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Short Communication

Development and use of advanced mass spectrometry techniques for the characterization of cellular lipidomic profile of fibroblasts in early on-set Parkinson's disease patients

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Abstract

Parkinson's disease (PD) may be a progressive neurodegenerative disease involving the nigrostriatal pathway; patients' manifest motor symptoms dysfunction when quite 50% of neurons are lost. Though it's well recognized that alterations of lipid signaling, and metabolism plays a big role in many human diseases, little is understood about the role of lipids during this specific disease. Recently, it's been reported that altered lipid pathways within the primary visual area and therefore the anterior cingulate are possible in neurological disorders like PD by analyzing post-mortem tissues from patients in advanced neuronal degeneration stage. Such an approach, however, hinders the identification of the primary neuronal changes. Thus, understanding the mechanisms of PD and recognizing neuronal changes within the early phase of PD represents an important task. consistent with their polygenic predisposition and environmental etiopathology skin fibroblasts are today widely known as a useful model of primary human cells, capable of reflecting the chronological and biological aging of the patients. A lipidomics study of easily accessible primary human fibroblasts is presented here supported hydrophilic interaction liquid chromatography coupled to electrospray ionization-Fourier transform mass spectrometry, using both positive and negative polarities. Phospholipids (PL) from dermal fibroblasts of two unrelated PD patients with different parkin mutations and two controls were characterized by recurring to single and tandem MS measurements on a hybrid quadrupole-Orbitrap spectrometer . This untargeted approach enabled the identification of varied PL classes as phosphatidylethanolamines (PE), phosphatidylcholines (PC), sphingomyelins, lysoPC, lysoPE, phosphatidylinositols, phosphatidylserines, mono-, di- and tri-hexosylceramides and ganglioside GM1, GM2 and GM3. to spot the most lipids involved within the pathological condition of PD, lipidomics data on a better number of samples got to be collected and processed by multivariate statistical analyses. during this communication, a stimulating set of preliminary findings are going to be reported and discussed.

Lipidomics (a lipid-targeted metabolomics) aims at global analysis of lipids in biological systems. Recently, lipidomics research has received increased attention thanks to the well-recognized role of lipids in numerous human diseases. as an example , altered lipid pathways within the primary visual area and therefore the anterior cingulate are demonstrated in paralysis agitans (PD) by analyzing post-mortem tissues from patients in advanced neuronal degeneration stage. Such an approach, however, hinders the identification of the primary neuronal changes. Skin fibroblasts are recently proposed as a useful model of primary human cells, capable of reflecting the chronological and biological aging of the patients, consistent with their polygenic predisposition and environmental etiopathology. Here, hydrophilic interaction liquid chromatography coupled to electrospray ionization-Fourier-transform mass spectrometry was developed to characterize polar lipids occurring in human skin fibroblasts. Different lipid extraction protocols were tested, and Bligh Dyer strategy was selected because the most informative in terms of lipid extracted. Thus, single and tandem MS measurements were performed on a hybrid quadrupole-Orbitrap spectrometer for the characterization of fibroblast membrane lipids with the aim to use this strategy for successive biomarker discover in PD patients.

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Lipids play a crucial role in neurodegeneration, neuroinflammation, and psychiatric disorders, and an imbalance in sphingolipid levels is related to the disease. Although early diagnosis and intervention of those disorders would clearly have favorable long-term outcomes, no diagnostic tests currently exist which will accurately identify people in danger. Reliable prognostic biomarkers that are easily accessible would be beneficial to work out therapy and treatment response in clinical trials. Recent advances in lipidomic investigation methods have greatly progressed the knowledge of sphingolipids in neurodegenerative and psychiatric disorders over the past decades although more longitudinal studies are needed to know its exact role within these disorders to be used as potential tools in the clinic.

In this review, we give an summary of the present knowledge of sphingolipids in neurodegenerative and psychiatric disorders and explore recent advances in investigation methods. Finally, the potential of sphingolipid metabolism products and signaling molecules as potential biomarkers for diagnosis, prognostic, or surrogate markers of treatment response is discussed. Intraneuronal accumulation of aggregated -synuclein may be a pathological hallmark of Parkinson's disease. Therefore, mechanisms capable of promoting -synuclein deposition bear important pathogenetic implications. Mutations of the glucocerebrosidase 1 (GBA) gene represent a prevalent Parkinson's disease risk factor. they're related to loss of activity of a key enzyme involved in lipid metabolism, glucocerebrosidase, supporting a mechanistic relationship between abnormal -synuclein-lipid interactions and therefore the development of Parkinson's pathology. during this study, the lipid membrane composition of fibroblasts isolated from control subjects, patients with idiopathic Parkinson's disease (iPD), and Parkinson patients carrying the L444P GBA mutation (PD-GBA) was assayed using shotgun lipidomics. The lipid profile of PD-GBA fibroblasts differed significantly from that of control and iPD cells. it had been characterized by an overall increase in sphingolipid levels. It also featured a big change within the proportion of ceramide, sphingomyelin, and hexosylceramide molecules with shorter and longer hydrocarbon chain lengths; levels of shorter-chain molecules were increased while the share of longer-chain sphingolipids was decreased in PD-GBA lipid extracts. The extent of this shift was correlated to the degree of reduction of fibroblast glucocerebrosidase activity. Within the second set of experiments, lipid extracts from control and PD-GBA fibroblasts were added to incubations of recombinant -synuclein. The kinetics of -synuclein aggregation, as assessed by the binding of thioflavin T to amyloid structures, was significantly accelerated after the addition of PD-GBA extracts as compared to regulate samples. Amyloid fibrils collected at the top of those incubations contained lipids, indicating -synuclein-lipid co-assembly. Lipids extracted from -synuclein fibrils were also analyzed by shotgun lipidomics. Data revealed that the lipid content of those fibrils was significantly enriched by shorter-chain sphingolipids. Taken together, findings of this study indicate that the L444P GBA mutation and consequent enzymatic loss are related to a distinctly altered membrane lipid profile that gives a biological fingerprint of this mutation in Parkinson fibroblasts. This altered lipid profile, which incorporates an increased content of shorter-chain sphingolipids, could even be an indicator of increased risk for -synuclein aggregate pathology. Shorter-chain molecules may act as preferred reactants during lipid-induced -synuclein fibrillation.

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