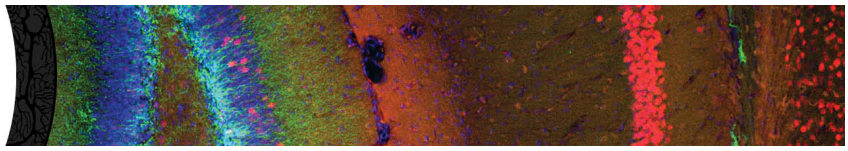

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Session P250 - Parkinson's Disease: Cellular Mechanisms II

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P250.01 - Transcriptomic changes linked to age-dependent neuromelanin accumulation in a new Parkinson's disease mouse model

November 9, 2021, 11:00 AM - 12:00 PM | Virtual Only

Grant Support
MJFF (MJFF-007184)

Grant Support
La Caixa (FBLC/HR17-00513)

Grant Support
MINECO (SAF2016-77541-R)

Grant Support
JPND-ISCIII (AC20/00121)

Grant Support
MINECO/SAF2015-73997-JIN

Grant Support
LCF/BQ/PR19/11700005

Grant Support
MINECO/BES-2017-080191

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Disclosures

N. Peñuelas: None. **A. Laguna:** None. **H. Xicoy:** None. **E. Markidi:** None. **M. Gonzalez-Sepulveda:** None. **A. Nicolau:** None. **M. Lorente-Picón:** None. **J. Compte:** None. **A. Parent:** None. **T. Cuadros:** None. **J. Romero-Giménez:** None. **L. Miquel-Rio:** None. **G. Pujol:** None. **B. Rodríguez-Galván:** None. **L. Giménez-Llort:** None. **A. Bortolozzi:** None. **I. Carballo-Carbajal:** None. **M. Vila:** None.

Abstract

In Parkinson's disease (PD) there is a preferential degeneration of neuromelanin (NM)-containing neurons, especially neurons from the Substantia Nigra (SN) but also from the Ventral Tegmental Area (VTA) and Locus Coeruleus (LC). We generated a new NM-producing mouse model, based on the tissue-specific constitutive expression of human tyrosinase (hTyr) under the tyrosine hydroxylase (TH) promoter (tgNM), that mimics the distribution and age-dependent accumulation of NM in the human brain (i.e. catecholaminergic groups A1-A14). TgNM mice exhibited major PD features, including both motor and non-motor behavioral alterations, inclusion body formation, neuronal degeneration in lower brainstem areas (LC) together with neuronal dysfunction in higher brainstem areas (SN and VTA). In order to understand the mechanisms by which NM accumulation in specific brain areas ultimately interferes with the normal functioning of cells, we characterized genome-wide transcriptomic changes linked to the intracellular presence and progressive accumulation of NM in two NM-accumulating neuronal subpopulations (SN and VTA) that are known to be differentially susceptible to PD pathology. We selectively isolated single dopaminergic NM-containing neurons by laser capture microdissection from male and female wild-type and tgNM animals at 3 months, 12 months and 20 months of age (n=4-6 mice per group). We performed differential expression analysis, resulting in statistically significant differentially expressed genes at all ages (p-value<0.01 and $\log_2$FC> <0.5). Gene-set enrichment analysis (GSEA) with Reactome Pathway Database led to the identification of altered biological pathways in tgNM related to neuroinflammation, vesicle-mediated transport and lipid metabolism, transcription and translation, mitochondrial function and cell cycle (senescence) (False Discovery Rate<0.05). Targeted-based validation of candidate RNA species was performed in microdissected samples by quantitative real-time PCR and candidate biological pathways were validated at the protein level by western blot in dissected ventral midbrain tissues from biological replicates. The transcriptomic profiles identified in this project contribute to our understanding of selective vulnerability in PD and brain aging, and points to key biological pathways and molecular targets in prodromal and early PD.