Dysregulation of the Metabolic-Inflammatory Axis in Progressive Multiple Sclerosis

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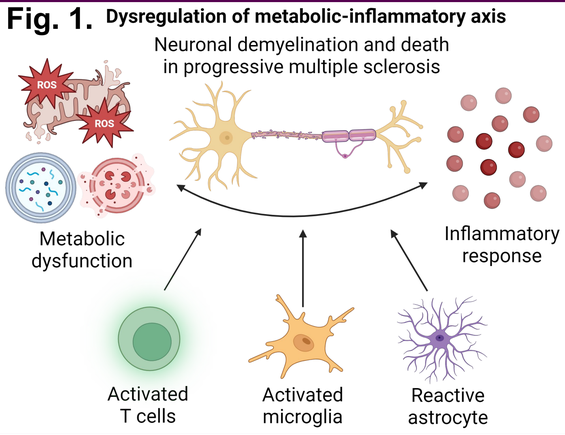
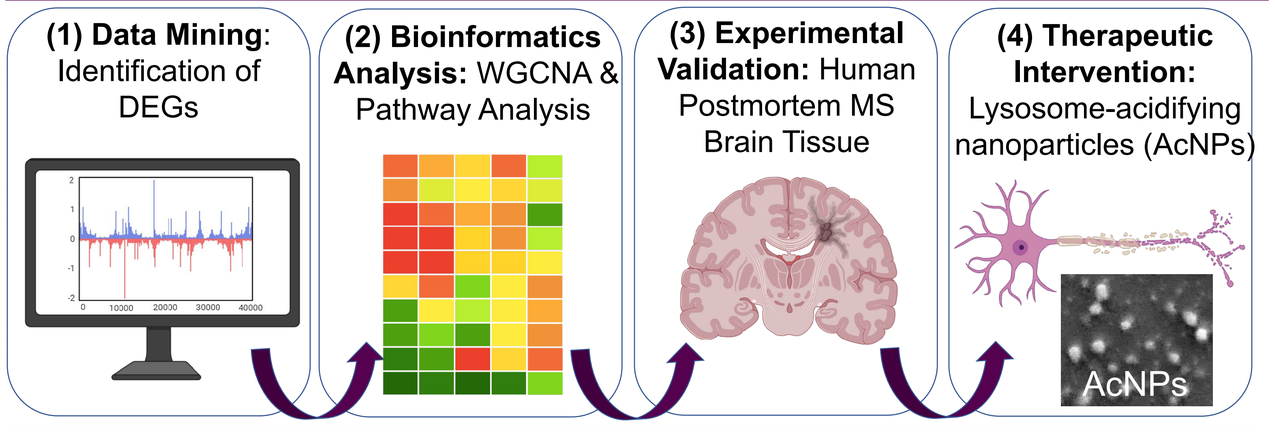
Metabolic-Inflammatory Axis in Multiple Sclerosis (MS)

- Recent studies have suggested that disruptions in metabolic processes such as mitochondrial activity as well as autophagy and lysosomal functions play a critical role in the pathogenesis of progressive multiple sclerosis (MS) by compromising energy production and waste clearance[1-3].
- Metabolic dysfunctions such as elevated oxidative stress intensify inflammatory responses within the central nervous system, leading to demyelination and progressive neuronal loss[4,5].

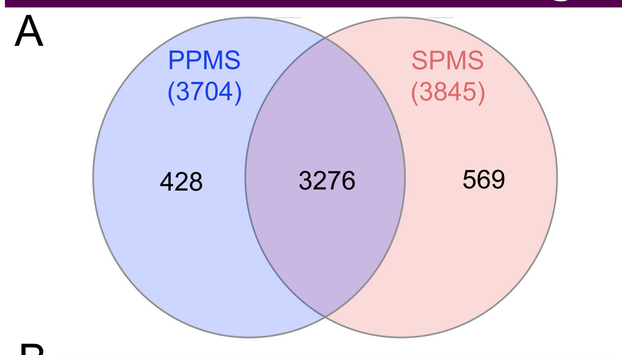
Fig. 1. Dysregulation of metabolic-inflammatory axis



Computational to Experimental: Uncovering MS Mechanism



Distinct and Shared Biological Pathways in Progressive MS



B

Genes of Interest	SPMS Fold Change (log_2)	PPMS Fold Change (log_2)
ATP6V1C1	-1.722	-2.310
NDUFA5	-2.086	-2.168
COX11	-2.467	-2.505
ATP5F1	-1.972	-2.466

