Functions of the multi-interacting protein KIDINS220/ARMS in cancer and other pathologies

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Abstract

Development of an organ and subsequently the whole system from an embryo is a highly integrated process. Although there are evidence that different systems are interconnected during developmental stages, the molecular understanding of this relationship is either not known or only to a limited extent. Nervous system development, amongst all, is maybe the most crucial and complex process. It relies on the correct distribution of specific neuronal growth factors and hormones to the specific receptors. Among the plethora of proteins that are involved in downstream signalling of neuronal growth factors, we find the Kinase-D Interacting Substrate of 220 kDa (KIDINS220), also known as Ankyrin-rich Repeat Membrane Spanning (ARMS) protein. KIDINS220 has been shown to play a substantial role in the nervous system and vascular system development as well as in neuronal survival and differentiation. It serves as a downstream regulator for many important neuronal and vascular growth factors such as Vascular Endothelial Growth Factor (VEGF), the neurotrophin family, glutamate receptors and ephrin receptors. Moreover, activation and differentiation of B- and T-cells, as well as tumour cell proliferation has also shown to be related KIDINS220. This review comprehensively summarises the existing research data on this protein, with a particular interest in its role in cancer and in other pathologies.

Keywords: KIDINS220/ARMS, cancer, development, pathologies

Introduction

Interaction of different proteins plays an important functional role in the development of interconnected systems of all organisms. In human beings, nervous system development and differentiation is one of the most sophisticatedly regulated mechanisms. Among many neurotrophic factors, a group of closely related compounds called neurotrophin (NT) has a crucial role in controlling the number, growth, and differentiation of neurones, the functional unit of the nervous system. These neurotrophic factors bind to high-affinity Tropomyosin Receptor Kinases (Trks) and/or the low-affinity pan-neurotrophin nerve growth factor receptor (NGFR) present on neuronal cells surface. Binding of NTs to these receptors initiates specific intracellular signalling cascades resulting in many important functions such as neuronal survival and proliferation, growth and differentiation of axon and dendrite, and the expression and function of important proteins like ion channels and neurotransmitter receptors[1–3]. Synaptic strength and plasticity are also regulated by Trk receptors in the adult nervous systems, and the activation of cell surface receptors leads to one of many intracellular signalling pathways. The specificity of the receptors to NTs and the corresponding intracellular signalling cascade depends on the expression of Trk/NGFR on cell surface and availability of signalling intermediates inside the neuronal cell. At the intracellular level, activated Trk/NGFR provide docking sites at phosphorylated tyrosine residues for different adapters present in the cytoplasm depending on cell type. The most important initial adapter proteins involved in the corresponding intracellular signalling events are RAS protein family, Extracellular regulated Kinases (ERK or MAPK), Phospholipase-CϒPLC-ϒ), Phosphatidyl Inositol-3 Kinase (PI3-K), AKT and KIDINS220[4,5] (Figure 1). Among these, KIDINS220 was successfully cloned and identified in 2000 as the first physiological substrate of Protein Kinase-D (PKD)[6]. It is a transmembrane protein phosphorylating proteins at serine and threonine residues. At the same time, it was also identified as a downstream signalling target of neurotrophin receptor tyrosine kinase NTRK[7] and named ARMS (Ankyrin-rich Repeat Membrane Spanning) owing to its characteristic structural features. Later studies revealed that it is a hub for several cellular interactions of paramount importance. Through protein-protein interactions, it plays a major role in the development of various systems[8,9]. This is exemplified by nervous system processes such as neuronal outgrowth[10], neuronal polarity[11] and differentiation[12], neuronal survival[13], synaptic transmission[14], vascular system development[15], neuroblastoma cell proliferation[16], UV irradiation-induced apoptotic cell-death in melanoma[17] and B and T-cells activation and differentiation[18,19]. KIDINS220 also forms a ternary complex with Trk and NGFR [20] and plays an important role in human immunodeficiency virus type-1 Tat-induced microglial activation[21]. Finally, a recent study has shown that

KIDINS220 acts as an interactional partner of synembrin-B and thus plays a role in the NGF-induced cellular secretions[22]. Recent reviews on KIDINS220 have been published and summarise the available data on the history, structure and associated functions of this protein[5,9]. Therefore, we will focus on the functions and importance of KIDINS220 in the development of human pathologies, with a particular interest in cancer in this review.

