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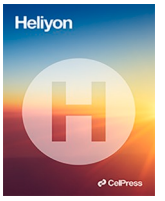

Review article

The biological functions and pathological mechanisms of CASK in various diseases

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ABSTRACT

Background: As a scaffold protein, calcium/calmodulin-dependent serine protein kinase (CASK) has been extensively studied in a variety of tissues throughout the body. The *Cask* gene is ubiquitous in several tissues, such as the neurons, islets, heart, kidneys and sperm, and is mostly localised in the cytoplasm adjacent to the basement membrane. CASK binds to a variety of proteins through its domains to exerting its biological activity.

Scope of review: Here, we discuss the role of CASK in multiple tissues throughout the body. The role of different CASK domains in regulating neuronal development, neurotransmitter release and synaptic vesicle secretion was emphasised; the regulatory mechanism of CASK on the function of pancreatic islet β cells was analysed; the role of CASK in cardiac physiology, kidney and sperm development was discussed; and the role of CASK in different tumours was compared. Finally, we clarify the importance of the *Cask gene* in the body, and how deletion or mutation of the *Cask* gene can have adverse consequences.

Major conclusions: CASK is a conserved gene with similar roles in various tissues. The function of the *Cask* gene in the nervous system is mainly involved in the development of the nervous system and the release of neurotransmitters. In the endocrine system, an involvement of CASK has been reported in the process of insulin vesicle transport. CASK is also involved in cardiomyocyte ion channel regulation, kidney and sperm development, and tumour proliferation. CASK is an indispensable gene for the whole body, and CASK mutations can cause foetal malformations or death at birth. In this review, we summarise the biological functions and pathological mechanisms of CASK in various systems, thereby providing a basis for further in-depth studies of CASK functions.

1. Introduction

Calcium/calmodulin-dependent serine protein kinase (CASK) is a member of the membrane-associated guanylate kinase (MAGUK) protein family [1], and was originally identified by yeast two-hybrid screening of the rat brain library using the C-terminal region of

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neurexin as bait. It is highly conserved in evolution [2] and the rat CASK protein shows an amino acid sequence similarity of 99% with mice, 98% with humans, 97% with *Xenopus laevis*, and 94% with zebrafish [2]. CASK is a multi-domain protein that contains, from the N-terminal to the C-terminal, a CaMK domain, two L27 domains, a PDZ domain, an SH3 domain and a C-terminal GK domain homologous to guanosine monophosphate kinase [1]. CASK is involved in regulating neurotransmitter release, insulin secretion, cardiomyocyte electrophysiology and kidney and sperm development through its different domains. Consequently, abnormalities in CASK may contribute to tumourigenesis or cause embryonic lethality. Therefore, the aim of this review is to provide a systematic description of the function of CASK in various tissues, as well as to summarise the impact of CASK mutations on body development, with the goal of delivering provide an important reference for the study of CASK function.

2. The biological functions and pathological mechanisms of CASK in nenurology

CASK is an abundantly expressed multi-domain scaffold protein in the mammalian nervous system. Its expression level is 3–5 times higher in the brain than in other organs [3] and it is very important for brain development and function. CASK is widely distributed in neurons, including synapses, dendrites, axons and somatosomes [4]. In the brain, CASK interacts with other proteins through its different domains and is involved in memory formation, neurotransmitter release, cell adhesion and pre- and postsynaptic signalling. Several reviews have reported the characteristics and molecular functions of different domains of CASK in neurons [5–7]. Here, our goal is to will build on previous research to share recent research advances regarding the importance of the different CASK domains in the nervous system.

2.1. The CaMK-like domain of CASK

The lack of key residues binding to Mg^{2+}-ATP at its catalytic site leads to the consideration of the CASK-CaMK domain as a pseudokinase [8]. However, another study has shown that the CaMK domain of CASK has a unique kinase activity and that its activity does not require magnesium [9]. In fact, the presence of magnesium inhibits the CASK kinase activity of the CaMK domain. The inhibition of synaptic activity can decrease the concentration of divalent cations in neurons and increase the CaMK activity of CASK. Because CASK has very low kinase activity, it can only phosphorylate its binding partners, such as the tail of cytoplasmic neurexin. However, whether the phosphorylation of CASK regulates the function of neurexin remains unclear [10]. CASK has also been reported to regulate CaMKII phosphorylation through its CaMK domain and to play a role in memory formation [11]. In addition to acting as a protein kinase, the CaMK domain of CASK can also act as a junction protein that binds to many different proteins, including Mint1, Liprins α, and Caskin1 [12,13].

