THE MER TYROSINE KINASE MEDIATES THE INTERNALIZATION OF ALPHA-SYNUCLEIN FIBRILS BY HUMAN MICROGLIA

Marie-France DORION[1], Konstantin SENKEVICH[2], Moein YAQUBI[1], Wen LUO[1], Amber WALLIS[3], Irina SHLAIFER[1], Jack P. ANTEL[1], Ziv GAN-OR[2], Tim BARTELS[3], Thomas M. DURCAN[1], Luke M. HEALY[1]

1. Montreal Neurological Institute, McGill University, Montréal, QC, Canada
2. Department of Human Genetics, McGill University, Montreal, QC, Canada
3. UK Dementia Research Institute, University College London, London, UK

*correspondence: **marie-france.dorion@mail.mcgill.ca**

BACKGROUND

Fibrils of alpha-synuclein (aSYN) which accumulate in Lewy body diseases such as Parkinson's disease (PD) or Lewy body dementia (LBD) are thought to have causal role in neurodegenerative processes. Promotion of aSYN fibril clearance by microglia has been proposed as a promising therapeutic strategy.[1]

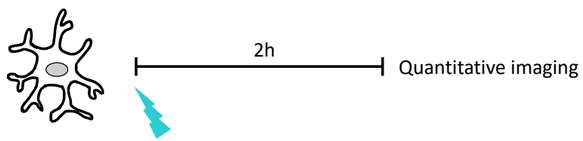
TAM receptors (Tyro3, AXL, MerTK) are a family of receptor tyrosine kinases among which MerTK, highly expressed on microglia, mediates the phagocytosis of various substrates.[2] Its expression has been previously observed to be elevated in a mouse model of Parkinson's disease.[3] Yet, its role in aSYN fibril uptake has never been explored.

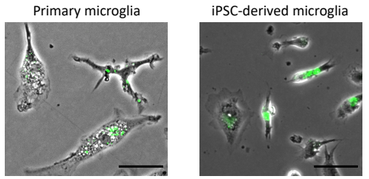
AIM

We aim to investigate the role of MerTK in aSYN fibril engulfment by human microglia.

METHODS

Primary or iPSC-derived microglia





RESULTS

Pharmacological inhibition of MerTK results in decreased microglial uptake of aSYN fibrils

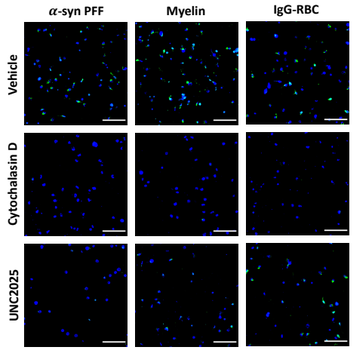


Figure 1. Effect of the TAM receptor inhibitor UNC2025 on aSYN PFF uptake by microglia. iPSC-derived microglia were treated with vehicle, UNC2025 or cytochalasin D for 1 hour and then challenged with pHRodo Green-labelled aSYN PFF, myelin debris or opsonized red blood cells (IgG-RBC). Scale bar = 150 μm.

MERTK knockdown results in decreased microglial uptake of aSYN fibrils

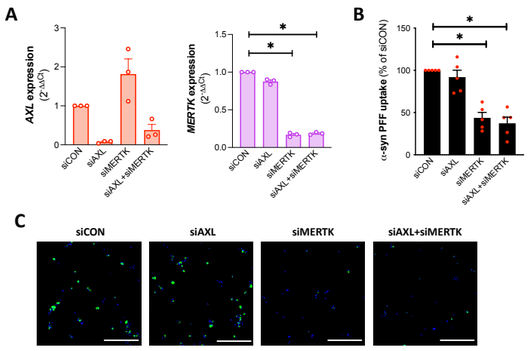


Figure 2. Effect of AXL/MERTK knockdown on aSYN PFF uptake by microglia. Primary microglia were incubated with control (siCON) or *AXL*/*MERTK*-targeting siRNAs for 48 hours and then challenged with pHrodo Green-labelled aSYN PFFs. (A) Knockdown efficiency assessed by qRT-PCR (n=3). (B) Quantification of green fluorescence intensity per cell (n=4). (C) Fluorescence images (scale bar = 200 μm). *p<0.05

