

NOX-inflicted oxidative stress in neurodegeneration and inflammation

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Academicum, Medicinargatan 3, onsdagen den 4 juni 2025, klockan 9.00

av **Andreas Törnell**

Fakultetsopponent: Håkan Widner, Professor, Lunds universitet, Sverige

Avhandlingen baseras på följande delarbeten:

- I. **Törnell A**, Kiffin R, Haghighi S, Mossberg N, Andersen O, Hellstrand K, Martner A. Impact of *CYBA* genotypes on severity and progression of multiple sclerosis. *Eur J Neurol.* 2022;29(5):1457-64.
- II. **Törnell A**, Lagerstrom N, Mossberg N, Kiffin R, Farman H, Lycke J, Andersen O, Axelsson M, Hellstrand K, Martner A. *CYBA* allelic variants are associated with severity and recovery in Guillain-Barre syndrome. *J Peripher Nerv Syst.* 2023;28(3):407-14.
- III. **Törnell A**, von Below D, Levander D, Nissbrandt H, Bergquist F, Hellstrand K, Martner A. Gene variants entailing increased enzymatic ROS formation may accelerate long-term progression in idiopathic Parkinson's disease. *In manuscript.*
- IV. **Törnell A**, Waldenström J, Kiffin R, Akhiani AA, Thorén FB, Hellstrand K, Martner A. Bruton's tyrosine kinase activates the NOX2/ROS axis to drive myeloid immunosuppression in cancer. *Submitted.*

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Abstract

Further understanding of mechanisms that promote neuronal decay in neurodegenerative diseases may pave the way for new therapies. Aberrant activation of the reactive oxygen species (ROS)-generating enzyme NADPH oxidase 2 (NOX2) in myeloid cells is suggested to contribute to neurodegeneration in experimental models. However, its exact role in human disease is not known. We aimed to define the impact of NOX2 activity on neurodegeneration and identify potential therapeutic strategies for NOX2-inflicted pathologies. To this end, we examined single nucleotide polymorphisms (SNPs) that affect the magnitude of NOX2-derived ROS formation in the context of the neurodegenerative and neuroinflammatory diseases multiple sclerosis (MS), Guillain-Barré syndrome (GBS), and Parkinson's disease (PD). Furthermore, we investigated the NOX2-inhibitory potential of inhibitors of Bruton's tyrosine kinase (BTKi), which regulates myeloid cell activation. We identified two SNP alleles (rs4673 A and rs1049254 G in *CYBA*, encoding the NOX2 subunit p22^{phox}) that were associated with reduced NOX2-derived ROS production. In MS, these low-ROS alleles heralded reduced disease severity and a markedly delayed onset of secondary progressive MS (**paper I**). Patients with GBS carrying low-ROS alleles were less likely to require assisted ventilation during the acute phase and experienced a rapid recovery of motor function (**paper II**). Furthermore, an analysis of clinical milestone cumulation in idiopathic PD revealed that patients with low-ROS alleles showed a reduced rate of disease progression (**paper III**). In **paper IV**, we demonstrated that BTKi effectively blocked activation of NOX2 in myeloid cells in response to surface receptor stimulation. This translated into potentiated natural killer cell-mediated clearance of malignant cells in the presence of immunosuppressive myeloid cells *in vitro* and *in vivo*. In conclusion, our results suggest that NOX2-derived ROS may contribute to neuronal death in MS, GBS, and PD. This implies that NOX2 might serve as a generic driver of neurodegeneration and invites research on its role in additional neurodegenerative diseases. The NOX2-inhibitory potential of BTKi makes them conceivable candidates to target myeloid immunosuppression in both hematological and solid cancers, as well as to alleviate other NOX2-dependent pathologies.

Keywords: NADPH oxidase, NOX2, oxidative stress, neurodegeneration, multiple sclerosis, Guillain-Barré syndrome, Parkinson's disease

ISBN: 978-91-8115-253-1 (TRYCK)

<http://hdl.handle.net/2077/85338>

ISBN: 978-91-8115-252-4 (PDF)