As early as 1998, CASK was reported to bind to Mint through its CaMK domain and participate to in the trafficking and processing of amyloid precursor proteins in C*aenorhabditis* elegans [14]. The crystal structure of this Mint1 fragment in a complex with CASK-CaMK reveals the super-strong interaction between CASK and Mint1. Furthermore, truncating the N-end half of the N-terminal (called "MID-CID" because this area contains both the Munc18 and CASK interaction domains) does not weaken the interaction [12]. CASK also interacts with liprin α through its CaMK and L27 domains. The Mint1-CASK-Veli-liprin α protein complex has been shown to control the release of neurotransmitters [15]. However, Mint1 is considered to bind the strongest to CASK. Research has shown that the binding of CASK to Mint1 is entirely separate from its binding to Liprins-α and that Mint1 has priority in binding to CASK if both Mint1 and Liprins-α are present together in a cellular compartment [12]. Other studies have also reported that Mint1 can compete with Caskin1 to bind CASK. Caskin1 can also bind to the CaMK domain of CASK and can bind to Velis to form a tripartite complex similar to CASK-Mint 1–Veli, which may be the mechanism by which they compete [16,17].

2.2. The L27 domain of CASK

CASK contains two L27 domains, which are located between CaMK and the PDZ domain [5]. The first L27 domain, namely the L27A or L27 N domain, directly interacts with SAP97 to regulate the conformation of SAP97 and its subsequent targeting to AMPARs and NMDARs during synaptic transport [18,19]. The second L27 domain, namely the L27B or L27C domain, binds to the N-terminal L27 domain of mammalian LIN-7/Veli/Mals located on the basolateral surface of the renal epithelium and Madin-Darby canine kidney cells [20]. The L27-mediated protein–protein interactions usually occur as three proteins that form complexes of four L27 domains to regulate the formation and correct localisation of scaffold proteins and receptor proteins. The trigonal complexes consist of four L27 domains, two of which are provided by the CASK or MPP family and serve as a platform for the construction of the complex [21,22]. The L27 domain from CASK is also essential for the tripartite assembly of Dlg1/CASK/Mals2 complexes, which establish and maintain cell polarity in epithelial cells and neurons [23,24].

2.3. The PDZ domain of CASK

The PDZ domain consists of three proteins: PSD-95 (postsynaptic density-95), DLG (large disc) and ZO-1 (blocking region-1). CASK acts as a scaffold molecule that anchors channels and receptors through its PDZ domain [25]. For example, a PDZ-mediated interaction between parkin and CASK in neurodegeneration may be related to a protein ubiquitin involved in synaptic transmission and plasticity [26]. CASK also uses its PDZ domain to interact with the C2 motif of syndecan-2 [27] at the postsynaptic site. In addition, the CASK PDZ domain can bind to the C-terminal of the syndecan-4 cytoplasmic domain to coordinate the aggregation of receptors and connections with the actin cytoskeleton [28]. The PDZ domain of CASK also binds to the C-terminus of the trans-membrane protein

neurexin [29]. Consequently, disruption of the CASK-neurexin interaction can induce microcephaly and cerebellar hypoplasia [30].

2.4. The SH3 domain of CASK

The Src homologous 3(SH3) domain is recognised as a modular protein–protein interaction domain with an affinity for certain proline-rich motifs [3]. A missense mutation of the SH3 domain of CASK increases the tendency of the protein to aggregate, destroys the interface between the PDZ and SH3 domains of CASK, and inhibits the CASK–neurexin interaction [30]. In addition to the interaction with proline-rich motifs, protein fragments containing the proposed SH3 and GK regions of MAGUK proteins also interact with each other and may oligomerise the MAGUK scaffolds [30]. Therefore, CASK proteins can form homodimers through intermolecular SH3–GK interactions. CASK also forms heterodimers with other MAUK proteins through intermolecular SH3–GK interactions [31].

