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REVIEW

The Potential Role of Krüppel-Like Zinc-Finger Protein Glis3 in Genetic Diseases and Cancers

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Abstract Gli-similar 3 (Glis3) belongs to a Glis subfamily of Krüppel-like zinc-finger transcription factors characterized to regulate a set of downstream targets essential for cellular functions, including pancreatic development, β-cell maturation and maintenance, and insulin production. Examination of the DNA-binding domain of Glis3 reveals that this domain contains a repeated cysteine 2/histidine 2 (Cys2/His2) zinc-finger motif in the central region where the recognized DNA sequence binds. The loss of the production of pancreatic hormones, such as insulin 1 and 2, is linked to the down-regulation of β cells-related genes and promotes the apoptotic death of β cells found in mutant Glis3. Although accumulating studies converge on the Glis3 functioning in β cells, recently, there have been developments in the field of Glis3 using knockdown/mutant mice to better understand the role of Glis3 in diseases. The Glis3 mutant mice have been characterized for their propensity to develop congenital hypothyroidism, polycystic kidney disease, and some types of cancer. In this review, we attempt to comprehensively summarize the knowledge of Glis3, including its structure and general function in cells. We also collected and organized the academic achievements related to the possible mechanisms of Glis3-related diseases.

Keywords Glis3 · Diabetes mellitus · Cys2/His2 zinc-finger domains · Congenital hypothyroidism · Polycystic kidney disease · Cancer

Introduction

The Gli-similar family including Glis1–3 constitutes a subfamily of Krüppel-like zinc-finger proteins, also termed Krüppel-like factors (KLFs), with the capability to bind GC-rich sequences. KLFs belong to a large and evolutionarily conserved set of transcriptional factors, and the name comes from studying segmentation defects in Drosophila (Pearson et al. 2008). This family of KLFs is involved in many aspects of the biological process including differentiation, development, proliferation, and apoptosis (Pearson et al. 2008). For example, deletion of KLF5 causes a developmental defect in the lung (Wan et al. 2008). Another example showed that the genes involved in the differentiation of erythroid are controlled by KLF1 (Pearson et al. 2008). The KLF7 null mouse has also indicated that increased apoptosis of sensory neuron was due to the absence of KLF7 (Pearson et al. 2008). The characteristic of the Krüppel family is the presence of two or more highly conserved cysteine 2/histidine 2 (Cys2/His2) zinc fingers, whereas the homology of the region outside zinc fingers shows a little similarity among the family members. The zinc-finger building up of a DNA-

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binding domain could positively or negatively regulate the target genes (Kaczynski et al. 2003). Glis proteins are somewhat related to some subfamilies in the Krüppel-like zinc-finger proteins including the Gli and Zic subfamilies. This review will focus on the established knowledge of the Gli-similar family and specifically discuss the relationship between Glis3 and cancer, type 1 and 2 diabetes, and other Glis3-related diseases.

Gli-Similar Family

The Gli-similar family contains five Cys2/His2 zinc-finger domains sharing a high homology between the members. However, the sequences outside zinc-finger domain share a little homology. The Gli-similar family exhibits high conservation across species proven by amino-acid sequence alignment (Kim et al. 2003). The similarity between human and mouse is up to about 99%, and the homology of Glis3 has also been identified in Drosophila and *Oryzias latipes* (Furlong et al. 2001; Hashimoto et al. 2009; Kang et al. 2010). Under general conditions, three types of human Glis members, including Glis1–3, were expressed alone or in collaboration with two or three Glis members in an organ-dependent manner. Notably, the simultaneous presence of all Glis members is identified in the brain and kidney (Table 1).

Chromosomal Location and Subcellular Localization of Three Glis Members

The human Glis1–3 genes are located, respectively, on chromosomes 1p32.3, 16p13.3, and 9p24.2. The molecular weight of proteins encoded by human Glis1–3 genes is presented in the following order: 65.9, 55.7, and 90 kD (Lichti-Kaiser et al. 2012) Delineation of zinc-finger domains involved in the Glis family reveals a high degree of similarity, shown in Table 2. Besides, the Glis proteins are identified as primarily residing in the cell nucleus. Zinc-finger (ZF) domains of Glis2 and Glis3 are responsible for nuclear location (Kim et al. 2002, 2003; Zhang et al. 2002). The sequence containing ZF4 is required for Glis3 nuclear translocation (Beak et al. 2008) and ZF3 is required for Glis2 (Vasanth et al. 2011). However, the mechanism of how Glis proteins translocate to the nucleus still needs further studies to be elucidated.