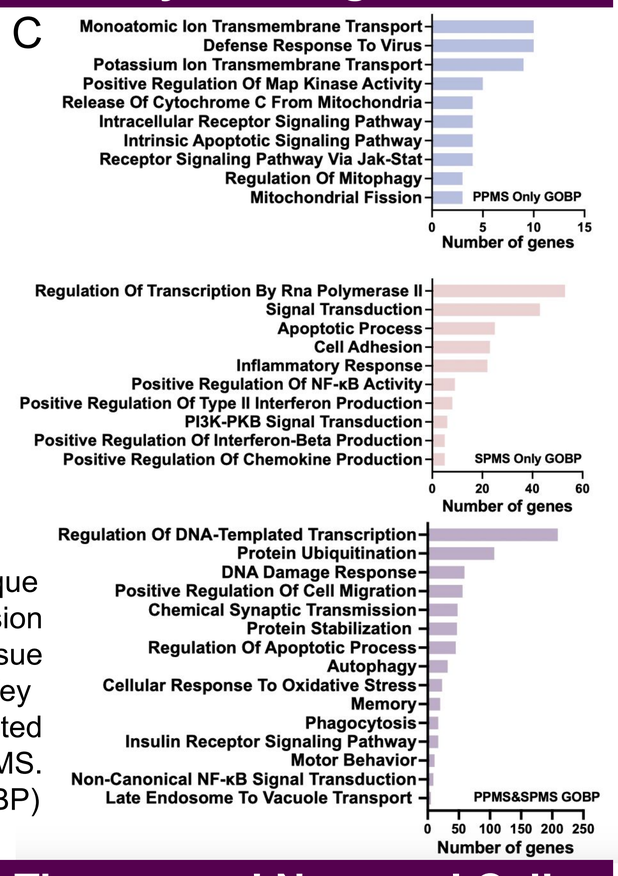
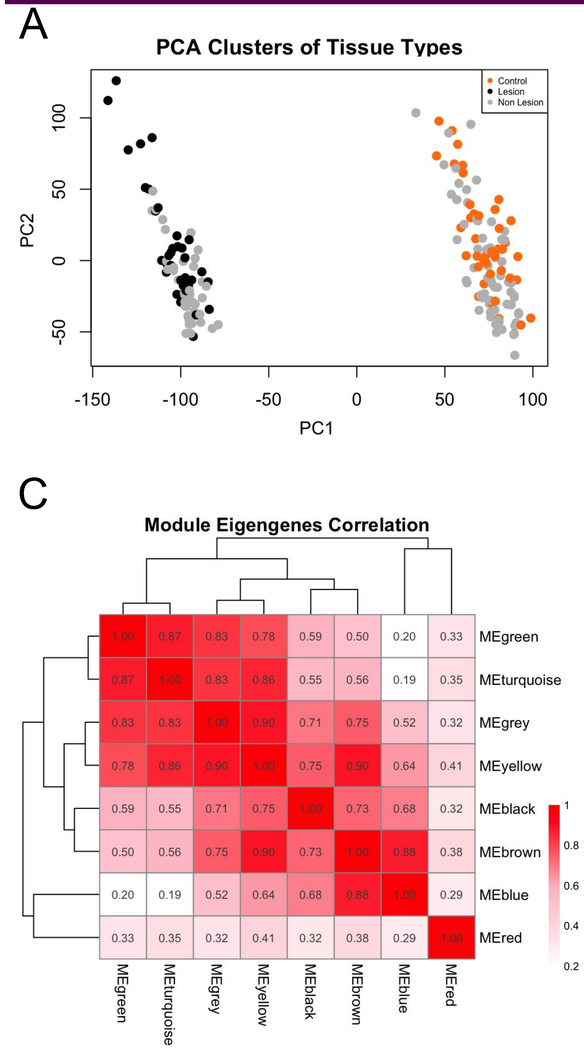
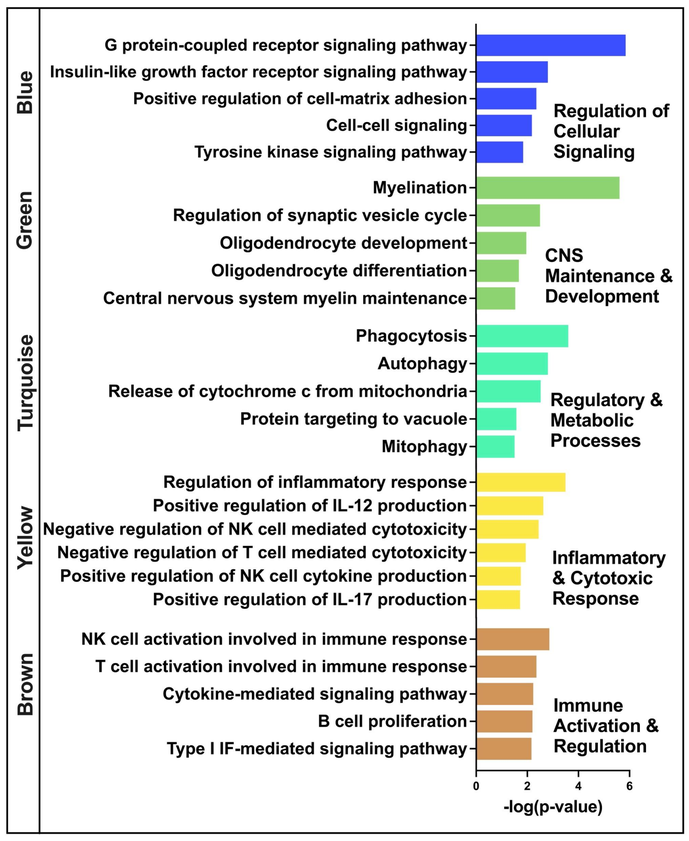
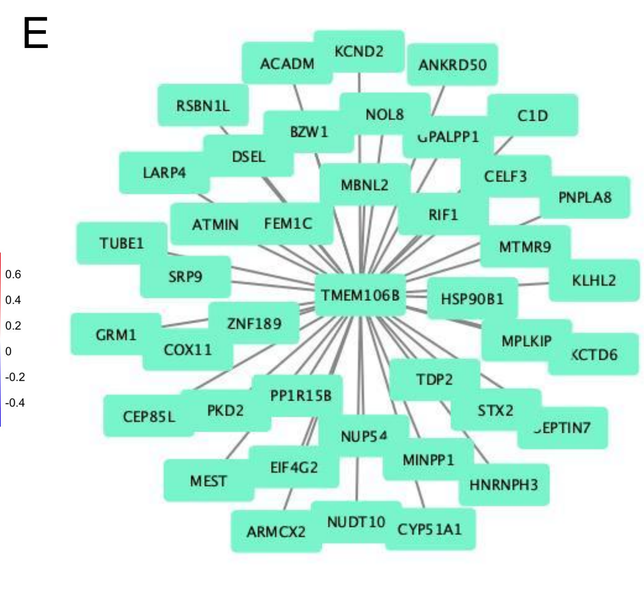