2.5. The GK domain of CASK

The guanosine kinase (GK) domain of the rat CASK shares a high sequence similarity with yeast guanylate kinase (yGMPK); however, at present, no evidence indicates that the GK domain of CASK has any enzymatic activity [32]. On the contrary, as with other CASK domains, the GK domain also functions as a protein–protein interaction domain. The CASK GK domain interacts with the T-box transcription factor Tbr-1 involved in forebrain development to regulate transcription [33]. Using the GK domain of CASK as bait, researchers identified Tbr-1as the binding partner of CASK in yeast two-hybrid screening [33]. The C-terminal region of Tbr-1 is necessary for interaction with CASK, which increases the transcriptional activity of Tbr-1 by recruiting the nucleosome assembly protein CINAP (CASK interacting nucleosome assembly protein) to the promoter region containing T-box DNA-binding motifs [34]. CINAP also interacts with the GK domain of CASK, but it does not compete with Tbr-1 for CASK binding. On the contrary, Tbr-1, CASK and CINAP can form a trigonal complex to regulate the expression of Grin2b [34,35].

CASK is a well-known pathogenic gene for X-linked mental retardation [36]. The interaction between CASK and Tbr-1 and their effect on the regulation of Grin2b are known to contribute to the neural development of patients with CASK mutations [5]. The GK domain also participates in intermolecular and intramolecular interactions of the SH3 domain of MAGUK, which regulates the binding of SAP-97 to GKAP and the PSD-95/SAP-90 aggregation of ion channels [37–39]. In addition, mutations in the SH3 and GK domains of the DlG protein are carcinogenic during larval development, while the absence of GK domains leads to the loss of normal growth without affecting the epithelial structure [40,41]. Similarly, the GK domains of mouse Dlg and CASK are essential for craniofacial and palatal morphogenesis in mice [42], as mutations in the CASK GK domain will affect the binding of CASK to the nucleosome assembly proteins CINAP and Tbr-1. The Tbr-1-CASK-CINAP complex regulates the expression of NMDA receptor subunit 2b (NR2b), and a point mutation can also affect the activity of the NR2b promoter [43,44].

Through its GK domain, CASK enters the nucleus and binds to a specific DNA sequence in the Tbr-1 complex. CASK can act as a co-activator of Tbr-1 to induce the transcription of genes containing T elements, including reelin, a gene critical to cortical development [33]. In addition, mutations in the GK and PDZ domains can affect the binding of CASK to neurexin, a presynaptic cell adhesion molecule, and interfere with neurexin-induced CASK oligomerisation [43].

3. The biological functions and pathological mechanisms of CASK in diabetes

β-cell dysfunction determines the development and progression of type 2 diabetes (T2DM) [45–48]. Extensive studies have examined the physiological mechanisms of biogenesis and sorting and exocytosis of insulin granules; however, the precise mechanisms that control these processes and their disorders in the development of diabetes remain an important research field. The β cells of the pancreatic islets seem to have evolved from neuronal precursors; therefore they retain exocytosis mechanisms similar to those of neurotransmitter release [49–51]. The β cells also express many scaffold and synaptic vesicle proteins that are important for neurotransmitter secretion and that also seem to be key components of the insulin secretion mechanism [52–54]. The involvement of CASK in the secretion of neurotransmitter vesicles has been widely reported [55,56] and Western blot analysis has shown that CASK is also highly expressed in rat and human pancreatic islets and the rat insulinoma (INS-1) cell line [57]. Proteomic analysis has revealed that insulin stimulation of Rat1 cells stably expressing the human insulin receptor significantly reduced the expression of CASK in the cytosol and nucleus. By contrast, CASK expression in the membrane was significantly increased by about 4.5-fold, demonstrating for the first time an involvement of CASK in insulin signal transduction [58].

Knockdown of *Cask* in INS-1 cells reduced the high-potassium stimulation of insulin secretion, whereas overexpression of *Cask* reversed this reduction [59]. The knockdown of *Cask* weakened the insulin release promoted by an adenylate cyclase agonist (lanolin), while the overexpression of *Cask* did not affect the inhibition of insulin secretion by a calcium channel blocker (nifedipine), thereby confirming that silencing *Cask* will lead to insufficient insulin secretion under both normal and stimulated conditions [59]. In addition, stimulation by high potassium and high glucose caused a movement of CASK from the cytoplasm to the plasma membrane, suggesting that CASK was involved in the downstream functions of the insulin secretion pathway [58,59]. Transmission electron microscopy showed that silencing *Cask* in INS-1 cells did not change the shape, size or number of insulin-containing vesicles; however, the number of vesicles anchored to the cell membrane significantly decreased. F-actin is a cytoskeletal protein that can prevent the anchoring and fusion of insulin vesicles onto the plasma membrane [60,61] and CASK seems to induce the local assembly of F-actin, leading to a more local distribution of that protein. In addition, CASK seems to reduce the inhibitory effect of F-actin on granule anchoring and fusion during exocytosis. This regulatory effect indicated that CASK was involved in insulin vesicle exocytosis by binding with other