DNA Binding Through Cys2/His2 Zinc-Finger Domains

Zinc-finger domains (ZFDs) are not only responsible for nuclear location but also essential for DNA binding. The Glis proteins contain five Cys2/His2 zinc fingers. Cys2/His2 is the most common and classical type in 20 different zinc-finger proteins. Moreover, Cys2/His2 is constructed of a ββα-structural feature and preserves a tetrahedral structure stabilized by a zinc ion interacting with two pairs of cysteine and histidine residues (Brayer and Segal 2008). Glis proteins could not only recognize the Glis-binding site (5-(G/C)TGGGGGGT(A/C)) but also bind to the Gli-binding site (5-GACCACCCA) based on the high homology in zinc-finger domains existing in both Glis and Gli subfamilies (Beak et al. 2008). However, the binding preference of Glis is exhibited more toward the Glis-binding site than the Gli-binding site. The binding affinity could be regulated through posttranscriptional modification, the co-factor of Glis transcriptional regulator complex, and the promoter of the Glis-binding site.

The N- and C-Terminal Regions of Glis3 Modulate Its Transcriptional Activity

Apart from the ZFD of Glis3 believed to determine DNA recognition and subcellular localization, the regions outside the ZFD are likely to modulate the Glis3 itself in activating the transcription of target genes. The role of the N- and C-terminal regions about the ZFD of Glis3 becomes clear upon a comparison of the transcriptional activity of full-length with a series of N- or C-terminal truncated constructs. In these assays, a truncation up to 254 residues from the N-terminus resulted in a significant increase in the transcriptional activity of Glis3, whereas truncation of 306 residues from N-terminus almost completely abolished such activity (Kim et al. 2003). This finding is similar to another study demonstrating that a truncation of up to 288 residues from N-terminus showed an initial increase in transcriptional activity of Glis3, and further truncation to 302 residues showed the most efficiency in inducing such activity. However, all those truncated Glis3 constructs that removed more than 302 residues from the N-terminus resulted in a decrease in transcriptional activity but were more likely to have their protein half-life extended (ZeRuth et al. 2011).

On the other hand, the notion that the C-terminus of Glis3 is essential for its functions is suggested by the observation that Glis3 mutation was detected in the families with neonatal diabetes mellitus with congenital hypothyroidism (NDH) syndrome, a rare syndrome characterized by neonatal diabetes, congenital hypothyroidism, and facial anomalies. Such patients with NDH syndrome harbor a mutation in which an extra nucleotide is inserted at position 2067, causing a translational frameshift and thus encoding the C-terminal truncated Glis3 proteins (Senee et al. 2006). Besides, a role of Glis3 C-terminus in transcriptional activity has also been documented using the truncation strategy. C-terminal truncation of the first 16

Table 1 Expression of three Glis members in organs

Organs with apparent expression of Glis proteins	Glis1	Glis2	Glis3	References
Brain	○	○	○	Kim et al. (2002)
Kidney	○	○	○	Zhang and Jetten (2001)
				Zhang et al. (2002)
				Kim et al. (2003)
				Senee et al. (2006)
Colon	○	○	–	Kim et al. (2002)
				Zhang and Jetten (2001)
Thymus	○	–	○	Kim et al. (2002, 2003)
Lung	–	○	○	Zhang and Jetten (2001)
				Kim et al. (2003)
				Senee et al. (2006)
Brown adipose tissue	○	–	–	Kim et al. (2002)
Placenta	○	–	–	Kim et al. (2002)
Testis	○	–	–	Kim et al. (2002)
Heart	_	○	_	Zhang and Jetten (2001)
				Zhang et al. (2002)
Intestine	–	○	–	Zhang and Jetten (2001)
				Zhang et al. (2002)
Liver	–	○	–	Zhang and Jetten (2001)
				Zhang et al. (2002)
Prostate	–	○	–	
Ovary	–	–	○	Kim et al. (2003)
Pancreas	–	–	○	Kim et al. (2003)
				Senee et al. (2006)
Thyroid	–	–	○	Senee et al. (2006)
Uterus	–	–	○	Kim et al. (2003)

