Accessing the role of Neisseria oral taxon 14 and sphingolipid/ceramide metabolism on Parkinson's disease

Hanan Abdelgilil, Ashley Persons, Gena Tribble and Ransome van der Hoeven.

The University of Texas Health Science Center at Houston, School of Dentistry, Houston, Texas, USA.

Objectives: Parkinson's disease (PD) is currently one of the most incurable neurodegenerative disorders. A hallmark of this disorder is the accumulation of α-synuclein aggregates causing neurotoxicity. Recent studies have highlighted the influence of human gut microbiota on the progression of PD. However, few studies have investigated the role of the oral microbiota on PD. Nitric oxide producing gut bacteria and some genes associated with sphingolipid metabolism have shown to impact α-syn aggregation. We previously showed that nitric oxide producing Neisseria oral taxon 14 (NOT-14), a member of the human oral microbiota enhances the immune response in the nematode *Caenorhabditis elegans*. The objectives of the study were to assess the effect of α-syn aggregation in the presence of NOT-14 relative to non-pathogenic *E. coli* and to perform a comprehensive analysis of genes associated with sphingolipid and ceramide metabolism on the formation of α-syn aggregates in a humanized worm model for PD.

Experimental methods: To assess the effect of α-syn aggregation, worms expressing human α-syn fused to yellow fluorescent protein (YFP) were exposed to NOT-14 and non-pathogenic *E. coli* for 72 hours and the number of aggregates were scored using fluorescence microscopy. To determine the effects of sphingolipid and ceramide metabolism genes on α-syn aggregation, worms expressing α-syn::YFP were knockdown with ceramide and sphingolipid metabolism associated genes for 72 hours, and the number of aggregates were scored.

Results: Significant decrease in the number of aggregates were observed in NOT-14 worms compared to non-pathogenic *E. coli*. Further, we observed significant decrease in the number of aggregates in *asha-1*, *asm-1*, *cgt-1* and *spl-1* knockdown worms compared to the vector control.

Conclusion: Overall, our data suggests exposure of worms to NOT-14 significantly reduces the formation of α-synuclein aggregates, while some genes of the sphingolipid and ceramide pathways influence the formation of these aggregates.

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