secretion-related cytoskeletal proteins. Each CASK domain mediates specific protein–protein interactions [3]. Zhang et al. used immunoprecipitation, liquid chromatography–mass spectrometry and bioinformatics analysis to identify the proteins interacting with CASK in the insulin secretion process of INS-1 cells [62]. Immunoprecipitation studies confirmed that Mint1 and Munc18 may cooperate with CASK in insulin secretion by forming a ternary complex. CASK promoted the binding of Mint1 and Munc18 and mediated their movement to the cell membrane during insulin secretion. Overexpression of CASK promoted the function of the ternary complex, thereby remedying the impairment of insulin secretion induced by hyperlipidaemia. A previous study also showed that Mint1 interacted with the CaMK domain of CASK through the CASK interaction domain (CID) and with Munc18 through its Munc18 interaction domain (MID) [63]. However, how these three proteins directly form the ternary complex is not yet clear. Chen et al. [64] found that CASK can bind to Mint1 in the presence or absence of Munc18-1. However, surprisingly, CASK did not coprecipitate with Munc18-1 in the absence of Mint1. More interestingly, the interaction between Mint1 and Munc18-1 was significantly reduced in the absence of CASK, as an in vitro pulldown binding experiment showed the Munc18-1 band with the Mint1-MID band, but not with the Mint1-CID, CASK-CaMK, or other CASK domains.

Increasing the CASK expression dose-dependently enhanced the Mint1–Munc18-1 interaction, suggesting a necessity for the binding of CASK to Mint1 to maintain the formation of ternary complexes. Mint1 mutants lacking the CASK interaction domain (Mint1/Δ CID) can still bind to Munc18, but the insulin secretion of INS-1E cells is inhibited, suggesting that the formation of CASK-driven Mint1 and Munc18-1 ternary complexes may have important physiological significance for insulin secretion. CASK is also involved in the pancreatic β-cell dysfunction induced by palmitate [59], glucotoxicity [65] or interleukin-1-β [66]. Palmitate treatment inhibits the expression and transcriptional activity of *Cask* in INS-1 cells [59], and similarly, the expression of *Cask* mRNA decreases to about 55% in the islets of diabetic db/db mice [67]. Chromatin immunoprecipitation (ChIP) shows that the forkhead box transcription factor O1 (FOXO1) negatively regulates CASK expression by binding to its gene promoter [67]. In addition, palmitic acid can enhance the binding of FOXO1 to the CASK promoter region to induce insulin secretion disorders [59]. High glucose in the culture medium can also decrease the expression of CASK in INS-1E cells. The use of the Matinspector software predicted that hypoxia inducible factor-1α (HIF1α) could bind to the CASK promoter, suggesting that hypoxia may induce alternative CASK splicing in endothelial cells [68]. When treated with high glucose, the INS-1E cells showed significant increases in the protein level and activity of HIF1α. By contrast, culturing INS-1E cells for 48 h in the presence of $CoCl_2$, an HIF1α agonist, significantly decreased the levels of CASK protein. However, simultaneous stimulation with 25 mM glucose and a supply of a selective inhibitor of HIF1 α partially reversed this decrease, indicating that the negative regulation of CASK by high glucose may be partly caused by HIF1 α [65].

