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“Functional Roles for Histidine Kinase Signaling 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, a novel post-translational modification with potential relevance for a broad range of cancers. We have confirmed strong associations between *NME1* gene expression and neuroblastoma patient outcomes and prognostic features, and we have demonstrated NME1 histidine kinase activity in neuroblastoma cell lines and xenograft tumors. We have also identified associations between NME1 expression and neuroblastoma cell differentiation and migration. However, the functional roles of NME1 and histidine kinase signaling in the pathogenesis of neuroblastoma are unknown. We hypothesize that NME1 histidine kinase activity regulates neuroblastoma tumor cell differentiation and metastasis, and we therefore will evaluate the functional roles of NME1 expression and histidine kinase activity in the process of neuroblastoma differentiation and in tumor growth and metastasis. The potential novel roles of NME1 and histidine kinase 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 have poor cure rates despite intensive treatment, and new therapies are needed. Treatments that inhibit important proteins and pathways in neuroblastoma tumors are likely to be more effective with fewer side effects. We have identified an association between expression of the *NME1* gene and the survival rates of children with neuroblastoma, suggesting that NME1 may be a good candidate target for new neuroblastoma treatments. NME1 can act as a histidine kinase by adding phosphate to the amino acid histidine in other proteins in neuroblastoma cells, representing a previously undiscovered way for cells to control the function of proteins required for neuroblastoma growth and survival. We propose to explore how the NME1 histidine kinase affects neuroblastoma tumor cell maturation, 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.