Identification of the mechanism by which thymoma implicates autoimmune neuromuscular diseases, including myasthenia gravis

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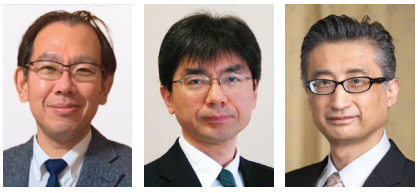

Abstract

Myasthenia gravis (MG) is an autoimmune disease characterized by autoantibodies against acetylcholine receptors at the neuromuscular junction. MG commonly occurs in patients with thymoma. In addition to MG, autoimmune neurological diseases such as autoimmune encephalitis and stiff-person syndrome are also accompanied by thymoma. In this study, we try to elucidate the mechanism by which these autoimmune neuromuscular diseases occur in patients with thymoma by analyzing open database of thymoma, pathological and clinical data and single cell RNA Sequencing(scRNASeq). We found that thymomas show high levels of various neuromuscular antigens with chemokines, such as CXCL12. In addition, we were able to identify neuromuscular TECs (nmTECs), which have the ability to trigger autoimmune reactions by presenting autoantigens and recruiting lymphocytes.

Background & Results

MG is an autoimmune disease in which the neuromuscular junction is disrupted by acetylcholine receptor antibodies and is highly associated with thymoma. Thymoma is a tumor composed of tumorigenic thymic epithelium (TEC) and lymphocytes. In a normal thymus, TEC induces immune tolerance by expressing autoantigens, however, the relationship to pathogenesis of MG remains unknown.

In an attempt to further understand this relationship, we analyzed the thymoma data in The Cancer Genome Atlas and searched for MG-related genes. Among the genes identified were target antigens for autoantibodies that appear in thymoma patients, including neurofilament, GABA receptor, potassium channel, glycine receptor, ryanodine receptor, and myosin. To examine which cells express these MG-related genes, scRNASeq of thymoma and peripheral blood mononuclear cells from patients with thymoma-associated MG was performed. As a result, we found that they cluster in the subpopulation of TECs not consistent with known TEC. Consistently, immunohistochemistry revealed expression of neuromuscular-related proteins including neurofilaments and GABA receptors in TEC. We termed these cells neuromuscular-TECs (nmTECs), meaning TECs expressing neuromuscular antigens. Gene-set analysis showed that Class I and II MHC antigen processing and presentation pathways are enriched in nmTECs. These cells also highly expressing the chemokine CXCL12/SDF-1, which was postulated to form a microenvironment that attracts lymphocytes to the thymoma. This result could suggest that the induction of neuromuscular antigen-reactive lymphocytes by nmTEC in thymomas plays a crucial role in the development of autoimmune neuromuscular diseases including MG.

Significance of the research and Future perspective

Our findings suggest that the nmTECs we identified could trigger thymoma-associated autoimmune neuromuscular diseases including MG. We believe that further studies on nmTECs could possibly contribute to the unveiling of the pathogenesis of organ-specific autoimmune diseases, as well as the development of the spontaneous animal model of MG and the therapies selectively targeting nmTEC.

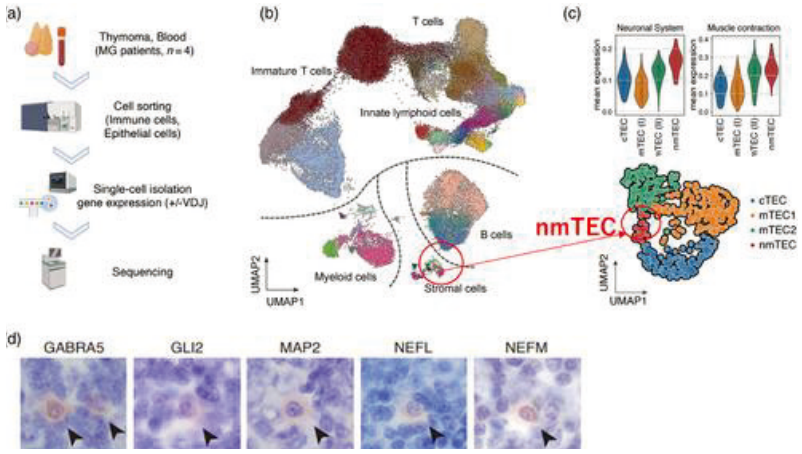

Figure 1. Identification of nmTec. (a) The experimental design of the scRNAseq analysis. Immune cells and non-immune cells from MG-type thymoma and immune cells from the blood of patients were collected for scRNAseq. (b). UMAP plot for 65,935 cells displaying the clusters from the thymoma and blood of patients with MG. Arrow indicates nmTec. (c). Violin plots of mean expression of the REACTOME gene sets; neuronal system (left) and muscle contraction (right) in TEC clusters. (d). Immunohistochemistry of the neuronal genes in nmTec. [Scale bar: 20 μm]. GABRA5; gamma-aminobutyric acid type A receptor subunit alpha5, GLI2; GLI Family Zinc Finger 2, MAP2; microtubule associated protein 2, NEFL; Neurofilament Light Chain, NEFM; Neurofilament Medium Chain, These figures were reproduced from Yasumizu et al. doi: 10.1111/cen3.12743

Patent
Treatise Yasumizu, Yoshiaki; Okuno, Tatsusada; Mochizuki, Hideki et al. Myasthenia gravis-specific aberrant neuromuscular gene expression by medullary thymic epithelial cells in thymoma. Nature Communications 2022, 13(1), 4230. doi: 10.1038/s41467-022-31951-8
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