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EDITORIAL

The role of KPNβ$_1$ in neuro-oncology

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KPNβ$_1$, 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. KPNβ$_1$ 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]

KPNβ$_1$ 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 KPNβ$_1$ correlated with the World Health Organization (WHO) grades of human glioma, with higher expression of KPNβ$_1$ correlating with more severe WHO glioma classification.[5] Additionally, higher expression of KPNβ$_1$ 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] KPNβ$_1$ has recently been elucidated as a regulator of glioma-cell proliferation via the Wnt–β-catenin pathway.[5] Down-regulation of KPNβ$_1$ has been shown to inhibit glioma proliferation in vitro. Additionally, cells with lower levels of KPNβ$_1$ showed decreased nuclear β-catenin, demonstrating that KPNβ$_1$ played a role in the nuclear transport of β-catenin in the Wnt–β-catenin pathway.[5] KPNβ$_1$ has previously been shown to play a role in translocating β-catenin, which accelerates glioma proliferation.[5]

Another role of KPNβ$_1$ 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, Smoothened (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]

KPNβ$_1$ binds GLI1 with high affinity, and the GLI1-binding site on the N-terminus for SuFu overlaps with the GLI1-binding site for KPNβ$_1$. This results in competitive

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binding of GLI1 based on relative concentrations of KPNβ$_1$ and SuFu.[8] When KPNβ$_1$ 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 KPNβ$_1$ has the potential to inhibit oncogenesis in gliomata as a novel therapeutic strategy.[8] Interestingly, KPNβ$_1$ 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 KPNβ$_1$ in oncogenesis and cancer-cell viability and suggests its potential use as a predictive factor for secondary brain tumors. In conclusion, KPNβ$_1$ 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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