Fig. 2. (A) Identification of shared and unique DEGs between comparisons of PPMS lesion tissue vs. healthy control and SPMS lesion tissue vs. healthy control (grey matter). **(B)** Key differentially expressed genes (DEGs) associated with metabolic dysfunctions in SPMS and PPMS. **(C)** Gene ontology biological processes (GOBP) enrichment under respective conditions.

Interconnected Gene Modules in MS Lesions







Validation in Human MS Brain Tissues and Neuronal Cells

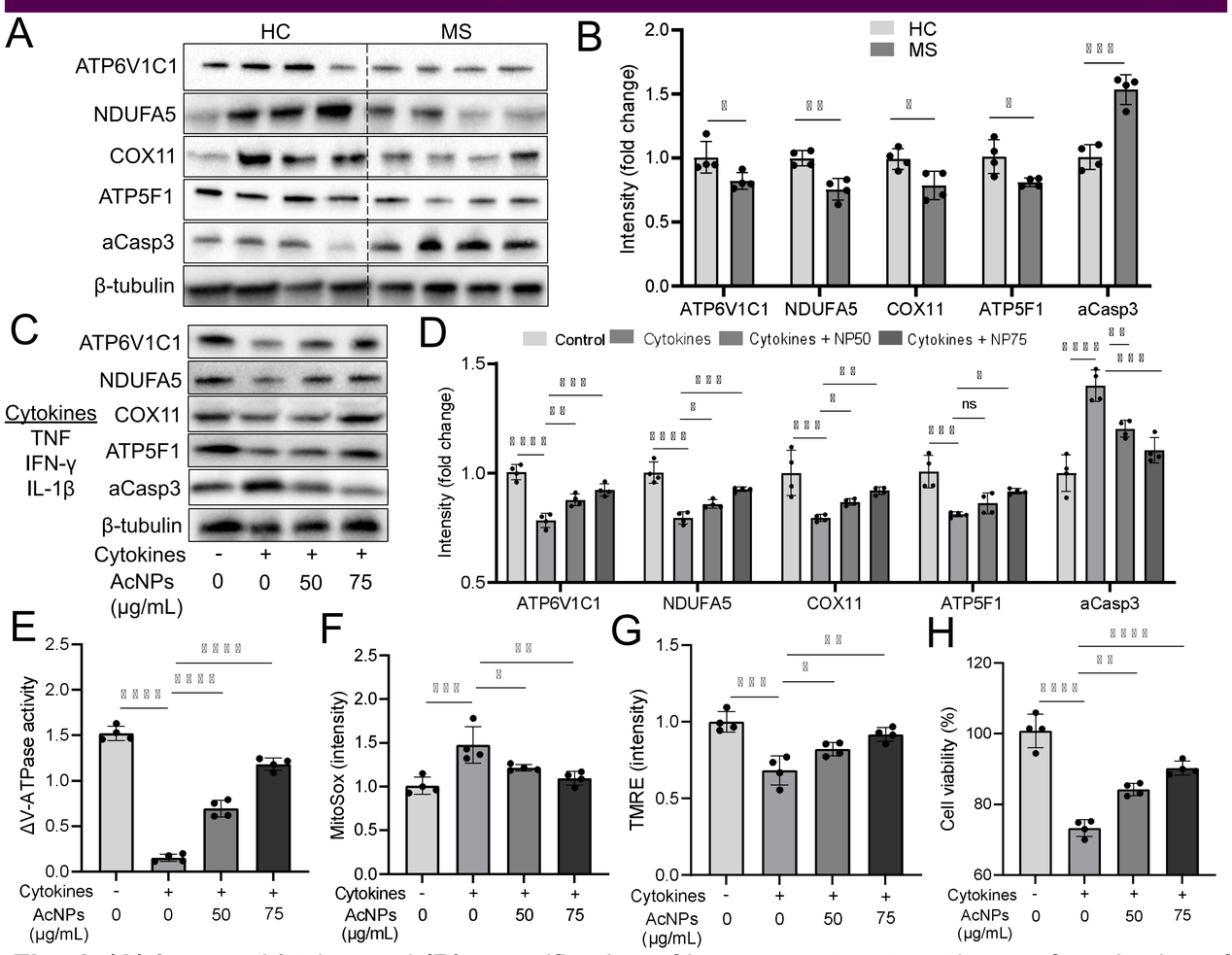
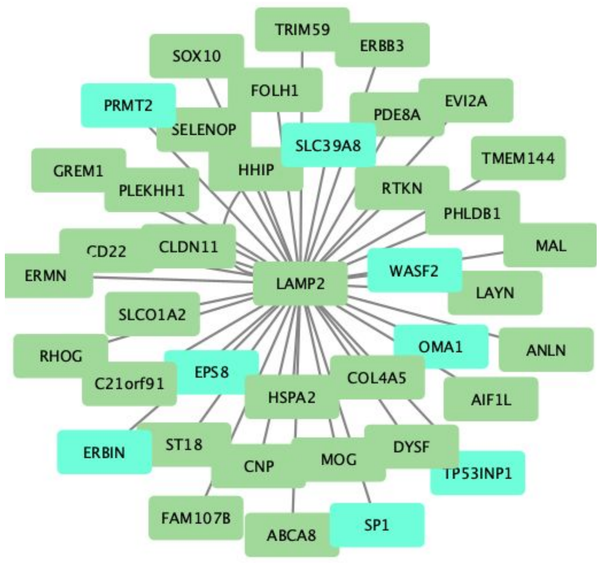


Fig. 4. (A) Immunoblotting and **(B)** quantification of human postmortem tissues from brains of healthy control (HC) and MS patients. **(C)** Immunoblotting and **(D)** quantification of SH-SY5Y neuronal cells stimulated with inflammatory cytokines TNF, IFN-ɣ and IL-1β, with and without lysosome-targeting acidic nanoparticles (AcNPs). **(E)** Lysosomal V-ATPase activity, **(F)** mitochondrial superoxide (MitoSox) production, and **(G)** mitochondrial membrane potential (TMRE), and **(H)** cell viability of SH-SY5Y cells under different treatment conditions.

