

Kidins220 and tumour development: Insights into a complexity of cross-talk among signalling pathways (Review)

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Abstract. The mechanistic complexes of kinase D-interacting substrate of 220 kDa/ankyrin repeat-rich membrane spanning (Kidins220/ARMS) bind and integrate a variety of cellular cues to mediate neuronal activities such as neuronal differentiation, survival, and cytoskeleton remodelling by interacting with a variety of binding partners. Accumulated evidence has also indicated its role in the regulation of vascular development. Mice with Kidins220 knockdown phenotypically present with cardiovascular abnormalities. Kidins220 also contributes to immunomodulation in combination with B cells and T cells. Moreover, emerging evidence has revealed that this protein regulates many crucial cellular processes and thus has been implicated in an increasing number of malignancies. Here, we review recent advances in our understanding of Kidins220 and its role in cancer development. Further investigation is warranted to shed light on the role played by Kidins220 in the dynamic arrangement of the cytoskeleton and epithelial–mesenchymal transition, and its implication in tumourigenesis and cancer progression.

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1. Introduction

Scaffold proteins have evolved for efficiently interacting with certain signalling pathways and maintaining cellular structure. This is achieved through the regulation of the cytoskeleton, cell adhesion, and migration, allowing cells to survive and grow in variable environments. Dysregulation of certain scaffold proteins has been implicated in malignancies, including cancer development and metastasis. In mammals, an example of such multi-functional transmembrane scaffold proteins, is kinase D-interacting substrate of 220 kDa/ankyrin repeat-rich membrane spanning (Kidins220/ARMS). Kidins220 is a highly conserved integral membrane protein, which was initially identified as a substrate for protein kinase D (PKD), a serine/threonine kinase responsible for regulation of several cell processes (1). Despite recent studies demonstrating the role of Kidins220 in neurotrophin response, it is increasing apparent that Kidins220 is involved in the regulation of many cellular functions. Dysregulation of Kidins220 occurs in several human diseases including neurodegeneration and cancer, and thus there is increasing effort to pharmacologically target this protein. Here, we review our current understanding of Kidins220 and further discuss the possible links of Kidins220 to malignancies.

2. Kidins220/ARMS

Initially discovered in the nervous systems, Kidins220 responds to variable environment cues and coordinates neuronal survival, differentiation and plasticity (2-4). In the nervous system, Kidins220 is one of the downstream substrates for tropomyosin-related kinase (Trk) signalling (5). In mammal neural tissues, Kidins220 has a high binding affinity for neurotrophins and localizes to the tips of neurites abundant and enriched in expression of ephrin receptors and neurotrophins (6). In the nervous system, Kidins220 acts as a platform for protein-protein interactions, where its multiple domains recruit downstream receptor substrates

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resulting in the activation of signalling pathways which lead to neuronal differentiation, survival, cytoskeleton remodelling, synaptic plasticity and dendrite and synapse development (7). Development of the vascular system involves the interaction of Kidins220 with vascular endothelial growth factor receptors (VEGFRs). Knockout of Kidins220 resulted in impairment of the VEGF signalling pathway, while an *in vivo* study revealed that mice lacking Kidins220 developed cardiovascular abnormalities (8).

3. Kidins220 structure, expression and localization

The Kidins220 gene encodes a protein of 1715 amino acids. Kidins220 protein is comprised of 11 ankyrin-repeats within the N-terminal region, a proline-rich stretch, a sterile α motif (SAM) domain (9), kinase light chain (KLC)-interacting motif (KIM), and a PSD-95, Dlg, ZO-1-binding motif (PDZ) at its C-terminal. It contains four transmembrane segments in the central part of the molecule and N- and C-terminal tails both exposed to the cytoplasm. Kidins220 is the target of a molecule called protein kinase D, which first gained attention due to its broad regulation of neuronal properties. Biochemical processes led to the purification and identification of multiple Kidins220 domains which act as regulators in a variety of cell signalling pathways.

