Plasma cell-free DNA analysis clarifies novel mechanism of autoimmune neurological disease

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Abstract

Fragments of nuclear DNA is released in biofluids as cell-free DNA (cfDNA) by various types of cell death. In this project, we identified the source of plasma cfDNA in the patients with neuromyelitis optica spectrum disorder (NMOSD) by investigating the cell type–specific DNA methylation patterns. NMOSD is an autoimmune disease of the central nervous system (CNS), characterized by severe inflammation predominantly observed in the optic nerves and the spinal cord. The primary source of plasma cfDNA in NMOSD was revealed to be neutrophils. Further analysis showed that plasma cfDNA derived from NMOSD enhance type1 interferon expression in the peripheral blood mononuclear cell (PBMCs), thus elucidating the novel role of neutrophils in establishing the foundation of NMOSD immune signature. Our bioinformatics approach to identify the origin of biofluid cfDNA is a powerful method that can be applied to various types of diseases, and is expected to clarify novel pathogenic mechanisms.

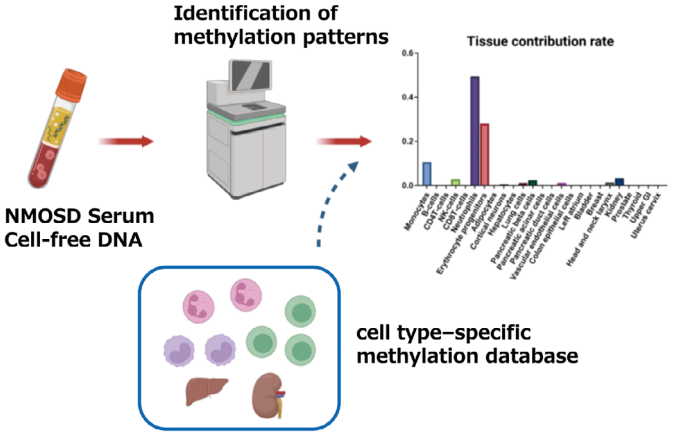
Background & Results

NMOSD is an autoimmune-mediated disease of CNS. Autoantibody targeted against aquaporin-4 (AQP4), water channels expressed on the endfeet of astrocytes, is the specific marker of the disease. Although the pivotal role of anti-AQP4 antibody is well-appreciated in the pathogenesis of NMOSD, the immune signature that leads to the production of autoantibody in the patient with NMOSD remained elusive.

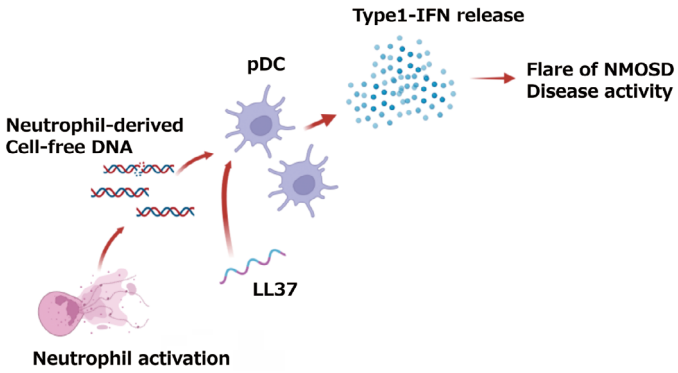
In this project, we identified the source of plasma cfDNA in the patients with NMOSD by investigating the cell type–specific methylation patterns. Bioinformatics approach showed that neutrophils are the major types of cells responsible for cfDNA release in NMOSD. Further *in vitro* studies showed that blood cfDNA induce type1 interferon expression in PBMC, especially plasmacytoid dendritic cells, in coordination with LL-37. In addition, the transcriptome analysis of PBMC derived from NMOSD elucidated neutrophil activation as the major pathway establishing the immune signature of NMOSD. These results highlighted the previously unidentified role of neutrophils in the pathogenesis of NMOSD, and showed their pivotal capacity to induce type1 interferon production in the disease.

Significance of the research and Future perspective

In this project, we elucidated a novel pathogenic mechanism of NMOSD by identifying the cellular source of plasma cfDNA. Our bioinformatics approach to clarify the origin of biofluid cfDNA is expected to reveal novel pathogenesis in various types of disease in future studies.



Identification of the source of cell-free DNA by cell type-specific methylation patterns



Activation of Type1-IFN pathway by neutrophil-derived cell-free DNA in NMOSD

Patent

Treatise Murata, Hisashi; Kinoshita, Makoto; Yasumizu, Yoshiaki et al. Cell-Free DNA Derived From Neutrophils Triggers Type 1 Interferon Signature in Neuromyelitis Optica Spectrum Disorder. Neurol Neuroimmunol Neuroinflamm 2022, 9: e1149. doi:10.1212/NXI.0000000000001149

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Keyword cell-free DNA, autoimmune disease, bioinformatics, neurological disease