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Douglas A. Andres
University of Kentucky, dandres@uky.edu

Lyndsay E. A. Young
University of Kentucky, Lyndsay.Young@uky.edu

Matthew S. Gentry
University of Kentucky, matthew.gentry@uky.edu

Ramon C. Sun
University of Kentucky, ramon.sun@uky.edu

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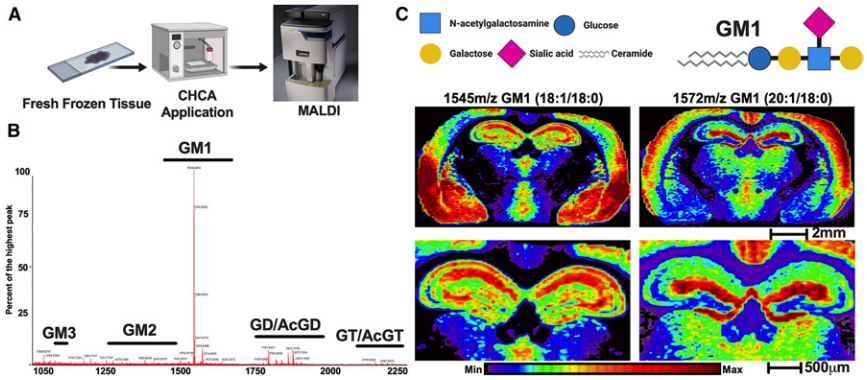
Spatial profiling of gangliosides in mouse brain by mass spectrometry imaging

Douglas A. Andres[1], Lyndsay E. A. Young[1], Matthew S. Gentry[1,2], and Ramon C. Sun[2,3]

[1]Department of Molecular and Cellular Biochemistry, University of Kentucky College of Medicine, Lexington, KY 40536, USA; [2]Markey Cancer Center, University of Kentucky, Lexington, KY 40536, USA; [3]Department of Neuroscience, University of Kentucky, Lexington, KY 40536, USA



Gangliosides are glycan-lipid hybrid metabolites that play both structural and signaling roles within a cell (1). Although they were named after the cell body where they were first discovered, they are particularly abundant in the central nervous system and account for 10% of lipid mass in the brain (1). Defects in ganglioside metabolism result in metabolic pathologies in multiple neurological disorders, such as being implicated in Alzheimer's disease pathogenesis by binding to β-amyloid and amyloid precursor protein (2). Recently, MALDI-MS has been employed to study gangliosides with significant improvement in detection and imaging of their spatial distribution (3). Despite recent advancements, a consistent hurdle has been the inability to uniformly deposit matrix crystals. This obstacle limits both sensitivity and image resolution. Recently, 32 combinations of temperature-controlled, accelerated-velocity robotic matrix spraying were tested on kidney samples to improve these parameters (4). Based on this workflow, we optimized parameters for matrix deposition to generate high-resolution MALDI images of gangliosides. Fresh frozen C57BL/6J mouse brain was sectioned at 10 μm (~ −1 mm Bregma), dehydrated under vacuum, and the MALDI matrix α-Cyano-4-hydroxycinnamic acid (7.0 mg/ml) was applied by an HTX-M5 robotic dry-sprayer with a heated nozzle (79°C) at a spray velocity of 1,300 m/min (A). Images were acquired at a pixel size of 50 μm using a Waters Synapt G2Si Mass Spectrometer with a mass range of 1000–2500 *m/z* (A and B). Our analyses demonstrate that gangliosides are predominantly localized in the cortex and hippocampus of mouse brain, but with notable differences in abundance and localization between specific brain regions (B and C). For example, a coronal view of the whole brain reveals differential cortex localization for GM1 18:1/18:0 and 20:1/18:0, two of the most abundant ganglioside subtypes (C). GM1 18:1/18:0 is most abundant in the piriform, amygdala nucleus, and striatum, while 20:1/18:0 is localized in the anterior region in layer 1 and 2 of primary and supplemental somatosensory and dorsal auditory areas. Magnified analysis (3×) reveals a unique localization for each subtype in different cell layers of the hippocampus. GM1 18:1/18:0 is most abundant in the CA1 layer of Ammon's horn and the polymorph layer of the dentate gyrus, whereas 20:1/18:0 resides in the molecular layer of the dentate gyrus. These data suggest divergent functional roles for these two gangliosides. The ability to accurately quantitate gangliosides with high spatial resolution will be crucial to interrogating their functional roles in multiple neurological disorders.

EQUIPMENT: MALDI-enabled high-resolution Time-of-Flight Synapt G2Si Mass Spectrometer (Waters); Controlled Drying Matrix Deposition system (HTX Technologies)

REAGENTS: α-Cyano-4-hydroxycinnamic acid (CHCA, Sigma)

Author ORCIDs
Matthew S. Gentry https://orcid.org/0000-0001-5253-9049;
Ramon C. Sun https://orcid.org/0000-0002-3009-1850

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