Islet inflammation is a common sign in all types of diabetes. Accumulating evidence now indicates that chronic islet inflammation plays an important role in pancreas β cell dysfunction, including impaired insulin secretion and decreases in islet β cells numbers [69]. IL-β has been identified as the main inflammatory mediator that damages islet β cells in diabetes [70,71]. Exposure of INS-1 cells to 1 ng/mL IL-1β for 48 h reduced *Cask* mRNA expression to nearly 40% of the control rate. The islets of Sprague-Dawley rats also showed down-regulation of *Cask* expression after 48 h of treatment with 1 ng/mL I IL-1β. Upregulation of CASK could partly restore the dysfunction of insulin secretion induced by IL-1β in INS-1 cells. IL-1β treatment of INS-1 cells can elevate the methylation levels of the *Cask* promoter region by the DNA methyltransferase, while treatment with methyltransferase inhibitors (5-Aza-dC) and si-DNMTs can partially restore the CASK expression inhibited by IL-1β [66]. In vitro studies have shown that CASK is regulated by a variety of factors in β cells, such as INS-1 cells treated with rosiglitazone (oxidosome proliferator activated receptor-γ high-affinity agonist) could increase *Cask* promoter region activity [72]. The expression of CASK in INS-1 cells is also regulated by Exendin-4 (Ex-4), which can increase the transcription of *Cask* mRNA and the expression of CASK, while not altering the cellular location of CASK. By contrast, knockdown of *Cask* significantly reduces the Ex-4–enhanced insulin release [73]. These findings indicate that CASK plays an important role in regulating the function of pancreatic islets, but these studies presently are limited to in vitro studies of the β-cell line. Liu et al. found that mice with a β-cell-specific *Cask gene* knockout (βCASKKO) show abnormal insulin secretion and impaired glucose tolerance when fed a normal diet [74]. However, obese βCASKKO mice have improved glucose tolerance and insulin sensitivity, and further studies have confirmed that this phenomenon is mainly due to the enhancement of insulin signalling pathways in adipose tissue. In short, these in vitro and in vitro studies show that CASK plays an indispensable role in islet β cells, especially regarding insulin vesicle secretion. However, the role of CASK in the progress of T2DM needs further studies.

4. The biological functions and pathological mechanisms of CASK in cardiology

The expression and role of CASK in the myocardium have been studied since 1998 [20]. Myocardial CASK expression determined by a proteomic study showed the presence of multiple protein complexes formed between CASK and SAP97, Veli-3 and Mint1, as well as a relationship with inward rectifier Kir2 potassium channels [75]. The Kir2.1, Kir2.2 and Kir2.3 channels reacted with the DGC and SAP97/CASK/Veli complex [75,76]. CASK also regulates the Na V 1.5 channel through its L27B and HOOK domains [77]. A GST pull-down experiment using the C-terminal of NaV 1.5 (SIV motif) showed that CASK directly interacts with NaV 1.5, providing new insight into the process by which CASK regulates NaV 1.5. CASK did not change the transcription or translation of NaV1.5, but CASK silencing increased NaV1.5 expression in the lateral membrane of myocardial cells. Treatment with brefeldin A (an inhibitor of forward transport between the endoplasmic reticulum and Golgi apparatus) can prevent this effect, indicating that CASK blocks the early steps of NaV1.5 transport [78].

In human and rodent models of chronic hemodynamic overload, the expression of CASK was decreased during atrial dilation/remodelling, while its cellular location remained unchanged. This suggests that the down-regulation of CASK during heart disease may change the functional expression of NaV1.5 in the lateral membrane of the myocardium. These observations not only strengthen the concept of a differentially regulated population of NaV1.5 channels in cardiac myocytes, which thus play a unique role in cardiac

physiology, but they also indicate that CASK can participate in maintaining a low level of NaV1.5 in the lateral membrane of the myocardium, thus contributing to anisotropic conduction [79].

The N-terminal region of CASK has a CaMKII homologous domain, that is associated with CaMKII in the human ventricular myocardium and will affect CaMKII activity. A lack of CASK in mice enhances the activity of CaMKII by increasing the T286 site of CaMKII and reducing the phosphorylation of the T305 site. This leads to myocardial systolic dysfunction and pressure overload and increases the tendency towards ventricular arrhythmia. On the contrary, induction of CASK expression inhibits CaMKII activity and improves calcium ion treatment, thereby identifying CASK as a key regulator of cardiac excitation contraction coupling through its regulation of CaMKII activity [78].