Structural insight of KIDINS220

KIDINS220 is a large protein with 1771 amino acids and an apparent molecular weight of 220 kDa, encoded by the human gene *KIDINS220* situated at 2p25.1. The amino acid sequence of KIDINS220 can be divided into several different structural domains including protein interaction domains, transmembrane domains and phosphorylation site. The central part (amino acids 500-706) has four transmembrane domains whereas both N- and C-terminals are cytoplasmic. The cytoplasmic N-terminal domain harbours 11 ankyrin repeats (amino acids 37-402) that serve as a docking site for different protein partners[10]. Next to this region (amino acids 467-474) is a consensus motif ATP/GTP binding site (P-loop, AQWGSGKS). Due to the presence of nucleotide-binding Walker A and Walker B motifs in juxtamembrane regions of KIDINS220, it has been suggested as a P-loop Nucleotide Phosphatases of the "KAP Family", named after KIDINS220/ARMS and PIFA[9].However, the functional role of these latter motifs in KIDINS220 is still unclear. At its C-terminal end, KIDINS220 harbours several other important interacting domains. Some of these domains include; KIM region (amino acids 1356-1395) for binding of KIDINS220 with Kinesin-1[12], Proline-rich region (amino acids 1080-1092) that binds the adapter protein CRKL[9,23], a sterile alpha motif (SAM; amino acids 1231-1300) and a PDZ-binding motif (PSD-95/Disc large/Zonula occludens-1) which comprises of the last four amino acids of the KIDINS220 sequence[7,24].

Sequence evolution of KIDINS220

KIDINS220 protein or orthologues thereof are found in a large selection of diversely evolved organisms (Table 1). The analysis of the sequence evolution of KIDINS220 shows a more than 90% homology and identity within higher mammals. For avian and reptilian proteins, sequence similarities with the human protein decrease to between 80 and 90%. Orthologues of KIDINS220 are found in several metazoans like *Caenorhabditis elegans* (26.4% identity, 42.7% homology) and *Drosophila melanogaster* (28.6% identity, 42.0% similarity)[6,7]. This highly conserved protein sequence from nematodes to humans strongly

suggests that KIDINS220 plays evolutionarily conserved functions, which is confirmed in particular by the protein-protein interactions (see hereunder). Overall, the N-terminal region of KIDINS220 is highly conserved, unlike the more divergent C-terminal region, suggesting a differential evolutionary importance of properties associated with N- or C-terminal domains of the protein.

Presence of KIDINS220 in cells of different tissues and its role in different systems, like immune system[25,26,18,19], the vascular system[8,15], nervous system, and pathological conditions like tumour proliferation and neural disorders, can also be a consequence of the evolutionary divergence that some parts of KIDINS220 have underwent.

KIDINS220/ARMS and human diseases

In addition to its involvement in cancer (see next paragraph), KIDINS220 has been associated with different pathological situations in humans (Figure 2).

NGF is considered to be an important player in bronchial hyper-responsiveness and inflammation in asthma patients[27,28]. Recent studies revealed that KIDINS220 is overexpressed in the lung, spleen and peripheral blood of BALB/c mice after allergen challenge[29,30]. On the other hand, a significant reduction in the expression of KIDINS220 occurs after intra-nasal administration with anti-NGF antibodies to mice, suggesting that KIDINS220 is regulated by NGF signalling in the asthma[30]. Interestingly, the ovalbumin-induced expression of NFKB, IL1B, IL-4, and TNF in ovalbumin-sensitized mice was limited by the treatment with anti-KIDINS220 antibodies. Based on these findings, it is clear that NGF/NTRK1-KIDINS220-ERK signalling pathway holds a major position in the pathogenesis of allergic asthma[29] and, if validated in humans, KIDINS220 can serve as a new therapeutic approach towards the allergic diseases of the airway[30,31].