Symbols placed horizontally next to the name of organs are indicated for the presence (○) and the absence (–) of Glis members, respectively

Table 2 Summary of the size of Glis encoded proteins, located chromosome, and the similarity within zinc-finger domains

	Glis1	Glis2	Glis3	References
Size (kD)	65.9	55.7	90	Lichti-Kaiser et al. (2012)
Located chromosome	1p32.3	16p13.3	9p24.2	
Similarity in the zinc-finger domain (compared to Glis1)	100%	58%	93%	Kim et al. (2002, 2003)

residues slightly suppressed Glis3 transcriptional activity, while further deletions of 66 residues substantially diminished the activity to almost background levels (Kim et al. 2003). These results suggest that there exist undefined regions within the N- and C-terminuses of Glis3 in modulating its transcriptional activity.

Transcriptional Modulation of GLIS3RE-Containing Promoter by Glis3 and Other Cofactors

Glis3 has many roles in controlling the critical factors during pancreatic islet development. It was identified as a positive regulator of rodent *Ins2* gene expression, and also found to bind the Glis3 response element (GLIS3RE) in the *Ins2* promoter, thus activating insulin gene transcription. Regarding the ability of the β-cell-specific transcription factors to synergize with Glis3 to augment insulin gene transcription, several co-activators have been resolved, particularly v-maf musculoaponeurotic fibrosarcoma oncogene family, protein A (MAFA), and pancreatic duodenal homeobox 1 (PDX1) (Yang et al. 2009). Subsequently, a sequence alignment analysis revealed that the GLIS3RE also exists in mouse *Neurog3* promoter. Neurogenin 3 (*Neurog3*), a basic helix-loop-helix

transcription factor, is essential for driving the early differentiation of pancreatic islet cells (Schwitzgebel et al. 2000). Glis3 can directly bind to the GLIS3RE located between −2718 and −2703 in the mouse *Neurog3* promoter, activating the transcription of *Neurog3* gene. However, the transcriptional activity of Glis3 toward the mouse *Neurog3* promoter can be modulated by other proteins, hepatic nuclear factor 6 (HNF6) and forkhead box A2 (FOXA2); both of them can interact with Glis3 in co-immunoprecipitation experiments and synergistically enhance the *Neurog3* transcription rather than suppressing it (Yang et al. 2011).

In contrast, a conserved VYGHF motif corresponding to amino acids 348-352 in Glis3 was identified as contributing to the suppression of Glis3's transcriptional activity through interaction with a tumor suppressor protein, named suppressor of fused (SUFU) (ZeRuth et al. 2011). This interaction between Glis3 and SUFU is implicated not only in negatively regulating the insulin gene transcription, but also in protecting the Glis3 from proteasomal degradation. Collectively, the regions of Glis3 involved in the interaction with MAFA, PDX1, HNF6, and FOXA2 are not yet understood, but as evidence indicates their ability to serve as a prominent activator, it is unlikely that the SUFU acts as a repressor of Glis3-mediated transcription (Fig. 1).

Glis3, acting through its five Krüppel-like Cys2/His2 zinc fingers, modulates the transcription of target genes possessing GLIS3RE sequence within their promoters. Interactions of Glis3 with MAFA, FDX1, HNF6, and FOXA2 act to promote transcription, while interaction of Glis3 with SUFU acts to repress transcription of the *Ins2* gene. The tetrahedral structure of Cys2/His2 zinc finger, composed of two short β-strands followed by a α-helix, is depicted as a ribbon diagram. The zinc ion is shown as a pink sphere.

