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“Novel Pathways Regulated by NME1 in Neuroblastoma”

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SCIENTIFIC ABSTRACT

There is a critical need for new treatment options for children with high-risk and relapsed neuroblastoma, and therapies directed against biologically relevant pathways are likely to be more effective with less toxicity. *NME1* expression has been linked to neuroblastoma patient outcomes, but the functional role of *NME1* in neuroblastoma pathogenesis has not been defined. *NME1* was recently demonstrated to have activity as a histidine kinase, and histidine phosphorylation is a post-translational modification with potential relevance for a broad range of cancers. We have confirmed significant associations between *NME1* gene expression and neuroblastoma patient outcomes and prognostic features, and we have identified histidine phosphorylation of multiple proteins in neuroblastoma cell lines and xenograft tumors. Using a novel Boolean analysis, we have also identified a potentially critical functional link between *NME1* expression and signaling pathways involved in neuroblastoma pathogenesis. We hypothesize that *NME1* expression and activity regulate intracellular signaling pathways responsible for neuroblastoma tumor development, growth, and spread, and we therefore propose to identify signaling pathways linked to *NME1* expression and evaluate the functional roles of *NME1* expression and *NME1*-mediated signaling activity in neuroblastoma preclinical models. The potential novel roles of *NME1* and *NME1*-mediated signaling in neuroblastoma pathogenesis represent an opportunity to identify novel therapeutic targets for the development of innovative, biologically-based therapies, potentially leading to improved success of neuroblastoma therapy and improved survival rates for children with neuroblastoma.

LAY ABSTRACT

Children with aggressive neuroblastoma tumors have poor rates of survival and cure despite intensive treatment, and new therapies are needed. Treatments that block the actions of important proteins and pathways in neuroblastoma tumors are likely to be more effective with fewer side effects. We have identified an association between the levels of the *NME1* gene and the rates of survival of children with neuroblastoma, and we have also identified an association between the levels of the

NME1 gene and signaling pathways that potentially control neuroblastoma cell growth and spread, suggesting that NME1 may be a good candidate target for new neuroblastoma treatments. We propose to determine the genes and pathways in neuroblastoma cells that are controlled by NME1 and to explore how NME1 expression levels and activity affect neuroblastoma tumor cell growth, survival, and spread. The results of these studies will likely identify new proteins that could serve as targets for new types of treatment, leading to improved success of neuroblastoma therapy and improved chances of survival for children with neuroblastoma.