KIDINS220 has also shown its pivotal role in HIV-associated neurocognitive disorders (HAND). HIV infects central nervous system-resident immune cells, microglia, which in turn releases proinflammatory molecules causing HANDS[32,33]. KIDINS220 has shown to be expressed in microglial cells of central nervous system and to be involved in the activation of NFKB[21]. A study showed that production of tumour necrosis factor alpha and activation of NFKB falls down remarkably when KIDINS220 is downregulated[34].

It is well established that KIDINS220 holds a pivotal position in neuronal disorders through its role in the signalling of neurotrophins. It has also been shown that KIDINS220 expression is regulated by certain

pathological conditions *e.g.* cerebral ischemia. The underlying mechanism of this behaviour relies on N-methyl-D-aspartate receptors (NMDAR) excitotoxicity due to the overproduction of glutamate during ischemic conditions[35]. Hyper-activation of NMDARs causes an increased influx of Ca^{2+} in the post-synaptic neurons[36,37]. This influx of Ca^{2+} causes downregulation of KIDINS220 in two different ways which are either calpain dependent (cleavage of C-terminals of KIDINS220 and NR2A/NR2B subunits of NMDARs) or calpain-independent (transcriptional inhibition of *KIDINS220* gene)[35]. These findings suggest that neuronal degeneration induced by cerebral ischemia might be due to cleavage of PDZ-binding domain on C-terminal of KIDINS220 which is responsible for the downstream signalling during neuronal differentiation and survival.

Unlike its reduction in cerebral ischemia, KIDINS220 has shown an enhanced expression in Alzheimer's disease (AD) where it correlates with TAU[38]. TAU is a microtubule-associated protein which is hyperphosphorylated in AD[39,40]. Necropsies from AD patients with different progression stages showed that KIDINS220 expression levels are increased in human brain owing to the increased resistance to calpain cleavage associated with a hyperphosphorylation of KIDINS220[38]. Potential mechanisms of the involvement of KIDINS220 in the AD have been suggested elsewhere[41]. Based on all this data and a short study on KIDINS220 expression in AD brain and cerebrospinal fluid using an anti-KIDINS220 antibody, it has been suggested that KIDINS220 can serve as a novel biomarker for AD neurodegeneration[42]. Further studies, however, would have a far-reaching importance concerning regulation of KIDINS220 expression in other similar pathologies like hypoxia, acute trauma and other neurodegenerative diseases.

Still, in relation to neurological diseases, it was shown that genetic variation in the signalling pathways of neurotrophins, and thereby in *KIDINS220*, was associated with increased risk of schizophrenia and psychosis. These include A557V, H1085R and A1299G mutations in patients with schizophrenia-related psychosis, and the mutations are probably modifying the interaction with CRKL and the subsequent MAPK signalling, or the SAM-domain-related properties[43,44]. Although rare, such genetic variants in *KIDINS220*, together with other genes, can explain certain cases of psychiatric disorders[45].

Three childhood cases of a new syndrome named SINO have been associated with variants of KIDINS220 with premature stop codons[46]. SINO syndrome is characterized by spastic paraplegia, intellectual disability, nystagmus and obesity. The variants of KIDINS220 responsible for this sort of syndrome were closely related to an isoform of KIDINS220 with alternative splicing and present only in adult tissues[47]. The study has shown the importance of the delicate balance of KIDINS220 isoforms' expression during the developmental phases of an embryo[46]. Other genetic variants were found in unborn fetuses

corresponding to a premature termination codon in exon 25 resulting in nonsense-mediated mRNA decay and absence of protein [48]. The fetuses had enlarged cerebral ventricles and limb contractures that suggested the association between the phenotype and KIDINS220.

KIDINS220 and cancer

There is currently a growing amount of published data showing the involvement of KIDINS220 in various cancers (Figure 2). Here, we discuss the link between KIDINS220 and cancer by separating what has been shown directly with this protein (table 2), what can be suggested from indirect studies, and how these data constitute the basis for new therapeutic approaches.

