Transgenic Overexpression of GPNMB Protects Against MPTP-Induced Neurodegeneration

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Parkinson's disease (PD) is the second most prevalent neurodegenerative disease worldwide behind Alzheimer's disease. One prominent feature of PD is the marked loss of dopaminergic and motor dysfunction. Motor symptoms of PD include resting tremor, rigidity, bradykinesia, and akinesia. Currently, there are no therapies to effectively slow disease progression. Thus, novel drug discovery is of paramount importance. Glycoprotein non-metastatic melanoma protein B (GPNMB) is a transmembrane glycoprotein, with reported anti-inflammatory, reparative, and neuroprotective functions. Recent reports indicate that GPNMB has neuroprotective functions in mouse models of amyotrophic lateral sclerosis (ALS). Furthermore, recent work from our group has shown that GPNMB reduces the inflammatory response in astrocytes. Here, we investigated whether GPNMB has neuroprotective effects in Parkinson's disease. To accomplish this, we first assessed the role of GPNMB in an acute 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of Parkinson's disease. Western blot analysis of the striatum revealed a significant decrease in tyrosine hydroxylase (TH) and dopamine active transporter (DAT) expression in MPTP-treated wild-type mice. However, MPTP-treated GPNMB transgenic (TG) mice had a significant increase in TH and DAT compared to the wild-type MPTP-treated mice. Additionally, MPTP induced significant neuron loss in wild-type mice, but this was attenuated in GPNMB-TG mice. Furthermore, we have shown that MPTP induces microgliosis and microglial morphological changes in wild-type mice, while this response was attenuated in GPNMB-TG mice. These data indicate that GPNMB may play a role in microglia function and we are investigating this role further.