Insights into pediatric diffuse intrinsic pontine glioma through proteomic analysis of cerebrospinal fluid.


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Abstract
Diffuse intrinsic pontine glioma (DIPG) is a leading cause of brain tumor-related death in children. DIPG is not surgically resectable, resulting in a paucity of tissue available for molecular studies. As such, tumor biology is poorly understood, and, currently, there are no effective treatments. In the absence of frozen tumor specimens, body fluids—such as cerebrospinal fluid (CSF), serum, and urine—can serve as more readily accessible vehicles for detecting tumor-secreted proteins. We analyzed a total of 76 specimens, including CSF, serum, urine, and normal and tumor brainstem tissue. Protein profiling of CSF from patients with DIPG was generated by mass spectrometry using an LTQ-Orbitrap-XL and database search using the Sequest algorithm. Quantitative and statistical analyses were performed with ProteoIQ and Partek Genomics Suite. A total of 528 unique proteins were identified, 71% of which are known secreted proteins. CSF proteomic analysis revealed selective upregulation of Cyclophilin A (CypA) and dimethylarginase 1 (DDAH1) in DIPG (n = 10), compared with controls (n = 4). Protein expression was further validated with Western blot analysis and immunohistochemical assays using CSF, brain tissue, serum, and urine from DIPG and control specimens. Immunohistochemical staining showed selective upregulation of secreted but not cytosolic CypA and DDAH1 in patients with DIPG. In this study, we present the first comprehensive protein profile of CSF specimens from patients with DIPG to demonstrate selective expression of tumor proteins potentially involved in brainstem gliomagenesis. Detection of secreted CypA and DDAH1 in serum and urine has potential clinical application, with implications for assessing treatment response and detecting tumor recurrence in patients with DIPG.