Direct roles of KIDINS220 in cancer

First of all, KIDINS220 is clearly involved in cell proliferation and survival, as KIDINS220 knock out mice have a large rate of increased apoptotic cells as compared to control mice[8]. Melanoma, a tumour ontogenetically originating from neural crest, highly expresses KIDINS220 which protects tumour cells from stress-induced apoptotic death by activation of ERK signalling pathway[17]. KIDINS220-depleted melanoma cell lines expressed a significant inhibition of anchorage-independent growth in soft agar and an extended cell death by UVB-induced apoptosis. Its down-regulation also decreased the tumorigenicity in severe combined immunodeficient mice, strongly evidencing the functional role of the protein in this disease[17]. This was validated in another study by the same authors, together with the finding of a correlation between KIDINS220 protein expression and clinical outcome for melanoma patients[49]. Indeed, there was a better overall survival of patients with a negative KIDINS220 expression as compared to those with weak, moderate or strong expression.

Another study showed that an increased expression of KIDINS220 stimulated cell proliferation in human neuroblastoma cells, another neural crest tumor[16]. The underlying mechanism of this function suggested that the downregulation of KIDINS220 is associated with a decreased level of cyclin D1/CDK4 during the G1 phase of cell cycle. CCND1/CDK4 is a protein frequently overexpressed and associated with tumorigenesis in many cancers[50]. Decreased KIDINS220 also upregulates P21 (a cyclin-dependent kinase inhibitor, CDKN1A) which in turn reduces the hyperphosphorylation of RB1, a tumour suppressor protein, by suppressing the kinase activity of CCNG1/CDK complexes[16]. KIDINS220 is expressed in

different neuroblastoma tumours and cell lines from these tumours in which its downregulation results in a decreased NGF induced-MAPK signalling. However, its downregulation has no effect on BDNF induced-MAPK signaling[51]. Depletion of KIDINS220 in neuroblastoma cell lines has also been associated with the neural to Schwann like transition[52]. Quantification and presence of Schwannian cells in the peripheral neuroblastic tumours is one of the markers for favourable prognosis[53] and is being used by the International Neuroblastoma Pathology Classification (INPC) guidelines to stage these tumors[54]. Thus, KIDINS220 promoting the decrease of these cells is thus associated with a bad prognosis.

In prostate cancer, KIDINS220 is involved in angiogenesis and castration resistance[55]. KIDINS220 binds with VEGFR2 and VEGFR3 which act as co-receptors for the interaction between VEGF and VEGFR. This leads to the activation of VEGF/PI3K/AKT signalling pathway, which in turn promotes proliferation and vasculogenic mimicry formation. It also impairs apoptosis of prostate cancer cells as well as increases the expression level and secretion of VEGF to stimulate angiogenesis in an autocrine manner. The micro-RNA miR-4638-5p targets KIDINS220 3'-UTR sequence and thereby down-regulates its expression in prostate cancer cells, which is associated with an increased sensitivity to castration. This is hypothesized to be the functional explanation of the tumour suppressor activity of this micro-RNA.

A fusion protein between KIDINS220 and PAX5 has been described in acute lymphoblastic leukaemia (ALL)[56]. This protein corresponds to the 306 first amino acids of PAX5 and the 901 last amino acids of K220 (871-1171). Paired box-5 (PAX-5) is a transcriptional regulator that ensures the commitment to B-lymphoid lineage and maintenance of its normal phenotype[57,58]. Any tempering in the functions of protein due to fusions at genetic level causes an abnormal deviation from the development and differentiation of B-cells at an uncommitted progenitor stage. It preludes to the development of B-cell ALL[59,60]. The fusion protein between KIDINS220 and PAX5 contains the N-terminal region of PAX5 which incorporates its DNA-binding domains, and the C-terminal region of KIDINS220[56]. This latter is therefore still able to interact with other proteins through the proline-rich domain.