Originating from monocytes, immature dendritic cells in peripheral blood have been shown to express high levels of Kidins220. Therefore, currently the cytoskeleton remodelling which is driven through Kidins220 is best characterised in immature dendritic cells (10). Upon migration onto extracellular matrices, highly polarized immature dendritic cells change stage, from monopolar to symmetrical bipolar. During this process, Kidins220 is highly expressed at dendritic cell polarized membrane edges where F-actin localises (10). Further immunocytochemistry analysis has revealed that Kidins220 expression is concentrated around proteins which are associated with the raft compartment (10). Lipid rafts are microdomains of the cell plasma membrane and contain distinctive protein and lipid constituents, which are involved in the regulation of signalling transduction. Chemically induced disruption of lipid rafts resulted in the loss of Kidins220 from the enriched polarized edges, indicating a regulatory role of Kidins220 in cell morphology changes and motility (10,11). Kidins220 has also been observed at the neuromuscular junction suggesting that Kidins220 also plays a role in muscle development (12). Luo *et al* proposed a possible model in which Kidins220 bridges a link between α -syntrophin and Eph4, thus contributing to the regulation of synapse formation and plasticity. Further evidence has shown that this interaction occurs through α -syntrophin induction of Kidins220 clustering at the neuromuscular junction. This Kidins220-mediated localisation subsequently results in the activation of Eph4 which in turn stimulates postsynaptic signal cascades (12). By interacting with a variety of proteins, Kidins220 regulates neuronal activities. For instance, kinesin light chain 1 (KLC1) is a binding partner for Kidins220. In PC-12 cells, it was demonstrated that after nerve growth factor (NGF) stimulation, intracellular trafficking of Kidins220, from *trans*-Golgi network to the plasma membrane, relied on KLC1-based transport mechanism (13).

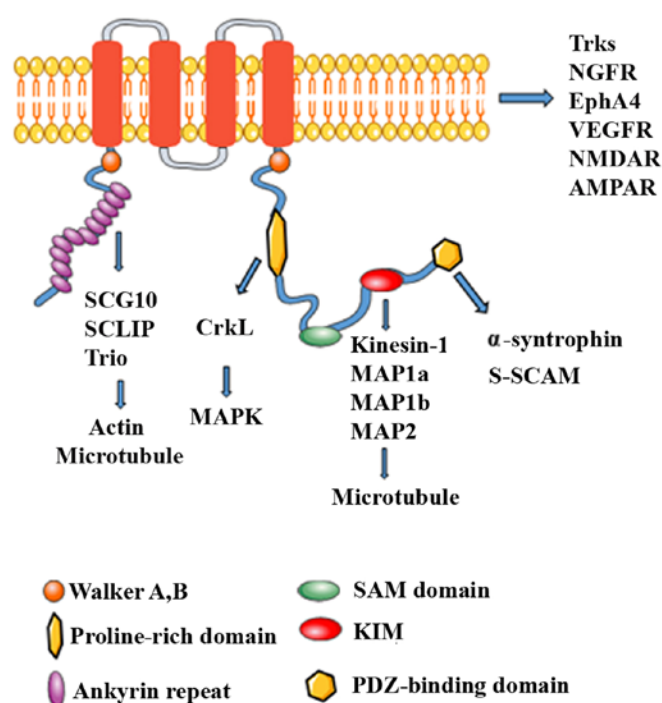


Figure 1. Structure of Kidins220 and its binding interaction partners. Schematic structure of Kidins220 scaffold protein. An archetypal Kidins220 scaffold protein contains multiple protein binding domains and post-translational modified sites, through which Kidins220 coordinates signal transduction of various pathways, such as Trk and MAPK. The scaffolding role of Kidins220 appears to be directed based on the different binding partners within the protein. Kidins220, kinase D-interacting substrate of 220 kDa/ankyrin repeat-rich membrane spanning; SAM, sterile α motif; MAP, microtubule-associated protein; KIM, kinase light chain (KLC)-interacting motif; PDZ, PSD-95, Dlg, ZO-1-binding motif; Trks, tropomyosin receptor kinase; NGFR, nerve growth factor receptor; VEGFR, vascular endothelial growth factor receptor.

4. Interacting partners

Kidins220 binds with a variety of interacting partners and is involved in various neuronal activities (Fig. 1). Kidins220 acts as a downstream substrate of protein kinase D (PKD), where enhanced PKD activity stimulates phosphorylation of Kidins220 at serine 919 in PC12 cells (1). The most significant role identified of Kidins220 is to act as a downstream substrate of Trk receptor tyrosine kinase. Kidins220 is currently the only known membrane-associated protein which interacts with both Trk and p75 neurotrophin receptors, often forming a ternary complex (14). Kong *et al* identified that within hippocampal neurons which were stimulated by neurotrophin, rapid phosphorylation of Kidins220 was exhibited indicating Kidins220 as a downstream target of neurotrophin (9). Further research by Arévalo *et al* revealed that rapid tyrosine phosphorylation of Kidins220 was induced in primary neurons after treatment with neurotrophin. They further identified that it was a specific site Tyr1096 which activated mitogen-activated protein kinase (MAP kinase) activity through phosphorylated Kidins220 recruits CrkL, an upstream component of the C3G-Rap1-MAP kinase cascade, in a neurotrophin dependent manner. This sustained MAP kinase activation was affected in PC-12 cells by a mutation within Tyr1096 affecting cell differentiation (15). Notably, it appeared that the mutation or