5. The biological functions and pathological mechanisms of CASK in urology

During the development of the kidney, CASK and Dlg1 maintain the key functions of nephron progenitor cells. Dlg and CASK double knockout (DKO) results in severely underdeveloped and abnormal kidneys, as well as a rapid and premature depletion of nephron progenitor cells/stem cells. Several cellular and molecular defects were observed in the DKO kidney, including decreased proliferation and increased apoptosis of cells in the nephrogenic region. In addition, Dlg1+/−; CASK −/− (het/null) mice showed moderately underdeveloped kidneys. The kidneys of mice with nephron progenitor cell–specific het/null were small and developed glomerular cystic nephropathy and renal failure [80]. CASK is the key factor responsible for Dlg1 membrane positioning during spindle orientation, and Dlg1 is essential for directional cell division and normal lumen formation in non-transformed mammalian epithelial cells. The absence of CASK leads to an incorrect 3D direction of cell division and to the formation of multicavity structures in cultured renal and breast epithelial cells. Blocking the interaction between CASK-Dlg1 and interfering peptides or deleting the CASK interaction domain of Dlg1 destroys the spindle direction, thereby initiating the formation of multiple cavities [81]. CASK is widely distributed in the whole cytoplasm of the renal podocyte foot process and cell body [82] and can bind to nephrin, which is mainly located in the podocytes [82–85]. Nephrin is a key component of the glomerular fissure diaphragm between epithelial foot processes. Mutation of the NPHS1 gene that encode nephrin leads to proteinuria and congenital nephrotic syndrome [86].

The structure and function of podocytes in patients with focal segmental glomerulosclerosis (FSGS) are seriously damaged, which may reflect the presence of systemic circulating factors that increase glomerular permeability. Confirmation of this circulating factor has been achieved by eluting proteins bound to a protein A column (therapeutic immunoadsorption) and analysing them by comparative electrophoresis and mass spectrometry. The circulating factor was identified as a soluble form of CASK. CASK was also the only protein immunoprecipitated in the serum of patients with recurrent FSGS after transplantation, but it was absent from control patients. Recombinant CASK (rCASK) induces a reorganisation of the actin cytoskeleton and the redistribution of synaptophysin, ZO-1, neusin and ENA in immortalised podocytes. In addition, rCASK induced changes in the permeability of monolayer podocytes and increased the in vitro mobility of the podocytes. The extracellular domain of CD98, a transmembrane receptor expressed on renal epithelial cells, has been found to co-immunoprecipitates with rCASK. The inactivation of CD98 with siRNA suppressed the structural changes induced by rCask, indicating an involvement of CD98 in the pathophysiology of renal diseases. In mice, recombinant CASK induced proteinuria and disappearance of the foot processes in podocytes [87].

6. The biological functions and pathological mechanisms of CASK in sperm development abnormalities

CASK is an epididymal secreted protein that is related to epididymal sperm maturation [88,89]. Immunoprecipitation studies have shown that CASK, plasma membrane Ca2+pump isomer 4b (PMCA4b) and attachment molecule A (JAM-A) are co-located at the proximal end of the sperm flagellum, where they serve as mutual interaction partners [26]. Importantly, CASK interacts with these molecules alternately and non-cooperatively through its PDZ domain to inhibit or promote Ca2+ efflux. In Jam-A-invalid sperm that lack the CASK-JAM-A interaction, an increase in the CASKPMCA4b interaction led to the inhibition of PMCA4b enzyme activity and impairment of Ca2+homeostasis [90]. PMCA4b is the main Ca2+efflux protein in rat spermatozoa; therefore, the loss of PMCA destroys Ca2+homeostasis, causes progressive and overactivated sperm vitality and ultimately leads to infertility [91,92].

7. The biological functions and pathological mechanisms of CASK in tumours

CASK can regulate cell proliferation, cytoskeleton remodelling and cell metastasis [19,68,93], which are all functions that are related to the progression of multiple cancers. Knockdown of CASK resulted in increased proliferation of cultured keratinocytes and organ-type raft cultures [94]. Similarly, inhibition of endogenous CASK expression led to an increase in the growth rate of the human endothelial-like ECV304 cell line, while overexpression of CASK decreased the cell growth rate [93]. CASK can bind to four cancer-related cell adhesion receptors (syndecan-1, - 2, - 3 and - 4) and thereby regulate cell proliferation, migration, invasion and gene expression through signal pathways [20,95–98]. Notably, CASK expression is associated with the inhibition of tumour activity and serves as a key regulator in the transformation of colorectal cancer (CRC) [95–97].

