Role of HLA/MHCII in Parkinsons Disease Pathogenesis

https://neurodegenerationresearch.eu/survey/role-of-hla-mhcii-in-parkinsons-disease-pathogenesis/

Principal Investigators

TANSEY, MARIA DE LOURDES G

Institution

EMORY UNIVERSITY

Contact information of lead PI
Country

USA

Title of project or programme

Role of HLA/MHCII in Parkinsons Disease Pathogenesis

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,557,967.89

Start date of award

30/09/2015

Total duration of award in years

4

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

HLA Antigens, Histocompatibility Antigens Class II, Parkinson Disease, MHC Class II Genes, Pathogenesis

Research Abstract

? DESCRIPTION (provided by applicant): A large genome-wide association study identified a common non-coding, single nucleotide polymorphism (SNP), rs3129882, which was significantly

associated with risk for late-onset Parkinson’s disease (PD). Individuals homozygous for the risk allele (GG) have a 1.7 fold higher risk for PD than homozygous individuals with the low risk allele (AA). rs3129882 is located in the first intron of the Major Histocompatibility Complex class II (MHC-II) Human Leukocyte Antigen (HLA)-DRA gene, providing the first genetic link between PD and this critical immune system locus. The conundrum introduced by this study was the fact that HLA-DRA is monomorphic and the polymorphic HLA genes were not found to be associated with PD in this study, suggesting that a protein coding polymorphism is unlikely to be the causative genetic lesion. Instead, we suggest the novel hypothesis that rs3129882 is linked to a novel regulatory element that alters the expression of the locus in antigen presenting cells that reside in and/or infiltrate into the brain, such that there is an increased risk for disease following an inflammatory event. Indeed, HLA-DR-expressing microglia, CD4+ T cells, and anti-CNS protein antibodies have been reported in the substantia nigra pars compacta of PD patients, supporting a role for adaptive immune responses in PD disease progression. We additionally posit that changes in genetic and/or epigenetic regulation of MHC-II genes could be linked to rs3129882 and explain the stochastic and sporadic nature of this disease. Preliminary studies revealed that IFN??treated monocytes from GG individuals with PD co-express HLA-DR and HLA-DQ proteins to a higher degree than monocytes from AA individuals irrespective of disease state. Furthermore, in response to IFN?, GG monocytes expressed up to 300-fold higher levels of both DR and DQ mRNAs than AA cells. Thus, the high risk, GG genotype, is associated with increased levels of MHC-II mRNA and protein. Identification of a direct linkage of rs3129882 to a regulatory mechanism would provide a specific target for neuroimmune modulation and novel therapy to delay, prevent, or attenuate disease. To provide a scientific basis for pursuing treatments to target MHC-II expression and this pathway, we propose to determine the regulatory bases for rs3129882 association with PD and determine a causal role for MHC-II aberrant expression and PD-like neuropathology in a model system through the following specific aims: Aim 1, Determine the extent to which MHCII expression and T-cell subset frequency are influenced by rs3129882 genotype; Aim 2, Identify the molecular bases for rs3129882-related changes in gene expression; and Aim 3, Determine the extent to which modulation of myeloid-specific (including microglia) MHC-II expression determines vulnerability to rAAV-human ?-synuclein-induced dopaminergic neurodegeneration. Together, these analyses will elucidate the molecular mechanism for understanding this important genetic association and potentially provide novel therapies for PD and other neurodegenerative diseases where inflammation plays a role.

Lay Summary

PUBLIC HEALTH RELEVANCE The proposed research addresses a novel and paradigm-shifting mechanism-based hypothesis on the role of the adaptive immune system in the pathogenesis of sporadic late-onset Parkinson’s disease (PD). We propose that a common genetic variant (rs3129882) is linked to a novel and specific regulatory mechanism that controls the expression of major histocompatibility complex class II genes and that this expression exacerbates PD by influencing adaptive immune responses. The proposed hypothesis has the potential to have an extremely high impact on clinical care because it may pave the way for novel HLA-based immunomodulation approaches to diagnose, treat, or prevent PD onset.

Further information available at:

Types:

Investments > €500k

Member States:
United States of America

Diseases:
Parkinson's disease & PD-related disorders

Years:
2016

Database Categories:
N/A

Database Tags:
N/A