Genetic Susceptibility to Manganese Neurotoxicity

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Research Abstract
? DESCRIPTION (provided by applicant): Environmental exposure to manganese (Mn) represents a health hazard of clinical and translational significance. Excessive exposure to Mn leads to a movement disorder with analogous symptoms to idiopathic Parkinson’s disease (PD). Clinically, manganism is characterized by rigidity, tremor, dystonia, bradykinesia and progressive neurodegeneration, predominantly due to the accumulation of excessive Mn in the

basal ganglia. Prevalent hypotheses on Mn-induced neurodegeneration include mitochondrial dysfunction, oxidative damage and protein misfolding. We recently identified in the nematode, Caenorhabiditis elegans (C. elegans), a novel protein – TMEM-135 that regulates levels of DAF-16 [homolog of mammalian forkhead box protein O (FoxO)], a forkhead/winged-helix transcription factor, which is critical for attenuating oxidative stress. Notably, the mammalian brain areas most susceptible to Mn- induced injury are also highly sensitive to oxidative stress. The TMEM-135 protein is highly expressed in dopaminergic (DAergic) neurons both in mammals and in C. elegans. Our data also show that in the worm TMEM-135 is involved in a genetic control of lifespan and mitochondrial function. Given these observations, the central hypothesis of this novel R21 is that TMEM-135 is critical in mediating oxidative stress responsiveness to Mn, and that loss of TMEM-135 leads to mitochondrial dysfunction and increased susceptibility to Mn-induced oxidant injury and DAergic neurodegeneration. Our hypothesis will be tested in the following two Specific Aims: Specific Aim 1. Determine the role of TMEM-135 in response to oxidative stress upon Mn exposure in C. elegans. In this aim, we will assess molecular, and biochemical determinants of oxidative stress response associated with Mn exposure. Specific Aim 2. Determine if TMEM-135 modulates Mn-induced DAergic neurodegeneration in a C. elegans model of PD (Pdat- 1::GFP). We will investigate DAergic neurodegeneration in response to Mn exposure in wildtype (WT), tmem-135 knockout and TMEM-135 overexpressing worms. Results from this study will have a broad clinical and translational impact as TMEM-135 may play a role in multiple chronic neurodegenerative diseases, such as Alzheimer’s disease and Huntington’s disease, to name a few, in which excessive generation of reactive oxygen species (ROS) and mitochondrial pathology are linked to progressive and irreversible neuronal death. Overall, findings derived from these studies will provide a clearer understanding of the exquisite sensitivity of DAergic neurons to Mn and its underlying mechanisms of neurotoxicity, identifying potential therapeutic targets for attenuating oxidative stress and maintaining optimal redox status.

Further information available at:

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