interference of Kidins220 only reduced neurotrophin-elicited signalling in the ERK pathway, suggesting an important role played by Kidins220 in mediating neurotrophin-induced signal transduction via the MAP kinase pathway (16). Kidins220 was also phosphorylated in NG108-15 cells following exposure to ephrin B, suggesting it acts downstream of ephrin receptors (9).

Based on yeast two-hybrid screening, Kidins220 activity in muscle has been linked to the binding of α -syntrophin, via the PDZ domain. Kidins220 displays clustering in response to increased expression levels of α -syntrophin which further augments EphA4 signalling (12). In nuclear factor- κ B (NF- κ B) signalling induced by brain-derived neurotrophic factor (BDNF), a neurotrophin with preference for targeting tropomyosin receptor kinase B (TrkB), Sniderhan *et al* demonstrated that silencing of Kidins220 or targeting the Kidins220-TrkB interaction abolished NF- κ B signalling elicited by BDNF. Further elucidation of the BDNF-induced interaction between Kidins220 and TrkB suggested that NF- κ B signalling was facilitated by the activation of MAP kinase and I κ B kinase (IKK) leading to the phosphorylation of RelA (17).

Septin 5, which has been implicated in cytoskeleton reorganisation, has also been identified as an interacting partner of Kidins220 and may serve as a regulatory element for intracellular signalling activities (18). The results of a yeast two-hybrid screen and co-immunoprecipitation revealed that these two proteins are co-localized in hippocampal neurons. In PC12 cells, Kidins220 and Septin5 are expressed on the tips of growing neurites induced by NGF. Andreazzoli *et al* performed a screening for brain cDNA products from a phage display library and demonstrated an interaction between the PDZ-domain of Kidins220 and Pdzn3, a protein comprised of a PDZ-domain and RING-finger. The co-localization of Kidins220 and Pdzn3 has been observed in PC12 cells in growing neurites induced by NGF (19).

5. Kidins220, neurite outgrowth, survival and death

Kidins220 binds and activates RhoGEFTrio in ankyrin-repeats. In NGF-differentiated PC12 cells, Neubrand *et al* found that Kidins220 and Trio were colocalized in specific sites with F-actin and Rac1 (20). Trio is a RhoGEF for Rac1, RhoG and RhoA and plays an important role in the regulation of neurite outgrowth. They identified that in PC12 cells, overexpression of Kidins220 in ankyrin repeats inhibited NGF-dependent neurite outgrowth regulated by Trio, and a similar mechanism was also verified in hippocampal neurons (20). Bracale *et al* conducted a yeast two-hybrid screen and identified KLC1, the subunit of kinesin1, as the interacting partner of Kidins220. In NGF-induced PC12 cells, Kidins220 colocalising with kinesin1 was impacted by the overexpression of KIM, a KLC-interacting motif in Kidins220, ultimately interfering with neurite outgrowth (13). Based on the preferential binding of NGF and TrkA neurotrophin receptor, López-Benito *et al* identified a novel signalling pathway, mediated by NGF which includes TrkA, Kidins220, synembryn-B and Rac1, implicated in neuronal secretion in PC12 cells (21). Rac1 is the downstream target of Kidins220 and synembryn-B, which themselves directly interact. NGF-mediated secretion is

blocked by the overexpression of Kidins220 and synembryn-B; however, basal secretion was unaffected (20). The secretion defects caused by high levels of Kidins220 were rescued by the expression of dominant-negative Rac1 (21).

