across tissues and disease states.

Recent studies using multidimensional mass spectrom-etry–based “shotgun” lipidomics (MDMS-SL) identifed almost 100 molecular species of CL in highly purifed mitochondria from mammalian brain (Cheng et al., 2008; Kiebish et al., 2008). Moreover, these molecular species form a unique pattern, consisting of seven major groups, when arranged according to fatty acid chain length and degree of unsaturation (Kiebish et al., 2008) (Box Fig. 5-2). This unique fatty acid pattern is expressed in CL analyzed from synaptic mitochondria (enriched in neurons) as

well as from non-synaptic (NS) mitochondria (enriched in cell bodies of neurons and glia). In contrast to the complex fatty acid molecular speciation found in brain CL, CL analyzed from non-neural tissues such as liver and heart contains mostly tetra 18:2 CL. The brain therefore appears unique among tissues in expressing a very complex distribution of CL fatty acid molecular species.

The unique distribution of molecular species in brain CL is thought essential for neural cell energy metabolism and could contribute to the metabolic compartmentation of the brain (Kiebish et al., 2008). In light of the role of CL in maintaining electron transport chain activities, disturbances in the content and composition of CL could profoundly infuence energy metabolism and neural cell viability and function. Analysis of CL composition and content in models of neurodegeration will elucidate the role of CL metabolism and mitochondrial function in various neurodegenerative diseases. Recent evidence demonstrates the role of α-synuclein in regulating the CL composition in brain, thus highlighting a role of altered mitochondrial lipid metabolism and function in Parkinson's disease. Defciencies in α-synuclein resulted in decreased remodeling of neural CL corresponding to decreased linked I/III electron transport chain activities, thus demonstrating an importance of cardiolipin maintenance in regulating neural mitochondrial functionality in neurodegeneration (Ellis et al., 2005). Additionally, changes in cardiolipin content have also been found in models of aging, traumatic brain injury, and familial amyotrophic sclerosis (Pope et al., 2008). Mutations in the Tafazzin gene, a characterized cardiolipin transacylase, is the cause of Barth syndrome, which results in severe alterations in cardiolipin remodeling and mono-lysocardiolipin accumulation, leading to dilated cardiomyopathy, neutropenia, muscle weakness, and a loss of mitochondrial function. The effect of Tafazzin mutations on the maintenance of brain cardiolipin has not yet been investigated. Additionally,

Tangier's disease, caused by mutations in the ATP-binding cassette transporter 1 gene (ABCA1), also results in abnormal cardiolipin composition and accumulation in lysocardiolipin (Fobker et al., 2001); however, the effects of ABCA1 mutations on brain cardiolipin have not been investigated. Thus, the accrual of further knowledge on the role of changes in brain cardiolipin in various diseases will greatly improve our understanding of disease pathology involving altered mitochondrial metabolism in brain function.

Major changes in the content and distribution of CL molecular species have also been reported in mouse brain tumors. In marked contrast to the symmetrical distribution of CL molecular species seen in NS mitochondria of normal C57BL/6J (B6) mouse brain, the syngeneic CT-2A astrocytoma and ependymoblas-toma (EPEN) tumors display a preponderance of shorter-chain molecular species, with reduced amounts of the longer-chain polyunsaturated species (Box Fig. 5-2). Additionally, the CL composition in mitochondria isolated from cultured non-neoplastic B6 astrocytes is markedly different from the CL composition of NS mitochondria from B6 brain. The CL composition of the AC is similar to that of the cultured CT-2A and EPEN tumor cells in expressing an abundance of short chain saturated or mono-unsaturated species characteristic of immature CL (Kiebish et al., 2009). Expression of immature CL is associated with signif-cant reduction of complex I activity, requiring a compensatory increase in glycolysis to maintain energy balance. These fnd-ings indicate that tumorigenesis and growth environment can alter the CL composition of neural cells in different ways. As CL infuences respiratory energy metabolism, alterations in CL composition can compromise mitochondrial function and neural cell physiology.

cell physiology.

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