KIDINS220 has also shown interaction with B-cell antigen receptor (BCR) in unstimulated B lymphocytes. However, B-cells stimulation and Src-independent signalling enhance this interaction[19]. Studies have shown that KIDINS220 expression is essential for bracketing BCR to the Ca^{2+} and RAS-ERK pathways and hence plays a vital role in BCR-mediated cellular activation and B cell development in bone marrow.

A detailed characterization of gene expression and protein localization of KIDINS220 during early phases of embryogenesis has shown that it is dynamically regulated during development and therefore has an

imperative role in distinct spatiotemporal differentiative events[61]. The nervous system, eye, branchial arches, heart and somites are different embryonic regions expressing KIDINS220 mRNA from neurula to larval stage. Protein expression has also shown a similar behaviour, with embryonic expression in central nervous system, cranial nerves, motor nerves, intersomitic junctions, retinal ganglion cells, lens, otic vesicle, heart and branchial arches. As compared to the earlier examined stages, embryos during stage 42 displayed a differential localization of KIDINS220 protein in some regions like retina and somites[61]. Aberrant re-expression of embryonic and developmental genes, eventually by epigenetic modifications, has been repeatedly shown to be associated with cancer progression[62]. Given the described roles for KIDINS220 in both development and cancer, this could also be a potential explanation of its role in certain cancers.

In summary, the available data clearly suggests that KIDINS220 is directly associated with cancer growth and development. For the moment, no clear and single molecular mechanism is identified as being responsible for this, and as shown in the previous paragraphs, multiple cancer types have been identified as being influenced by KIDINS220. Future work should therefore be performed in order to confirm both involvement in identified cancers and the underlying mechanisms, and to elucidate whether this complex protein can be considered an oncogene, used as a biomarker and if its cancer-related properties are related to its phosphorylation by protein kinase D (PKD) or not (see hereafter).

Indirect roles of KIDINS220 in cancer

In addition to studies focusing directly on KIDINS220, data exists on the potential involvement of this protein in cancer through its protein partners. First, KIDINS220 has been shown to interact with VEGFR2 and the intracellular signalling of VEGF in some conditions[15]. Thus, if this is also the case in tumours, KIDINS220 can be involved in the angiogenetic activity of VEGF and thus the cancer progression.

Protein kinases are enzymes responsible for catalyzing the phosphorylation of different proteins to modulate the activity inside the cell in response to activated membrane receptors by certain stimuli. They play major roles in cancer and have become an attractive target for cancer treatment[63]. PKD is a PKC-like serine/threonine kinase that phosphorylates the synthetic peptide Syntide 2, but, as compared to PKC, only very weakly physiological substrates that have been evaluated[64]. KIDINS220, and more precisely its serine 919, was thus identified as the first physiological substrate of PKD upon its cloning and initial characterization[6]. Since then, several substrates for PKD have been described, including

cancer-related proteins. The phosphorylation of SSHL1 by PKD, for example, causes a cofilin-mediated decrease in the migration of breast cancer cells[65–67]. PKD is also involved in the suppression of epithelial-to-mesenchymal transition through phosphorylation of the transcription factor Snail[68]. Moreover, PKD-HDAC5 pathway plays a vital role in VEGF regulation of gene transcription and angiogenesis[69]. Considerable evidence suggests PKD be a potential therapeutic target owing to its effective role in different types of cancers[70]. The phosphorylation of KIDINS220 by PKD has been shown to regulate the secretion of neurotensin[71]. In addition, studies have shown that loss of KIDINS220 and PKD1/2 have a similar phenotype *i.e.* multiple axons and aberrant dendrites[72], underlying the functional importance of the interaction between these two proteins. Therefore, it could be possible that some of the cancer-related properties of PKD could be mediated by KIDINS220. Additional work should be performed in order to clarify this association. Finally, the involvement of KIDINS220 in cancer could be related to Trks or to NGFR. There is indeed an increasing amount of data in the literature demonstrating the role of these receptors in cancer. Both receptors were recently shown to be highly expressed at the protein level in thyroid cancer and their targeting by siRNA decreased the cell viability[73]. Increased expression of NGFR or both NGFR and Trks was also shown in ovarian cancer[74], neuroblastoma[75], renal cell carcinoma[76] and Schwannomas[77], whereas NGFR expression has been shown to be decreased in both gastric cancer[78] and hepatocellular carcinomas[79]. In addition, the possibility to target neurotrophin receptors was shown in several of the cited here over as well as for melanomas[80] and pancreatic cancer cells[81]. The potential role of KIDINS220 was not evaluated in any of these studies on neurotrophin-receptors and cancer, but due to its central position in neurotrophin signalling, we imagine that it's involved as well. The precise role of KIDINS220 in this phenomenon should, of course, be confirmed by additional studies.