Glis3 and Type-1 and -2 Diabetes Mellitus

Type-1 and -2 diabetes are two main types of diabetes mellitus, both of which are metabolic disorders and diagnosed as hyperglycemia. The pathogenesis of both two types of diabetes is the dysfunction and death of pancreatic β cells (Cnop et al. 2005). β cells can synthesize and secrete insulin to homeostatically regulate the level of glucose that is sensed by β cells as well. Glis3 is expressed abundantly in the pancreas, especially in the insulin-producing β cells (Senee et al. 2006). It has been indicated that Glis3 is required for normal β-cell function (Kang et al. 2009b) and is related to the regulation of insulin gene transcription (ZeRuth et al. 2013). Glis3 is also reported as a risk locus for both type-1 and -2 diabetes (Nogueira et al. 2013).

Glis3 Is Related to the Development and Maintenance of β Cells

The previous study indicated that a significant increase in Glis3 expression during the second transition of pancreatic development, a process starting from embryonic day 12.5 to birth and beginning with β-cell differentiation, was specific to the pancreatic islets and ducts (Kang et al.

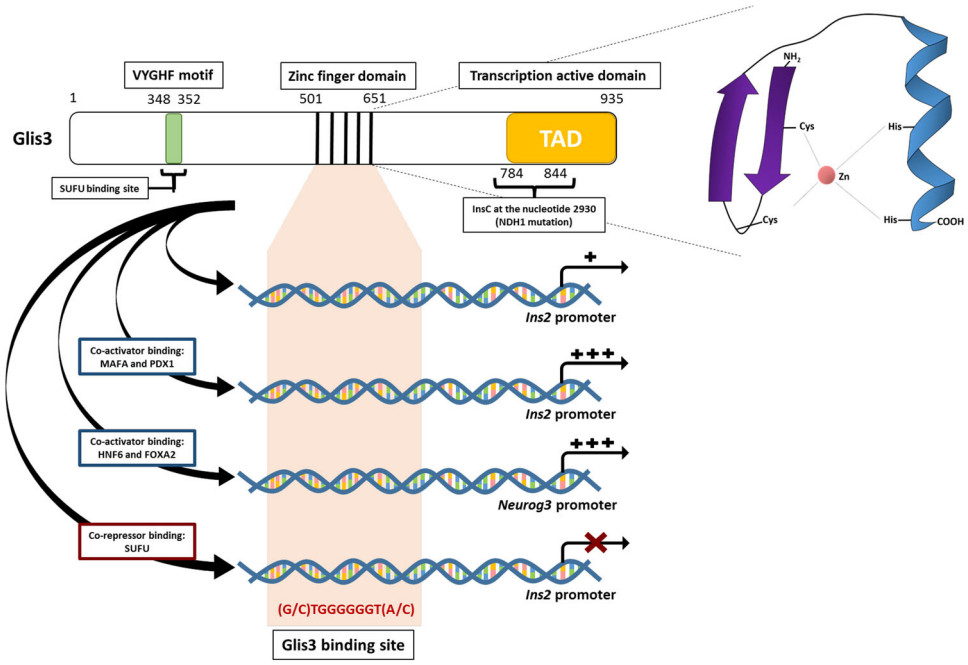

Fig. 1 Control of Glis3's transcriptional activity by other cofactors

2009b). During such period of time, β cells remain in an immature form in which the cells have less ability to secrete and synthesize insulin in response to the level of glucose, but during the second transition, they rapidly mature after birth (Benitez et al. 2012). Furthermore, the research reported that the expression of endocrine markers was decreased in Glis3 mutant mice where the transcription activity of Glis3 was deficient. Endocrine markers including a range of pancreatic hormones inclusive of insulin 1 and 2 (*Ins1* and *Ins2*), somatostatin (*Sst*), glucagon (*Gcg*), pancreatic polypeptide (*Ppy*), and ghrelin (*Ghrl*), and β-cell-related genes such as islet amyloid polypeptide (*Iapp*), ATP-binding cassette subfamily C8 (*Abcc8*), and *Glut2* were all down-regulated in Glis3 mutant mice (Kang et al. 2009b).