Overexpression of CASK in CRC is associated with poor patient prognosis [99]. The PDZ domain of CASK combines with heparan sulphate proteoglycan syndecan-2 [20] to regulate the tumorigenicity of colorectal cancer cells by regulating their adhesion and proliferation [97]. The Cask gene interacts with its target gene Reelin to participate in oesophageal cancer formation [100]. Similarly, the expression of CASK was upregulated in *Helicobacter pylori* infected positive tissues and cells and in gastric cancer tissues. Downregulation of CASK expression in gastric cancer can inhibit cell growth and invasion, while overexpression of CASK can reverse the inhibition of miR-203 on tumour growth [101]. In addition, the treatment of gastric cancer with NSAIDs, such as ibuprofen, indicate

have an inhibitory role in the Wnt signalling pathway by changes in the expression levels of some genes, including CASK [102]. CASK is significantly up-regulated in hepatocellular carcinoma (HCC), and HCC patients with a high expression of CASK have low overall survival rates. At the molecular level, the knockout of CASK activates the c-Jun N-terminal kinase (JNK) pathway, whereas treatment with the JNK inhibitor SP600125 or transient transfection with JNK-targeting siRNA can significantly reduce the knockout of CASK-mediated autophagic cell death [103].

Mass spectrometry analysis of the membrane proteins of seven pairs of pancreatic adenocarcinoma (PAAD) and adjacent normal tissues has also revealed an increase in CASK expression in the PAAD samples and cell lines and an associated poor prognosis of PAAD patients [104]. Enrichment analysis using the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway has shown that CASK-related genes are mainly related to the Notch pathway. Similarly, the knockdown of CASK inhibits the Notch pathway in pancreatic cancer cells. Taken together, these results confirm that knockdown of CASK inhibits the growth and invasion of pancreatic cancer cells by inhibiting the Notch the pathway to induce apoptosis of pancreatic cancer cells.

Among 84 patients with cholangiocarcinoma (CCA), CASK was found in the cytoplasm and nucleus of CCA cells in 38 (45%) patients. The overall survival and relapse-free survival were significantly better in patients with positive CASK expression than with negative CASK expression. Therefore, CASK may be a tumour suppressor, and its low expression is an independent risk factor for the poor prognosis of CCA patients, making CASK a valuable clinical prognostic marker [105]. In prostate cancer, CASK has a confirmed oncogenic role in the progression of prostate cancer (PCa), as the knockdown of CASK significantly inhibited colony formation of PCa cells and increased PCa cell apoptosis. Defects in CASK expression significantly hinder the migration and invasion of PCa cells and play a carcinogenic role in PCa [106].

8. Gene knockout or mutation of CASK

The physiological importance of CASK has been investigated using ‘knockdown’ (KD) mice, in which the expression of CASK was inhibited by 70%, and in knockout (KO) CASK mice, in which the expression of CASK was completely knocked out. The generation of ‘KD’ mice was feasible, but the resulting mice were smaller than the wildtype mice. By contrast, the KO mice died on the first day after birth [3,5]. Except for a partial overt cleft palate syndrome, the KO mice did not show significant developmental abnormalities. The neurons of the CASK-deficient KD mice showed normal electrical properties on the whole and formed synapses with normal ultra-structure. However, glutamate could spontaneously increase synaptic release events, while glutamate and γ-aminobutyric acid (GABA) reduced synaptic release events in the CASK deficient neurons [69]. Mutations in the X-linked gene encoding CASK were associated with severe neurological diseases that ranged from mental retardation to combined mental retardation and microcephaly with pons and cerebellar hypoplasia [5]. One female patient with a rare form of delayed seizures (ESS) was reported to have a heterozygous frameshift CASK mutation. Her phenotype was microcephaly with pons and cerebellar hypoplasia. At 3 years and 8 months of age, she had developed refractory ES, which was multifocal in EEG, especially in the discharge of bilateral frontal epilepsy [107]. In 2008, a loss of heterozygosity and a mutation of CASK were found in a series of girls and a boy with severe microcephaly and ponocerebellar

Table 1
The biological functions and pathological mechanisms of CASK in various diseases.

