SH3-domain kinase binding protein 1(SH3KBP1) and Tumor Microenvironment

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Abstract

SH3-domain kinase binding protein 1(SH3KBP1) also known as CBL-interacting protein, 85-KD/CIN85, functions as an adaptor protein. It is involved in multiple immune functions, expressed in immune organs and cells, specifically in the activation of B cells, the production of antibodies, and the activation of NFKB, following stimulation from B-cell receptors. It also plays a role in the prevention of EGFR degradation through the autophosphorylation of EGFR receptor sites. SH3KBP1 is also linked with other conditions, such as X-linked agammaglobulinemia. It shows its presence in other oncogenic activities, such as presence in glioblastomas and breast cancer, through overexpression via EGFR signaling and cell invasion. This review will discuss the role of SH3KBP1 in cancer development, tumor microenvironment, and potential therapeutic targeting.

Keywords: SH3KBP1/ CIN85/ 85-KD, SH3, adaptor protein, cancer development, therapeutic targeting

Introduction

SH3KBP1(also named: Cbl-interacting protein of 85 kD (CIN85) is a ubiquitous adaptor protein, containing SH3 domains (Kuhn et al., 2016). SH3 is identified as a member of the SRC homology domain, specifically as the non-catalytic portion of receptor tyrosine kinases, involved in mediating cell recognition and signalling, cell growth and proliferation, motility, differentiation, clathrin-mediated endocytosis, lysosomal degradation of ligand-induced receptor tyrosine kinases, cytoskeleton rearrangement, and cell adhesion (Kurochkina & Guha, 2013). SH3KBP1/CIN85 functions as an adaptor protein, playing vital roles in B cell activation and the prevention of EGFR degradation through the autophosphorylation of EGFR receptor sites (Dikic, 2002; Song et al., 2020). The two PXXXPR motifs in the carboxyl terminus transmit a signal, known as EGF & TGF-alpha, which serves to communicate to SH3 proteins (Yakymovych et al., 2015). Furthermore, SH3KBP1 has been demonstrated to show association with glioma tumorigenesis and breast cancer cell invasion (Luo et al., 2024). This review will discuss the role of SH3KBP1 in physiology and tumorigenesis, including oncogenic vs. tumor-suppressive Roles. Further, we will discuss the role of hematologic Malignancies development and the tumor microenvironment and potential therapeutic targeting.

SH3KBP1 Structure and Function

The protein SH3KBP1 has multiple isoforms due to alternative splicing, but its core structural features include (1) Three SH3 domains N-terminal region, (2) A proline-rich region, and (3) A C-terminal coiled-coil domain, as shown in Figure 1: SH3KBP1 contains 3 N-terminal SH3 domains responsible for binding to proline-rich motifs targeted proteins. The SRC homology (SH3) domain is composed of around 50 amino acid residues, identified as the non-catalytic portion of receptor tyrosine kinases (Kurochkina & Guha, 2013). SH3KBP1's proline region functions to manage protein-protein interactions; finally, the protein's overall structure and function also comprise a coiled-coil domain at the C-terminal (Dikic, 2002).

Figure 1: Diagram of the domain structure of SH3KBP1. This protein is composed of three N-terminal SH3 domains, followed by a proline-rich motif located in the centre. As well, there is a C-terminal coiled-coil domain at the end (represented by CC).

The SH3KBP1 performs multiple functions, including endocytosis, cell adhesion, cytoskeletal organization, and signal transduction. In endocytosis facilitation, the protein interacts with endophilins and CBL to regulate the lysosomal degradation of receptor tyrosine kinases, which include EGFR and MET (Song et al., 2020). As well, by interacting with PTK2B, PDCD6IP, and other proteins, SH3KBP1 becomes involved in cell adhesion (Dikic, 2002). In general, cytoskeletal organization through cell morphology regulation is one of many functions that SH3KBP1 is involved in as well(Guiraud et al., 2025). Modulating MAPK pathways and TNF-mediated apoptosis, the protein is also linked to signal transduction functions. SH3KBP1 also is involved in multiple immune functions, expressed in immune organs and cells, specifically in the activation of B cells, the production of antibodies, and the activation of NFKB, following stimulation from B-cell receptors(Kuhn et al., 2016).

SH3KBP1 and Cancer

SH3KBP1 heightened expression levels are linked to glioblastoma and breast cancer(Ahmed et al., 2021; Song et al., 2020).It plays a key role in promoting cancer progression via inhibiting Hypoxia-Inducible Factor (HIF) binding with Prolyl Hydroxylase 2 (PHD2)(Kozlova et al., 2019). Moreover, SH3KBP1 can promote breast cancer cell invasion with it's interactions with Casitas B lineage lymphoma (c-Cbl)(Sato et al., 2013). It's linked with other conditions as well, such as X-linked agammaglobulinemia (XLA), breast adenocarcinoma(Feng et al., 2011) and lung adenocarcinoma. In glioblastoma, SH3KBP1's overexpression promotes its tumorigenesis by directing interaction with EGFR, activating its signaling, and impairing its degradation. As well, the protein promotes self-renewal of glioblastoma stem cells, marking its high expression in association with a poor prognosis(Song et al., 2020).