Targeting KIDINS220 in cancer

Based on the existing data reviewed here, we believe that upcoming research will validate KIDINS220 as a potential target for cancer therapy. Various strategies could be used to target this large multifunctional protein based on the molecular mechanism involved in the tumour development. As no enzymatic activity of the protein is known, its inhibition would be based on less classical approaches. As several of its activities are based on the physical interaction with other proteins, small molecules inhibiting these interactions could be used to target a given effect mediated by a specific interaction. This approach has been successful in cancer as exemplified for example by compounds targeting the interaction between TP53 and MDM2[82]. This strategy would, however, need a better knowledge about the tridimensional

structure of either the complete KIDINS220 protein or the targeted domain in order to used bioinformatics tools to search for inhibitors. An enhanced understanding of the molecular mechanisms involved in each cancer type and for each protein interaction is also a prerequisite to this approach.

Based on whether the phosphorylation of KIDINS220 by PKD is needed for the cancer-promoting effects of PKD, this could be used by targeting, for example, the phosphorylation site of KIDINS220 with an antibody. This would then inhibit specifically the KIDINS220-related effect of PKD whereas other potentially interesting phosphorylated proteins would not be affected. For the specific case of ALL patients expressing the fusion protein PAX5-KIDINS220[56], a specific monoclonal antibody targeting the fusion protein could be developed and used for treatment purposes. This would however depend on the membrane expression of the fusion protein. Finally, targeting the extracellular domains of KIDINS220 with therapeutic monoclonal antibodies could be a possibility if this would be associated internalization of the protein, induction of cell death via the activation of the immune system (antibody-dependent cell cytotoxicity) or with structural modifications leading to decreased intracellular signalling or protein-protein interactions. This latter is, however, less likely as the extracellular domain of KIDINS220 is very small.

Concluding remarks

As described in this review, KIDINS220, a protein that was first studied at from a biochemical and a cellular biology point of view, has now clearly been associated with the development or the status of several diseases. Possible molecular explanations of these roles have sometimes been proposed, but much is still to be done both in order to understand the shown roles and to validate them in additional patient groups. As for cancer, KIDINS220 has a major role in cell proliferation in several cancer types, and the mechanism seems to be quite specific for each cancer and difficult to generalize. Since the inhibition of KIDINS220 expression, if often associated with decreased cell proliferation, this intriguing protein could turn out to be an interesting drug target. Another remaining part in the field of cancer and KIDINS220 is to understand the expression of this protein in some cancers, and whether this could be related to re-expression of embryonic genes or not.

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Figure legends

Figure 1. Structural features of KIDINS220 and signaling pathways of neurotrophins through KIDINS220 inducing cancer-related cellular processes. The pathways are multistep and involve several cellular proteins as indicated in the text and in references. ANK: Ankyrin repeats; WA: Walker A domain; WB: Walker B domain; PRD: Prolin-rich Domain; SAM: Sterile Alpha Motive; KIM: Kinesin-1 binding motif; PDZ: PDZ-binding Motif; Trks: Tropomyosin Receptor Kinases.

Figure 2. Known or suggested associations between KIDINS220 and human pathologies. Proven molecular mechanisms or cellular modifications are indicated in italic. See text for abbreviations and explanations.