6. Kidins220 in neuronal polarity, synaptic plasticity and neurotransmission

The diverse function of neurons depends on the highly polarised morphology regulated by axon and dendrites. Kidins220 interacts with tubulin (SCG10 and SCLIP) and microtubule-associated proteins (MAPs) to regulate neuronal polarity. As members of MAPs, the phosphorylation of MAP1b and stathmins were impaired following the downregulation of Kidins220. Furthermore, downregulation of Kidins220 also led to the aberrant dendritic arbors and extensions of the longer axon (22). AMPARs produce mature glutamatergic synapse by targeting the cell surface during neuronal development (23). As a subunit of AMPAR, GluA1 can be upregulated when Kidins220 is downregulated. Thus, in the process of neuronal maturation and synapse formation, the decreased expression of Kidins220 results in enhanced GluA1 expression and thus the establishment of a strong synaptic connection (7). In mature neuronal cultures, there is also a relevant evidence of interplay between Kidins220 and NMDA receptors. Upon overstimulation of NMDA receptors, such as during excitotoxicity, or when neurons are depolarised, Ca^{2+} activity-dependent Ca^{2+} influx, through NMDA receptors leads to a decrease in Kidins220 levels through both transcriptional downregulation and protein cleavage by calpain (21). Because Kidins220 knockdown causes a decrease in the amount of phosphorylated MAPK, a reduction in the expression of Kidins220 may contribute to neuronal death through a decrease in MAPK signalling (7). In hippocampal neurons, the decreased expression of Kidins220 prohibited GABAergic neurotransmission, whereas the overexpression of Kidins220 reverses this effect. Furthermore, the GABAergic neurotransmission regulated by Kidins220 is through a presynaptic mechanism (24). In hippocampal neurons with overexpression of Kidins220 increased long-term potentiation was impaired when calpain was prohibited (25). Sutachan *et al* found that Kidins220 is implicated in regulating the inhibition of neurotransmission (24).

7. Kidins220 and vascular development

Cesca *et al* addressed the potential role of Kidins220 in vascular development due to its targeting of and interaction with VEGFRs. Mice with a Kidins220 knockdown phenotype were found to present with cardiovascular abnormalities. These abnormalities appeared to be caused by impaired VEGF signalling pathways induced by lack of Kidins220 (26). Interestingly, Kidins220 interacts with VEGFR2 and VEGFR3 but not Nr1, although both VEGFR2 and VEGFR3 are co-receptors of Nr1 in endothelial cells. VEGF signalling is one of the key pathways in the process of angiogenesis especially mediated by VEGF/VEGFR2, Kidins220 was demonstrated to interact with VEGFR2 constitutively (27). However, mice with more severe vascular abnormalities were detected in the model with the knockdown of VEGF, VEGFRs, Nr1 than Kidins220^{-/-} itself (26), suggesting that Kidins220 regulation of angiogenesis may be limited.

Table I. Alteration of Kidins220 in tumourigenesis and the related signalling pathway.

Tumour type	Alteration	Effect	Signalling pathways	(Refs.)
Cutaneous melanoma	Increased expression	Melanoma formation, migration and invasion	MEK/ERK signalling pathway	(31,32)
Neuroblastoma	Increased expression	Proliferation	p21/cyclin D1	(35)
		NGF-regulated signalling		(33)
		Transition from N-type to S-type		(34)
Castration-resistant prostate cancer (CRPC)	Increased expression	Angiogenesis	VEGF/VEGFR and PI13K/AKT signalling pathways	(36)
Ph-like acute lymphoblastic leukemia (ALL)	Gene fusion with PAX5	Proliferation and survival	ERK signalling pathway	(44)
Pediatric high-grade glioma	Intragenic copy number breakpoint	n.d.	n.d.	(45)

Kidins220, kinase D-interacting substrate of 220 kDa; VEGFR, vascular endothelial growth factor receptors; NGF, nerve growth factor; n.d., not determined.

8. Kidins220 and immunomodulation

Apart from the role of Kidins220 in modulating neuronal activities, it also contributes to immunomodulation along with B cells and T cells. Kidins220 is expressed at the uropod of T lymphocytes and has been shown to be co-immunoprecipitated with ICAM-3 and caveolin-1 (28). Notably, in primary T lymphocytes, the colocalisation of Kidins220 and ICAM-3 is increased with the induction of morphological polarization. In contrast, Kidins220 displays different distribution upon change in cell polarity, and colocalisation with ICAM-3 becomes disrupted. The identification of Kidins220 in the regulation of T-cell motility was indicated in a Kidins220-knockdown model of human polarized T-cell lines in which the basal and stromal cell-derived factor-1 α -induced migration was increased following knockdown of Kidins220 (28). Based on mass spectrometry, Deswal *et al* demonstrated the interaction between Kidins220 and B-Raf in T lymphocytes. In immunoprecipitation and proximity ligation assays, the sustained ERK signalling relied on Kidins220 induced by T cell receptor (TCR) (29). Furthermore, Fiala *et al* reported that Kidins220 interacted with stimulated B cell antigen receptor (BCR), in an enhanced Src kinase-independent manner via BCR stimulation. In a B cell-specific Kidins220 knockdown (B-KO) mouse model, Kidins220 coupled the BCR to PLC γ 2, Ca²⁺, and ERK signalling and reduced the activation of B cells regulated by BCR *in vitro* and *in vivo*. The role of Kidins220 involved in the PLC γ 2 pathway was supported by a 6-fold reduction in B cells with positive λ light chain (30).