Rare deleterious *MERTK* variants are associated with PD cases

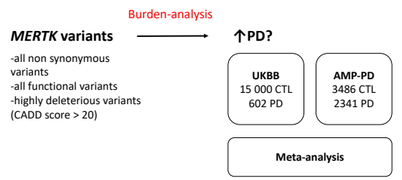


Figure 3. Burden analysis of *MERTK* and *AXL* variants in two independent patient cohorts. UKBB = UK biobank, AMP-PD = Accelerated Medicines Partnership – Parkinson's Disease, CADD = combined annotation dependent depletion.

Gene	All nonsynonymous, p			All functional, p			CADD score ≥ 20, p		
	UKBB	AMP-PD	Meta-analysis	UKBB	AMP-PD	Meta-analysis	UKBB	AMP-PD	Meta-analysis
MERTK	0.2	0.92	0.81	0.21	1	0.78	**0.002**	0.67	0.28
AXL	0.84	0.27	0.48	0.83	0.27	0.48	0.45	0.85	0.54

MERTK is upregulated in PD/LBD nigral microglia

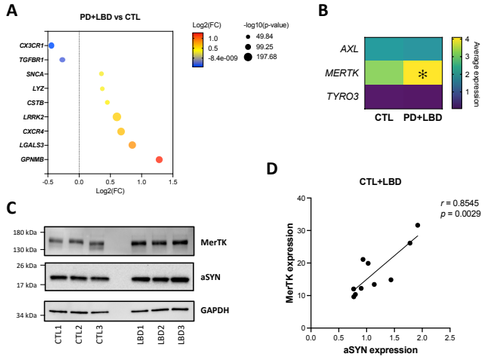


Figure 4. MerTK expression in Lewy body diseases. (A-B) snRNAseq data by Kamath *et al.*, 2022[4] were used. (A) Key results of DEG analysis between PD/LBD cases and control donors. (B) TAM receptor expression in PD/LBD microglia compared to control microglia. *p<0.05. (C-D) MerTK and aSYN expression in human cortex tissues from control (n=5) and LBD patients (n=5).

CONCLUSION

aSYN fibril uptake by human microglia is dependent on MerTK.

There is a possible genetic association between *MERTK* and PD.

MerTK expression is upregulated in contexts of aSYN accumulation.

MerTK- mediated aSYN clearance by microglia might have a protective role in Parkinson's disease pathogenesis.

References

1. Castonguay AM, Gravel C, Lévesque M. Treating Parkinson's Disease with Antibodies: Previous Studies and Future Directions. J Parkinsons Dis. 2021;11(1):71-92. doi:10.3233/jpd-202221
2. Lemke G. Biology of the TAM receptors. Cold Spring Harb Perspect Biol. 2013;5(11):a009076. doi:10.1101/cshperspect.a009076
3. Fourgeaud, L., Través, P.G., Tufail, Y., Leal-Bailey, H., Lew, E.D., Burrola, P.G., Callaway, P., Zagórska, A., Rothlin, C.V., Nimmerjahn, A., et al. (2016). TAM receptors regulate multiple features of microglial physiology. Nature 532, 240-244. doi: 10.1038/nature17630
4. Kamath T, Abdulraouf A, Burris SJ, et al. Single-cell genomic profiling of human dopamine neurons identifies a population that selectively degenerates in Parkinson's disease. Nature Neuroscience. 2022/05/01 2022;25(5):588-595. doi:10.1038/s41593-022-01061-1

Acknowledgement

biobank uk
Enabling scientific discoveries that improve human health
AMP PD
CIHR IRSC
Canadian Institutes of Health Research | Instituts de recherche en santé du Canada
HEALTHY BRAINS HEALTHY LIVES