Moreover, some transcription factors related to the endocrine differentiation, including *Ngn3*, *Nkx6.1*, *Pax4*, *Pax6*, *Isl1*, *NeuroD1,* and *MafB,* were also expressed at relatively low levels in Glis3 mutant mice (Kang et al. 2009b). Ngn3 is a transcription factor that has been implicated in inducing the differentiation of pancreatic progenitor into endocrine progenitor cells and controlling numerous genes related to the development of an endocrine system, such as *Nkx6.1*, *Pax4*, *Pax6*, *Isl1*, *NeuroD1*, and *MafB* (Wang et al. 2008). Furthermore, the expression of β-cell markers, including *Nkx6.1*, *Pdx1*, and *MafA* were all decreased in Glis3 mutant mice (Kang et al. 2009b). *Nkx6.1* and *Pdx1* (Nelson et al. 2007) are expressed in pancreatic progenitor and restricted to β cells after maturation. *MafA* served as a marker of mature β cells (Kataoka et al. 2002). This evidence indicates that Glis3 plays a critical role in the development of endocrine cells and the maintenance of β cells.

Mutated Glis3 Is Related to the Apoptosis of β Cells

The deficiency of Glis3 has been associated with an increased apoptosis of β cells and somehow rendering the β cells to become more sensitive to certain cytokines, such as interleukin 1β plus interferon γ or palmitate (Nogueira et al. 2013). The evidence supporting the role of Glis3 in maintaining the β-cell functions comes from the molecular observation demonstrating that the number of genes involved in activation of insulin gene transcription, such as *MafA* and *Pdx1*, glucose transporter *Glut2,* and the insulin gene, *Ins2* itself, were all decreased in INS-1E rat insulinoma β cells with Glis3 knockdown (Nogueira et al. 2013). Furthermore, the deficiency of Glis3 induces a decrease in expression of SRp55 (Nogueira et al. 2013), an alternative splicing factor described as a potential regulator of Bim splicing (Jiang et al. 2010). Bim is one of the pro-apoptotic proteins involved in the intrinsic apoptosis pathway. Bim has also already been reported to contribute to the apoptosis of β cells (Barthson et al. 2011). Nowadays, Bim is known to be alternatively spliced to three main isoforms composed of BimEL, BimL, and BimS (O'Connor et al. 1998). A previous study has indicated that the deficiency of Glis3 resulted in a unique increase in BimS expression, whereas this phenomenon was absent in other two Bim isoforms, BimEL and BimL (Nogueira et al. 2013). To sum up, the deficiency of Glis3 modulates the alternative splicing of Bim through decreasing the expression of SRp55 and thereby increases the expression of BimS. Ultimately, pancreatic β cells follow the death cycle through the intrinsic apoptotic pathway.

Glis3 Promotes the Transcription of Insulin Gene

The previous study showed that Glis3 was involved in the regulation of insulin gene transcription (ZeRuth et al. 2013). However, transcription of insulin gene could be initiated directly or indirectly from Glis3 (Yang et al. 2009). In a direct way of activating insulin transcription, Glis3 can recognize and bind unimpeded to a sequence motif in the promoter of the insulin gene. The motif sequence interacting with Glis3 was identified to be G(T/C)CCCC(T/A)GCTGTGA(A/G) with slight variations (Yang et al. 2009). In an indirect way, Glis3 interacts with the promoter of insulin gene through association with other transcription factors.

There are three major transcription factors, including MafA, Pdx1, and NeuroD1, assembling with Glis3 to modulate insulin gene transcription in β cells (Yang et al. 2009). Moreover, Glis3 also affects the expression of other β-cell-specific transcription factors, such as MafA, Nkx6-1, and Pax6, all of which were reported to regulate the expression of insulin genes directly. The previous study indicated that the overexpression of Glis3 increased the expression of MafA, but decreased the expression of Nkx6-1 and Pax6 (Yang et al. 2009). Collectively, Glis3 can positively regulate the transcription of insulin gene both directly through unimpeded binding to the promoter of insulin gene and indirectly through interacting concomitantly with the transcription factor of insulin gene or affecting the expression of other factors.