9. Kidins220 in tumours

Several observations support the importance of Kidins220 in cancer pathogenesis in addition to its function in neuronal activity. A growing body of evidence points to the deregulation of Kidins220 at the cell level affecting cell proliferation,

invasion, migration, and apoptosis, playing an important role in tumour formation and metastasis (Table I). Overexpression of the Kidins220 gene was initially reported in melanoma and was found to be associated with shorter overall survival. As a cutaneous malignancy, melanoma ontogenetically originates from the neural crest and increased expression of Kidins220 was detected in melanoma cell lines (31,32). Immunohistochemical staining of different surgical specimens subsequently revealed significantly increased expression of Kidins220 in primary and metastatic melanoma tissues with depths >1.0 mm compared with benign tumour tissues.

Kidins220 lies upstream of the BRAF gene that encodes proteins as part of the RAS/MAPK signalling pathway controlling several important cell functions. The overexpression of Kidins220 resulting in sustained activation of MEK/ERK signalling rather than BRAF mutation, has been identified as leading to acral lentiginous melanoma tumourigenesis. On the other hand, high levels of Kidins220 also enhance ultraviolet radiation B (UVB) (290–320 nm)-induced apoptosis in melanoma cells via targeting the activated ERK signalling pathway (31). The inhibition of melanoma cell migration and invasion associated with Kidins220 knockdown indicates that Kidins220 can promote tumour migration/invasion through MEK/ERK signalling (31,32). Taken together, Kidins220 expression is regarded as a predictor with which to evaluate melanoma patient outcomes, and its physiologic characteristics also provide evidence for targeted therapy by inhibiting the Kidins220/MEK/ERK/MAPK signalling pathways.

The regulatory role of Kidins220 in cancer development is tumour specific. For example, Kidins220 exerts different regulatory mechanisms to the MARK signalling pathway in neuroblastoma tumours. Rogers and Schor first reported that neuroblastoma tumours overexpress Kidins220, and that its forced overexpression promotes NGF-stimulated MAPK signalling activity, but not BDNF driven activation of MAPK signalling. Unlike melanoma, Kidins220 knockdown did not affect the survival of neuroblastoma cells under oxidative stress

within 24 h. Furthermore, loss of Kidins220 did not affect migration of neuroblastoma cells (33). During development, neuroblastoma undergoes a morphologic transition between Schwannian stromal (S-type) cells and neuroblastic (N-type) cells. S-type cells are highly adhesive to extracellular matrix (ECM) and are non-invasive, whereas N-type are less adhesive and highly invasive. DCX and STMN2 markers for neuronal lineage appear to be reduced in Kidins220-deficient N-type cells, whereas S-type cells containing low levels of Kidins220 (but not Kidins220 depletion) expressed considerable levels of both DCX and STMN2. This suggests an essential role of Kidins220 in regulating morphologic alteration in neural crest tumour cells (34). Jung *et al* generated Kidins220-knockdown neuroblastoma cell lines to determine whether Kidins220 is involved in cell proliferation. They found that wild-type cells were 1.8-fold higher in number than the matching knockdown cells on the fourth day of culture. Further analysis revealed that the decreased growth rate of Kidins220-knockdown neuroblastoma cells was due to cell cycle arrest at the G1 phase, which was accompanied with decreased expression of both cyclin D1 and CDK4, and also an upregulation of p21. This suggests that Kidins220 can coordinate the cell cycle through regulation of p21-cyclinD1/CDK4 (35).

