Meta-analysis of genetic and environmental Parkinson's disease models reveals a common role of mitochondrial protection pathways.

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Abstract:

Both genetic and environmental factors trigger risks of and protection from Parkinson's disease, the second most common neurodegenerative syndrome, but possible inter-relationships between these risk and protection processes were not yet explored. By examining gene expression changes in the brains of mice under multiple treatments that increase or attenuate PD symptoms we detected underlying disease and protection-associated genes and pathways. In search for potential links between these different genes and pathways, we conducted meta-analysis on 131 brain region transcriptomes from mice over-expressing native or mutated ?-synuclein (SNCA) with or without the protective HSP70 chaperone, or exposed to the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), with or without the protective acetylcholinesterase (AChE-R) variant. All these models showed shared risk-inducible and protection-suppressible transcript modifications. Self-organized map (SOM) classification revealed risk- and protection-associated alterations in nuclear and mitochondrial metal ion-regulated transcripts, respectively; Gene Ontology based analysis validated these pathways. To complement this approach, and identify potential outcome damages, we further searched for shared functional enrichments in the lists of genes detected in young SNCA mutant or in old SNCA mutants and MPTP-exposed mice. This post-hoc functional analysis identified early-onset changes in Parkinsonian, immune and alternative splicing pathways which shifted into late-onset or exposure-associated NFkB-mediated neuro-inflammation. Our study suggests metal ions-mediated cross-talk between nuclear and mitochondrial pathways by both environmental and genetic risk and protective factors involved in Parkinson's disease, which eventually culminates in neuro-inflammation. Together, these findings offer new insights and novel targets for therapeutic interference with the gene-environment interactions underlying sporadic PD.

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