In Song et al. reported that correlation between SH3KBP1 mRNA and protein levels' high expression to poor glioma patient prognosis. It is a novel regulator of oncogenic EGFR signalling by directly interacting with EGFR, acting as an adaptor protein in EGFR signal transduction. SH3KBP1 is prominently expressed in glioblastoma stem cells (GSCs) and may serve as a potential GSC therapeutic marker for patients with EGFR activation. Observing in vitro and xenograph tumors growth in vivo, the drastic impairment of GBM cell proliferation, migration, and GSC's self-renewal ability, when SH3KBP1 was silenced (Song et al., 2020). SH3KBP1 can prevent EGFR degradation through the autophosphorylation of EGFR receptor sites, which begins a signal via two PXXXPR motifs in the carboxyl terminus, known as EGF and TGF-alpha (SRC homology 3 proteins)(Song et al., 2020).

TGFβ stimulation in a TRAF6-dependent manner triggers TβRI's interaction with the three SH3 domains of CIN85. siRNA-mediated knockdown of CIN85 diminished TGFβ-stimulated Smad2 phosphorylation and accumulated TβRI in intracellular compartments. In contrast, overexpression of

SH3KBP1 increases the quantity of TβRI on the cell surface. It was observed that this outcome was inhibited by a dominant-negative mutant of Rab11, suggesting the recycling of TGFβ receptors was promoted by CIN85. SH3KBP1/CIN85 enhanced TGFβ-stimulated Smad2 phosphorylation, cell migration, and transcriptional responses. Expression of SH3KBP2 correlated with the degree of prostate cancer malignancy. In summary, the results confirm CIN85's promotion of TGFβ receptor recycling, hence positively regulating TGFβ signalling (Yakymovych et al., 2015).

Targeting SH3KBP1 for Cancer therapy

Inhibiting SH3KBP1 shows benefit for cancer therapy such as Glioblastoma (GBM), pancreatic, and cervical cancers through the interference of cancer signalling pathways such as the epidermal growth factor receptor (EGFR) pathway(Song et al., 2020). EGFR is a universally recognized kinase that functions in multiple cancer such as glioma cell proliferation and migration (Song et al., 2020). SH3KBP1 prevents EGFR degradation and activates EGFR signalling. Hence, it promotes glioma progression, dependent on the SH3KBP1-EGFR axis. Targeting SH3KBP1 led to significantly suppression of tumor cell proliferation, migration, and GSC sphere formation; inhibition of SH3KBP1 may also enhance the efficacy of cancer immunotherapies, indicating it may be a possible diagnostic marker and therapeutic target (Guo et al., 2023; Song et al., 2020). Furthermore, targeting SH3KBP1 especially hinders EGFR downstream signaling, expressly, p-AKT, p-ERK, and p-MAPK expression levels. Inhibitors that markedly inhibit SH3KBP1 expression in glioma cells may be developed to lengthen the lifespan of glioma patients(Song et al., 2020).

Casitas B-lineage lymphoma (CBL) is a ubiquitin ligase (E3) that activates upon Tyr371-phosphorylation, being involved in ubiquitin-mediated degradation, via targeting receptor protein tyrosine kinases. Observed in myeloproliferative neoplasms, breast, colon, and prostate cancer is the deregulation of CBL and its E3 activity. The progression of various cancers is notably linked with abnormal CBL expression; CBL mutants attain the ability to interact with SH3KBP1 in the absence of growth factor stimulation. In essence, CBL could act as an adaptor protein and recruit others, such as SH3KBP1, to promote breast cancer progression. New research documents that PepC1 inhibits the CBL-CIN85 interaction, which hinders breast cancer cell proliferation (Ahmed et al., 2021).

Discussion and conclusion

In summary, SH3KBP1 facilitates EGFR activation, thus promoting EGFR signalling pathway carcinogenic activity (Song et al., 2020). The roles of SH3KBP1 in EGFR-driven tumorigenesis substantiate the argument for SH3KBP1 as a prognostic marker for patients with gliomas and other types of cancer. SH3KBP1-PHD2 plays an essential survival function in tumors, by linking hypoxia signalling and growth factor adaptors. It plays a key role in promoting cancer progression via inhibiting Hypoxia-Inducible Factor (HIF) binding with Prolyl Hydroxylase 2 (PHD2)(Kozlova et al., 2019). An oxygen-independent mechanism of PHD2 regulation, having essential implications in cancer cell survival. Targeting SH3KBP1 led to suppression of tumor cell proliferation, migration, and sphere formation; inhibition of SH3KBP1 may also enhance the efficacy of cancer immunotherapies(Song et al., 2020). In the imminent future, it may be that we focus on screening particular inhibitors to determine their inhibitory effect on SH3KBP1/EGFR signalling. This holds promise in SH3KBP1 being used as a diagnostic and therapeutic target in succeeding studies.

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Acronym (Abbr.)	Definition
CBL	Casitas B-lineage lymphoma
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
GSC	Glioblastoma stem cell
HIF	Hypoxia-inducible factor
MAPK	Mitogen-activated protein kinase
MET	Mesenchymal-epithelial transition
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
p-AKT	Phosphorylated Akt serine/threonine kinase family
PDCD6IP	Programmed cell death 6-interacting protein
p-ERK	Phosphorylated extracellular signal-regulated kinases
PHD2	Prolyl Hydroxylase 2
PTK2B	Protein tyrosine kinase 2 beta
RAB11	Ras-associated binding protein 11
SH3	Src homology 3 domain
SH3KBP1	SH3-domain kinase binding protein 1
Smad2	Smad family member 2
TGF-α	Transforming growth factor alpha
TGF-β	Transforming growth factor beta
TNF	Tumor necrosis factor
TRAF6	Tumor necrosis factor receptor-associated factor 6
TβRI	TGF-β type I receptor