A recent study reported that Kidins220 is a direct target of miR-4638-5P. miR-4638-5P has been related to the growth of castration-resistance prostate cancer (CRPC) *in vivo* and *in vitro*. Wang *et al* discovered a significant downregulation of miR-4638-5P in CRPC. High expression of Kidins220 was detected in both CRPC cell lines and tissues compared with androgen-dependent prostate cancer (ADPC). Western blot analysis showed that only Kidins220 expression was significantly reduced in PC3 and DU145 cells in the presence of miR-4638-5P. Knockdown of Kidins220 led to reduced proliferation and growth of CRPC cells *in vitro* and *in vivo*. Furthermore, miR-4638-5P and Kidins220 regulated prostate cancer (PCa)-associated angiogenesis. Kidins220 knockdown or overexpression of miR-4638-5P resulted in similar inhibition of endothelial cell growth and the formation of vasculogenic mimicry. Their further molecular analysis indicated that pCDH-miR-4638-5p sponge, a competitive miRNA inhibitor, caused an increase in expression of VEGF, PI3K and AKT in androgen-independent PCa cells, whereas all three molecules were reduced in Kidins220-knockdown PCa cells, suggesting that both miR-4638-5P and Kidins220 may be involved in androgen-independent PCa-associated angiogenesis. Interestingly, a reduced level of cell growth and angiogenesis were also observed in AKT-knockdown cells which is in accordance with the result from Kidins220-knockdown cells. Taken together, loss of miR-4638-5 may result in the activation of Kidins220 and promote neoangiogenesis and androgen-independent PCa growth through the regulation of VEGF/VEGFR2 and PI3K/AKT signalling pathways (36).

As previously mentioned, Kidins220 is the substrate of PKD. At the *trans*-Golgi network, the family members of PKD were found to regulate secretory transport (37). PKD1 plays an important role in stimulating the secretion of neurotensin, a gut peptide, which modulates gastrointestinal functions such as secretion and growth, as well as being involved in the proliferation of neurotensin receptor-positive cancers (38-40). In human carcinoid BON cells, a novel endocrine cell line

that is derived from a human pancreatic carcinoid tumour, Kidins220 and PKD2 regulated the secretion of neurotensin (41,42). Further interest is the observation that in BON cells, Kidins220, PKD1 and PKD2 present the same localization pattern as neurotensin vesicles, and also co-exist with neurotensin vesicles. Interestingly the overexpression of PKD1 nullified Kidins220 expression and neurotensin secretion in BON cells (42). Thus, the PKD/Kidins220 signalling pathway provides evidence for their critical role in the regulation of neurotensin hormone secretion. Since neurotensin is involved in secretion and inflammation in both normal and tumour cell growth, the PKD/Kidins220 pathway and neurotensin-containing vesicles are considered as a novel drug target for clinical application (42,43).

Apart from its role in solid tumours, a recent study also demonstrated a gene fusion of PAX5 and Kidins220, which leads to leukemogenesis by inhibiting B lymphocyte differentiation. Kidins220-mediated activation of the ERK pathway may contribute to the increased cell proliferation and the survival of leukemic cells (44).

Controversially, Kidins220 plays a different role in glioma, which was demonstrated in a profiling study of its function as a tumour suppressor in pediatric high-grade glioma (45).

10. Conclusion and perspective

Kidins220 is involved in the regulation of diverse cellular activities, particularly in neural differentiation and cytoskeleton remodelling (13). Its different domains mediate the function of Kidins220 as well as act as a platform for protein-protein interactions, intracellular signalling and protein transportation. Dysregulation of Kidins220 is evident in several malignancies. Kidins220 binds to Trio, tubulin, SCG10 and SCLIP to modulate actin and microtubule cytoskeleton, which is critical in the coordination of cellular processes, such as cell migration, cell polarity and cell cycle progression (46). Tumour cell migration and invasion require the remodelling of the cell cytoskeleton. Reorganization of the actin cytoskeleton that enables dynamic cell elongation and directional motility is also found in epithelial-mesenchymal transition (EMT), a critical process involved in tumour development (47). Further investigation will shed light on the role played by Kidins220 in dynamic arrangement of the cytoskeleton and EMT, and its implication in tumourigenesis and cancer progression. Kidins220 regulates cell survival and death through MAPK signalling after the binding of neurotrophins and Trk receptors (7). Since dysregulation of MAPK signalling is linked to tumourigenesis in several types of cancer and inhibition of the MAPK signalling pathways is critical for the effectiveness of anticancer agents, it is necessary to gain insight into the corresponding involvement of Kidins220 (48,49). Targeting its specific multiple domains such as the proline-rich domain and transmembrane segments may provide the possibility of more precise targeting. In addition to its involvement in VEGF/VEGFR-regulated angiogenesis, Kidins220 has been shown as a target gene of miR-4638-5p and its overexpression has been observed in androgen-independent PCa and also tumour-associated angiogenesis (36). However, its potential for targeted therapy in these malignancies and tumour-associated angiogenesis warrants further investigation.

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