Glis3 and Cancers

The Glis3 expression patterns in each type of cancer may vary enormously from one tissue to the next. For example, the overexpression of Glis3 has been detected in the high proliferative group of ependymomas, which is one of the central nervous tumors (Lukashova-v Zangen et al. 2007). The amplification of *GLIS3* gene is also identified in proneural glioblastoma, which is the most common brain

tumor (Cooper et al. 2010). In contrast, the decreased expression of Glis3 was observed in chromophobe renal cell carcinoma (Yusenko and Kovacs 2009). Apart from the aberrant expressions of Glis3 observed in certain types of cancer, an abnormal chromosomal translocation resulting in the fusion of *GLIS3* and cleft lip and palate transmembrane protein 1-like (*CLPTM1L*) genes was detected in the cases of fibrolamellar hepatocellular carcinoma (Xu et al. 2015). This fusion protein is produced by the translocation between chromosome 5 and 9 (Xu et al. 2015). Moreover, it has been reported that CLPTM1L is associated with several cancer cell types, such as ovarian tumor cell line (Yamamoto et al. 2001), lung cancer (James et al. 2012), and cervical cancer (Vazquez-Mena et al. 2012). However, the CLPTM1L-GLIS3 fusion protein possesses pro-oncogenic effects and its association with fibrolamellar hepatocellular carcinoma suggests that it could play a causal role in driving tumorigenesis (Xu et al. 2015). Another example is that the Glis3 was regulated by N-myc downstream regulated gene-1 (NDRG1) in pancreatic cancer (Kovacevic et al. 2013). NDRG1 has been indicated to inhibit the progression of pancreatic cancer (Maruyama et al. 2006). One study reported that the expression of Glis3 was up-regulated by the presence of NDRG1 in pancreatic cancer (Kovacevic et al. 2013). Investigating the expression and the molecular network of Glis3 might be the way closer at hand to understand what role Glis3 plays in cancer progression.

Glis3 and Other Diseases

Glis3 and Congenital Hypothyroidism

It has been reported that the development of congenital hypothyroidism is because the frameshift mutation of Glis3 produces a truncated non-functional protein (Dimitri et al. 2011; Lichti-Kaiser et al. 2014). Congenital hypothyroidism is identified by the deficiency of thyroid hormone (TH) at birth (Rastogi and LaFranchi 2010). The lack of TH might be caused by defective development of the thyroid gland or trouble in thyroid hormone synthesis. The regulation between TH and thyroid-stimulating hormone (TSH) is controlled by the hypothalamus–pituitary–thyroid axis negative feedback loop (Mebis and van den Berghe 2009). The production of thyrotropin-releasing hormone (TRH) will be stimulated after the hypothalamus detects insufficient level of TH. The TRH will regulate the expression of TSH subsequently. TSH will further promote the release and production of TH, while TH will negatively control the expression of TSH through a negative feedback loop. Hypothyroidism has been investigated in Glis3 mutant mice (Watanabe et al. 2009). Moreover, it was also determined that the Glis3 mutation was related to the evaluated expression of TSH and the decreased expression of TH (Porcu et al. 2013). However, the deficiency of Glis3 did not show apparent effect on the development of the thyroid (Watanabe et al. 2009). It seems that Glis3 is associated with the development of congenital hypothyroidism, but the way in which Glis3 regulates the thyroid hormones needs to be further investigated.

Glis3 and Polycystic Kidney Disease

Polycystic kidney disease is one type of genetic disorder. The primary feature of this disease is the development of numerous cysts in the kidney, and these abnormal cysts could enlarge the kidney and invade the typical structure (Halvorson et al. 2010). Moreover, it has been reported that the development of cystic renal disease might be related to the dysfunction of primary cilium and cilium-associated pathway (Uhlenhaut and Treier 2008). There are several pieces of evidence indicating that the deficiency of Glis3 is related to the development of polycystic kidney disease (Kang et al. 2009a). First, the polycystic kidney was found in Glis3 mutant mice. The study determined that cysts in Glis3 mutant mice originated from glomeruli, tubules, and collecting ducts. Second, even though Glis3 expresses high level in primary cilium, the formation of cilium presents normally in Glis3 mutant mice. In other words, Glis3 is not essential for the formation of cilium but might be related to the signaling pathway in the cilium. Third, some markers of cell–cell interaction or markers of cell polarity appear mislocalized within Glis3 dysfunction cell lines. It has been reported that changes in cell–cell interaction or cell polarity are critical for the development of the renal cystic disease (Fedeles and Gallagher 2013; Kim et al. 2008).

