Phosphorylated Pak1 Level in the Cytoplasm Correlates with Shorter Survival Time in Patients with Glioblastoma

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Purpose: Glioblastoma is the most common primary malignant tumor in the brain. It aggressively invades the surrounding parenchyma, often allowing the tumor to progress after surgery. Accumulating evidence has shown that phosphorylated p21-activated kinase 1 (Pak1), a mediator of small guanosine triphosphatases, plays a role in the proliferation, survival, and invasiveness of cancer cells. Thus, we examined patterns of Pak1 expression in glioblastoma and sought to determine whether the level of phosphorylated Pak1 in glioblastoma cells is associated with patient survival time.

Experimental Design: We carried out immunohistochemical staining for phosphorylated Pak1 in tumor specimens from 136 patients with glioblastoma; the tumors were classified according to Pak1 protein levels in the cytoplasm and nucleus. We compared the patients' overall survival times using Kaplan-Meier analysis and estimated the effects of levels of cytoplasmic or nuclear phosphorylated Pak1. We then down-regulated Pak1 by using small interfering RNA to knock down Pak1 in two glioblastoma cell lines to determine whether Pak1 contributed to cell viability and invasion.

Results: Median overall survival was significantly shorter in patients with tumors showing a moderate or high level of cytoplasmic phosphorylated Pak1 than in patients with tumors showing no cytoplasmic phosphorylated Pak1. The level of nuclear phosphorylated Pak1 was not related to survival time. Knockdown of Pak1 suppressed the invasion, but not the viability, of U87-MG and U373-MG cells.

Conclusions: The presence of phosphorylated Pak1 in the cytoplasm of glioblastoma cells is associated with shorter survival, and Pak1 plays a role in the invasiveness of glioblastoma. These data suggest that Pak1 might be a potential target for the management of glioblastoma.