HLa-DRB1*04:01 has a Neuroprotective Role in a Mouse Model of Parkinson’s Disease

Bryce A. Pugh, Jonathan J. Carver, Cindy C. Martinis, Jeffrey B. Eells, Alessandro Didonna*

Department of Anatomy and Cell Biology, Brody School of Medicine, Greenville, North Carolina, USA

BACKGROUND

Parkinson’s Disease (PD) is the second most common age-related neurodegenerative disease in North America. The pathological features of PD include death of dopaminergic neurons in the substantia nigra, mitochondrial dysfunction, neuroinflammation, and accumulation of abnormal inclusions (α-SYN) aggregates termed Lewy bodies. Current treatment for PD relies on high dose L-DOPA replacement to improve motor function, but there is a lack of treatment for the underlying cause of PD. A recent study sequencing the HLA alleles from 1,597 PD patients and 1,408 healthy controls found a strong genetic association between this pathway containing HLA-DRB1*04:01 allele and PD risk. The shared epitope (SE) is a five amino acid sequence (DQA1:57/DRB1:04) in the HLA-DRB1 chain that was previously identified as a risk factor for a more severe rheumatoid arthritis (RA). The SE is not involved in the immune cell microenvironment presentation of the MHCI complex, but instead increased the innate immune response by binding other cell-membrane proteins on the immune cell surface including presentation. In the central nervous system (CNS), HLA-DRB1 expression is restricted to the resident immune microglia population which were previously implicated in PD to phagocytose and destroy abnormal α-SYN aggregates. To better understand the role of the HLA-DRB1*04:01 allele in PD, here we have used an in vivo mouse model of α-SYN in aggregation to show that the α4:01 allele caused increased microglial activation, neuroinflammatory changes in behavior, and protection against α-SYN-related pathogenesis.

RESULTS & DISCUSSION

Mouse Behavior Analysis

For the open field test, the 04:01/04:01 mice had a higher total distance that they traveled and their average velocity in an open arena (top left). At one month post-injection, the 04:01 mice, regardless of treatment, had significantly higher average velocity and benefitted longer total distance traveled. 2 to 3 months post-injection, the trend continued with 04:01 displaying significantly more locomotor activity than 04:02 mice. *P < 0.05.

Figure 1: HLA-DRB1*04:01 mice have increased locomotor activity during open field test (OFT).

For the Y maze test, the 04:01/04:01 mice had a higher total distance that they traveled and their average velocity in an open arena (top left). At one month post-injection, the 04:01 mice, regardless of treatment, had significantly higher average velocity and benefitted longer total distance traveled. 2 to 3 months post-injection, the trend continued with 04:01 displaying significantly more locomotor activity than 04:02 mice. *P < 0.05.

Figure 2: HLA-DRB1*04:01 mice have increased locomotor activity during open field test (OFT).

SUMMARY & FUTURE DIRECTIONS

Summary

The 04:01 mice had significantly less spread of α-SYN in the brain, providing an in vivo animal model to support the genetic association between HLA alleles and PD protection. The 04:01 mice had fewer microglial per higher levels of demineralization leading to increased prevalence of amyloidosis, including higher levels of microglial activation, even in PBS injected animals (not shown). The behavior of this was found to be significantly different between 04:01 and 04:02 in a variety of tasks. Interestingly, this trend was still observed among the control PBS mice that had not been exposed to α-SYN. These findings suggest a dual effect of HLA alleles variants with microglial activation and behavioral traits.

Future Directions

Mouse efforts will begin with the investigation of how the 04:02 genotype influences the peripheral immune response to α-SYN by using Luminescence panel to analyze the cytokine panel and chemokine cytokine and microglial activation of these mice. We plan to characterize dopaminergic neuron loss and investigate the molecular mechanisms underlying the observed microglial phenotypes. Further work is needed to understand the neurological mechanisms behind these changes.

ACKNOWLEDGEMENTS & REFERENCES

We would like to thank Jason S. Antonow and Steven Matthew-Levitsky and the Department of Comparative Medicine at ECU for surgical assistance. We would also like to thank Dr. Joseph Holzbach at the University of Michigan at Ann Arbor for providing us with the transgenic mouse variants. This work was supported by NIH R01NS075113 awarded to A.D. and ECUS NIH funds.

*Corresponding Author: Alessandro Didonna

Department of Anatomy and Cell Biology
Brody School of Medicine
600 Mose Blvd
Greenville, NC 27894
Didonnaali@ecu.edu