Neuroprotection by MC1R as the basis for the melanoma-Parkinsons disease link

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Neuroprotection by MC1R as the basis for the melanoma-Parkinsons disease link

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Melanocortin 1 Receptor, neuroprotection, melanoma, Parkinson Disease, 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine

Research Abstract

? DESCRIPTION (provided by applicant): Individuals with Parkinson’s disease (PD) are more likely to develop melanoma. Conversely, melanoma patients are at higher risk of developing PD. This bidirectional link has been observed not only in the patients themselves but also in their relatives, suggesting a genetic basis for the link between these two seemingly distinct conditions. Melanocortin 1 receptor (MC1R) is a major pigmentation gene and its loss-of-

function mutations are associated with red hair and increased melanoma risk. Loss-of-function red hair variants of MC1R have also been linked to an increased risk for PD. Mice carrying an inactivating mutation of MC1R (MC1Re/e mice) have a phenotype analogous to red hair in humans. Conversely transgenic human MC1R expression (MC1R Tg mice) rescues the dermal phenotype. Our preliminary data indicate reduced striatal dopamine and nigral dopaminergic neuron counts under basal conditions in young adult MC1Re/e mice and age-related decline in locomotor function in MC1Re/e mice. MC1Re/e mice also demonstrate exacerbated dopamine depletion induced by 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine (MPTP). In collaboration with leading melanoma researchers who reported MC1R-mediated pigmentation and melanoma carcinogenesis, we propose to investigate the role of MC1R in dopaminergic neuron survival and pathophysiology of PD, and of particular translational relevance, the neuroprotective potential of human MC1R. Complementary MC1Re/e mice and MC1R Tg mice will be used. Specific Aim 1 will assess whether MC1R inactivation compromises dopaminergic neuronal integrity under basal conditions and in complementary environmental (MPTP) and genetic (a-synuclein) models of PD. Specific Aim 2 will determine whether transgenic expression of human MC1R protects the nigrostriatal dopaminergic pathway under basal conditions and in the MPTP and a-synuclein models. Oxidative stress and inflammation related mechanisms will be explored. Based on compelling epidemiological and laboratory evidence, the proposed study strikes a balance between reasonable risk and high return. The insights gained from the proposed project will shed light on a virtually unexplored biological basis of the melanoma and PD link. Results from this study may advance our understanding of a dual role of MC1R in tumorigenesis in melanocytes and neurodegeneration of dopaminergic neurons. Furthermore, the proposed study may establish foundation for further investigations on potential of targeting MC1R as a novel therapeutic strategy for PD.

Further information available at:

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