Table 1. Percentage of protein homology and identity between Kidins220 from human and different species. Sequences were obtained from PubMed and compared be alignment using EMBOSS Needle nucleotide alignment (EMBL-EBI website).

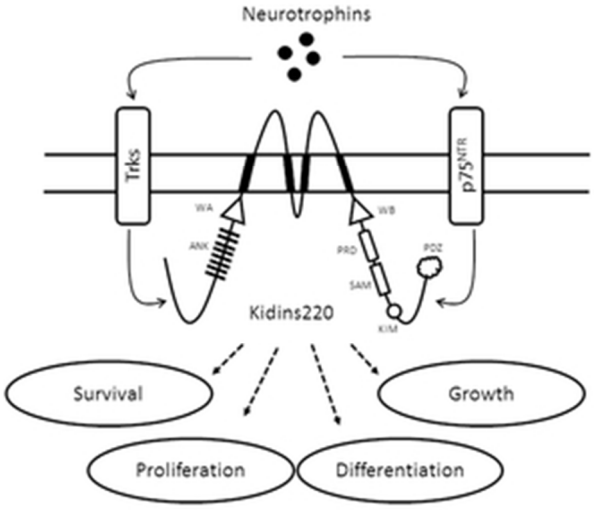
Taxon	Species	Biological nomenclature	Identity	Homolog
Mammalia	Monkey	*Macaca mulatta*	99.1%	99.5%
	Sumatran orangutan	*Pongo abelii*	98.4%	98.6%
	Dog	*Canis lupus familiaris*	96.9%	98.3%
	Cattle	*Bos Taurus(isoformX7)*	93.6%	95.9%
	Rat	*Rattus norvegicus*	93.1%	95.9%
	Mouse	*Mus musculus*	92.9%	95.8%
	Elephant	*Loxodonta africana*	92.9%	94.4%
	Rabbit	*Oryctolagus cuniculus*	83.4%	86.7%
	Brandt's bat	*Myotis brandtii*	74.4%	77.3%
Aves	Chicken	*Gallus gallus*	86.4%	91.9%
	Zebra finch	*Taeniopygia guttata*	86.1%	91.8%
Reptilia	Lizard	*Anolis carolinensis*	85.0 %	91.4%
	Green sea turtle (Reptiles)	*Chelonia mydas*	83.8%	89.2%
Amphibia	Frog	*Xenopus tropicalis*	79.2%	87.6%
Actinopterygii	Zebrafish	*Dario rerio*	70.0%	79.5%
	Tilapia	*Oreochromis niloticus*	69.7%	79.5%
	Puffer fish	*Tetraodon nigroviridis*	60.8%	69.1%
Insecta	Wasp	*Nasonia vitriopennis*	34.2%	48.9%
	Pea aphid	*Acyrthosiphon pisum*	34.2 %	50.2%
	Red Beetle	*Tribolium castaneum*	33.2%	47.3%
	Buff-tailed bumble	*Bombus terrestris*	31.2%	45.9%

	Common bumblebee	*Bombus impatiens*	31.1%	45.9%
	Carpenter ant	*Camponotus floridanus*	29.5%	43.6%
	Yellow fever mosquito	*Culex quinquefasciatus*	29.5%	43.6%
	Malaria mosquito	*Anopheles gambiae*	28.9%	42.8%
	Fruit fly	*Drasophila melanogaster*	28.6%	42.0%
	Jumping ant	*Harpegnathos saltator*	26.4%	38.3%
Chromadorea	Pig roundworm	*Ascaris suum*	27.1%	43.2%
Secernentea	Round worm	*Burgia malayi*	26.4%	43.8%
	Worm	*Caenorhabditis briggsae*	26.1%	4.8%
Chromadorea	Worm	*Caenorhabditis elegans*	26.4%	42.7%
	Eye worm	*Loa loa*	25.8%	42.1%
Appendicularia	Sea squirt	*Oikopleura dioica*	25.1%	37.7%
Hydrozoa	Hydra	*Hydra vulgaris*	20.1%	33.7%
Adenophorea	Pork worm	*Trichinella spiralis*	11.7%	17.6%

Table 2. Cancer-related studies on Kidins220.