Fig. 3. (A) Principal component analysis (PCA) of grey matter samples from MS lesion, MS non-lesion, and controls. **(B)** GOBP terms reflective of the key biological pathways under each WCGNA module. **(C)** Heatmap illustrating the correlation between module eigengenes (ME). **(D)** Heatmap displaying the significance of correlation between phenotypes and modules. **(E)** Visualization of the hub genes TMEM106B (turquoise module) and LAMP2 (green module) and their interconnected modules and genes.



Relevant Publications from the Lab

(1) O'Connor LM et al. Integrative multi-omics and systems bioinformatics in translational neuroscience: A data mining perspective. *J Pharm Anal*. 2023;13(8):836-850.

(2) O'Connor LM et al. Data Mining of Microarray Datasets in Translational Neuroscience *Brain Sciences*. 2023;13(9):1318.

(3) Pitt D et al. Toward precision phenotyping of multiple sclerosis. *Neurol Neuroimmunol & Neuroinflamm*. 2022;9(6)

(4) Lo CH et al. Astrocyte heterogeneity in multiple sclerosis: current understanding and technical challenges. *Front Cell Neurosci*. 2021;15:726479.

Summary and Future Work

- Metabolic and inflammatory pathways are differentially regulated in progressive MS, suggesting a crosstalk within the metabolic-inflammatory axis.
- Future work: (1) Dissect cell-type specific contributions to metabolic dysregulation & (2) Develop novel therapies for treatment of progressive MS

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