Disease	Functional mechanism	Biological functions	Refs
Nenurology	Phosphorylation of CaMKII	Memory formation	[11]
	Mint1-CASK-Veli-liprin α protein complex formation	Neurotransmitter release	[15]
	Dlg1/CASK/Mals2 complexes formation	Maintains cell polarity	[23, 24]
	Interaction with parkin	Synaptic transmission	[26]
	Interaction with Tbr-1	Forebrain development	[33]
Diabetes	Insulin vesicle anchoring disorder	Insulin secretion	[67]
	CASK/Mint1/Munc18 ternary complex formation	Insulin vesicle transport	[62, 63]
Cardiology	CASK/SAP97/Veli-3/Mint1 protein complexes	Inward rectifier Kir2 potassium channels	[75]
	Interacts with NaV 1.5	Regulates NaV 1.5	[79]
	Inhibits CaMKII activity	Promotes cardiac excitation contraction coupling	[78]
Urology	Guides DLg1 membrane localisation	Maintains the key functions of nephron progenitor cells	[80]
	Binds to nephrin	Maintains the normal structure of podocytes	[82]
Sperm abnormalities	Interacts with PMCA4b and JAM-A	Epididymal sperm maturation	[88–92]
Tumour	Interacts with syndecan-2	Promote colorectal cancer development	[99]
	Promotes cell growth and invasion	Promote gastric cancer development	[101]
	Mediates autophagic cell death	Promotes hepatocellular carcinoma development	[103]
	Promotes cell proliferation, colony forming ability and invasion potential	Promotes pancreatic adenocarcinoma development	[104]
	Hinders the migration and invasion of PCa cells	Promotes prostate cancer development	[106]
Gene mutation	Mutations in the X-linked gene encoding CASK	Mental retardation/microcephaly/cerebellar hypoplasia	[5]
	Heterozygous frameshift CASK mutation.	microcephaly with pons and cerebellar hypoplasia	[107]
	Loss of heterozygosity and a mutation of CASK	Microcephaly and ponocerebellar hypoplasia	[36]
	Missense mutations	Mental retardation phenotype with or without nystagmus	[109, 110]

hypoplasia [36].

CASK was found to affect synaptic formation and cerebral cortex development through interaction with Reelin and Tbr1 in the nucleus [3]. Later, the affected men showed mental retardation and oculomotor nerve abnormalities [108]. The microcephaly of female ponocerebellar hypoplasia is caused by invalid mutations, while the male subtype missense mutations can lead to the mental retardation phenotype with or without nystagmus [109,110]. The facial appearances seen in CASK mutations include a broad bridge and tip of the nose, a small nose, prominent maxilla or long human middle, short chin, big ears and arched eyebrows [110]. More than half of the female subjects suffered from epilepsy [111]. The affected males suffered from infantile epilepsy with a more severe phenotype, including Ohtahara syndrome and infantile convulsions [112]. The MRI findings of subjects with CASK mutations included pons and cerebellar hypoplasia of different degrees, and often simplified the gyrus pattern in the frontal lobe region [110]. Compared with the cerebellar forebrain, the corpus callosum may appear relatively thick [111]. Pan et al. used a co-expression and immunoprecipitation system to analyse which molecular effects and cellular functions would be changed by CASK missense mutation [43] and showed that a mutation in the L27 domain interferes with the binding of 97 kDa synaptic related protein. Mutations in the GK domain affect the binding of CASK with CINAP and Tbr1. Five mutations in the GK and PDZ domains affect the binding of CASK to the presynaptic cell adhesion molecule neurexin.

9. Conclusion

This review summarises the current key roles and molecular mechanisms of CASK in various systems (Table 1). CASK is an indispensable key gene and plays roles in the physiological functions and pathological mechanisms of a variety of tissues. In addition, given the similarity of the mechanisms by which CASK regulates multiple cellular functions, this summary provides an important scientific basis and identifies key molecular targets for further research on cellular physiological and pathological mechanisms.

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Data availability statement

No data was used for the research described in the article.

CRediT authorship contribution statement

Xingjing Liu: Writing – review & editing. **Haonan Qin:** Writing – review & editing. **Yuanyuan Liu:** Writing – review & editing. **Jingjing Ma:** Writing – review & editing. **Yiming Li:** Writing – review & editing. **Yu He:** Writing – review & editing. **Huimin Zhu:** Writing – review & editing. **Li Mao:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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