Cancer type	Sample / Model	Observation	Reference
Melanoma	Melanoma cell lines and 100 clinical samples	Kidins220 is overexpressed in melanoma samples and high expression of Kidins220 is associated with poor survival in patients. siRNA-mediated inhibition of Kidins220 is associated with decreased cell proliferation, colony formation, cell migration, *in vivo* growth and formation of metastasis, and with enhanced sensitivity to UVB radiations.	[17] [49]
Neuroblastoma	Neuroblastoma cell line	shRNA-mediated inhibition of Kidins220 is associated with decreased cell proliferation due to longer G1 phase	[16]
Neuroblastoma	Neuroblastoma cell lines and 62 clinical samples	Protein expression in cell lines and mRNA expression in patient samples siRNA-mediated inhibition of Kidins220 is associated with a lower pERK response to NGF and morphological changes, but is not associated with cell migration or sensitivity to cancer drugs	[51] [52]
Prostate cancer	Prostate cancer cell	shRNA-mediated inhibition of Kidins220 is	[55]

	lines and 48 clinical samples	associated with decreased cell proliferation, vascluar development and *in vivo* tumor growth, and with increased apoptosis. The effects of Kidins220 in prostate cancer cells seems to be regulated by miR-4638-5p	
Acute Lymphoblastic Leukemia	One clinical sample	A fusion protein PAX5-Kidins220 is potentially associated with a lack of differentiation of B cells and an increased proliferation of leukemic cells.	[56]



Structural features of Kidins220 and signaling pathways of neurotrophins through Kidins220 inducing cancer-related cellular processes. The pathways are multistep and involve several cellular proteins as indicated in the text and in references. ANK: Ankyrin repeats; WA: Walker A domain; WB: Walker B domain; PRD: Prolin-rich Domain; SAM: Sterile Alpha Motive; KIM: Kinesin-1 binding motif; PDZ: PDZ-binding Motif; Trks: Tropomyosin Receptor Kinases.

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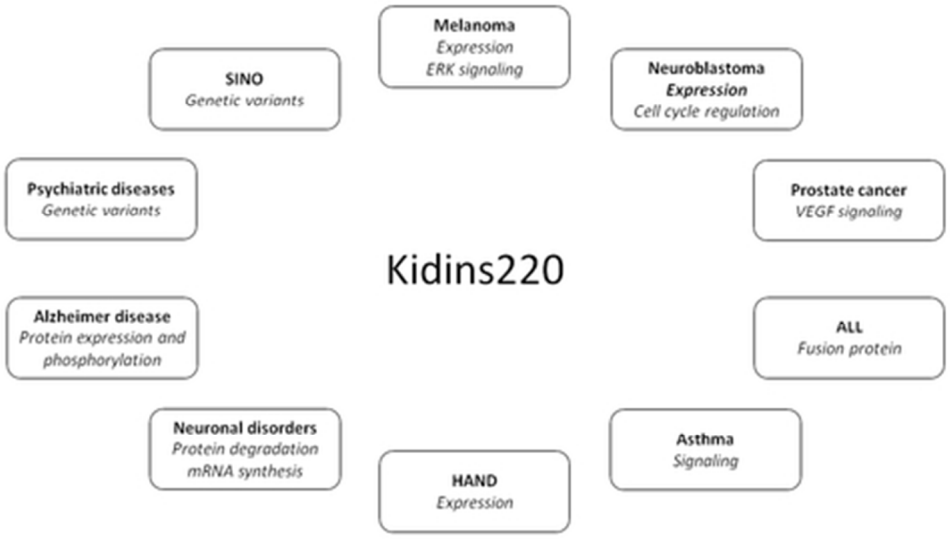

Known or suggested associations between Kidins220 and human pathologies. Proven molecular mechanisms or cellular modifications are indicated in italic. See text for abbreviations and explanations.

20x11mm (600 x 600 DPI)