

The role of KPN β_1 in neuro-oncology

Megan Lilley^{1,2}
Faris Farassati^{1,3}

¹Midwest Biomedical Research Foundation, Kansas City Veterans Affairs Medical Center, ²School of Medicine, University of Missouri, ³Saint Luke's Cancer Institute–Saint Luke's Marion Bloch Neuroscience Institute, Kansas City, MO, USA

KPN β_1 , also known as importin- β , is part of the karyopherin superfamily of nuclear transport proteins.¹ The classical importin- α/β system is believed to import up to half of the nuclear traffic.² Importins and exportins transport pro-oncogenic mediators across the nuclear membrane and are found to be overexpressed in a number of cancer types, including breast, colon, esophageal, gastric, lung, lymphoma, melanoma, pancreatic, and prostate cancer.³ The nuclear pore complex (NPC) is composed of approximately 30 proteins (nucleoporins) that are arranged octagonally around a central channel. KPN β_1 participates in the classical nuclear import pathway alongside its adaptor protein – importin- α . Importin- α first recognizes and binds the cytoplasmic cargo via its nuclear localization signals, and then associates with importin- β via the importin- β binding (IBB) domain. This complex (nuclear localization signals–importin- α –importin- β) then traverses the nuclear pore complex.⁴ This active transport is able to occur against the concentration gradient, due to varying levels of Ran, a GTPase.⁴

KPN β_1 has recently been shown to regulate proliferation of human glioma cells via the Wnt- β -catenin pathway.⁵ Glioblastoma multiforme is the most frequent brain cancer in adults and is highly infiltrative.⁶ Despite current treatments of neurosurgery and chemoradiotherapy, median survival remains around 14.6 months, and 5-year survival is <5%.^{5,7} Lu et al showed that the relative expression of KPN β_1 correlated with the World Health Organization (WHO) grades of human glioma, with higher expression of KPN β_1 correlating with more severe WHO glioma classification.⁵ Additionally, higher expression of KPN β_1 correlated with lower 5-year survival ratio on Kaplan–Meier survival curves.⁵ Wnts are glycoproteins that are involved in cell proliferation, differentiation, and oncogenesis, and regulate β -catenin in their pathway.⁵ KPN β_1 has recently been elucidated as a regulator of glioma-cell proliferation via the Wnt- β -catenin pathway.⁵ Down-regulation of KPN β_1 has been shown to inhibit glioma proliferation in vitro. Additionally, cells with lower levels of KPN β_1 showed decreased nuclear β -catenin, demonstrating that KPN β_1 played a role in the nuclear transport of β -catenin in the Wnt- β -catenin pathway.⁵ KPN β_1 has previously been shown to play a role in translocating β -catenin, which accelerates glioma proliferation.⁵

Another role of KPN β_1 and glioma is the transport of GLI1 into the nucleus.⁸ GLI1 was discovered in human gliomata,⁶ and is a nuclear regulator of the Hedgehog (Hh)-signaling pathway.⁸ Dysregulation of this pathway leads to aggressive tumorigenesis. Hh normally binds to and inactivates Patched (Ptc). When Ptc is inhibited, Smoothed (Smo) is released and triggers a signaling cascade that ends in nuclear localization of GLI.⁸ SuFu is an additional negative regulatory protein that anchors GLI in the cytoplasm during inactivation of the Hh-signaling pathway.⁸

KPN β_1 binds GLI1 with high affinity, and the GLI1-binding site on the N-terminus for SuFu overlaps with the GLI1-binding site for KPN β_1 . This results in competitive

Correspondence: Faris Farassati
Midwest Biomedical Research
Foundation, Kansas City Veterans Affairs
Medical Center, 4801 East Linwood
Boulevard, Kansas City, MO 64128, USA
Email ffarassati@gmail.com

binding of GLI1 based on relative concentrations of KPN β_1 and SuFu.⁸ When KPN β_1 is bound to GLI1 (rather than SuFu bound to GLI1), GLI1 can undergo nuclear import and thereby play a role in tumorigenesis.⁸ Various studies have found different levels of GLI1 in malignant gliomata. Zhu and Lo performed genome-wide copy-number analysis on 31 glioma samples and found that 22.6% of these samples had amplified *GLI1*.⁶ Therefore, inhibition of nuclear import of GLI1 via KPN β_1 has the potential to inhibit oncogenesis in gliomata as a novel therapeutic strategy.⁸ Interestingly, KPN β_1 has also been indicated in the development of secondary brain tumors.⁹ Childhood acute lymphoblastic leukemia commonly results in treatment-related secondary brain tumors.⁹ This is due in part to cranial irradiation (and treatment with antimetabolites), though a genetic predisposition is also necessary.⁹ In a study by Edick et al, ~20% of patients developed secondary brain tumors, comprised of glioblastoma multiforme, anaplastic astrocytoma, primitive neuroectodermal tumors, and embryoplastic neuroepithelial tumors.⁹ Genetic analysis of pretreatment acute lymphoblastic leukemia blasts indicated the *KPNB1* gene, along with *STAT4*, *NFIC*, and *HNRPL* (all involved in tumor growth and trafficking), to have high significance in the development of secondary brain tumors.⁹ This supports the role of KPN β_1 in oncogenesis and cancer-cell viability and suggests its potential use as a predictive factor for secondary brain tumors. In conclusion, KPN β_1 is a promising target for

anticancer therapeutics, including a potential for inhibition of certain neurological malignancies.

Disclosure

The authors declare no conflicts of interest in this work.

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