For example, the usual location of β-catenin, which is related to the cell junction, particularly basolateral membrane, has also been found in the cytoplasm and apical membrane in Glis3 mutant mice. Another example is that the location of ZO-1 in normal distal tubules is at the tight junction in the apical membrane, but mysteriously, it resides in the basolateral membrane of cystic tubules in Glis3 mutant mice. Furthermore, the location of epidermal growth factor receptor, which is associated with cell polarity, was somehow translocated from the apical membrane to basal membrane. The final piece of evidence is the interaction between Glis3 and Wwtr1, which is a kind of transcriptional modulator and is related to the development of cystic renal disease (Happe et al. 2011). The WW domain of Wwtr1 could recognize a P/LPXY motif in the C-terminus of Glis3 and form an interaction (as a complex with each other) (Jie et al. 2013). The recruitment of Wwtr1 to Glis3 reinforces its ability to translocate to the nucleus and promote the transcriptional activity of

Table 3 Pathophysiological mechanisms of Glis3-related diseases

Glis3-related diseases	Organ	Biological role	References
Congenital hypothyroidism	Thyroid	Higher expression of thyroid-stimulating hormone(TSH) and less expression of thyroid hormone(TH) were investigating in Glis3 mutant mice	Porcu et al. (2013)
Diabetes	Pancreas	Glis3 is related to the development of pancreatic β cells	Kang et al. (2009b)
		Mutant Glis3 is related to the apoptosis of β cells	Nogueira et al. (2013)
		Glis3 directly promotes the expression of insulin	Yang et al. (2009)
Polycystic kidney disease	Kidney	The polycystic kidney was found in the Glis3 mutant mice	Kang et al. (2009a)
		Glis3 might be related to the signaling pathway in cilium	Fedeles and Gallagher (2013)
		The interaction between Glis3 and Wwtr1 is critical of maintaining of normal renal function	Happe et al. (2011)
Cancer			
Chromophobe renal cell carcinoma	Kidney	Down-regulation of Glis3 was detected	Yusenko and Kovacs (2009)
Ependymomas	Brain or spinal cord	Glis3 was detected overexpression	Lukashova-v Zangen et al. (2007)
Fibrolamellar hepatocellular carcinoma	Liver	Related to the fusion protein of Glis3 and CLPTM1L	Xu et al. (2015)
Pancreatic cancer	Pancreas	The up-regulation of Glis3 by NDRG1 was able to inhibit the progression of pancreatic cancer	Kovacevic et al. (2013)
Proneural glioblastoma	Brain	Elevated expression of Glis3 was investigated	Cooper et al. (2010)

Glis3. This evidence suggested that the Wwtr1 acts as a coactivator of Glis3; however, the influence of Wwtr1 on Glis1 and Glis2 is not significant. To sum up, this evidence supports Glis3 as playing a critical role in sustaining the typical structure of renal and homeostasis.

Conclusions

Glis3 is one of the members of a transcriptional-regulated family, the Gli-similar family. It is also clear that Glis3 is implicated in the pathogenesis of several diseases, as shown in Table 3. Glis3 could upregulate the insulin expression and play a crucial role in the development of β cells in pancreas. Otherwise, the mutant Glis3 could induce the apoptosis of β cells. Notably, frameshift mutations are found within *GLIS3* gene in patients diagnosed with neonatal diabetes mellitus and congenital hypothyroidism, also known as NDH syndrome. Collectively, the above evidence indicates that the functional loss of Glis3 may increase susceptibility to develop both type 1 and type 2 diabetes. Besides, aberrant expression of Glis3 has been observed in several cancer cell lines. RNA sequencing data obtained from patients with fibrolamellar hepatocellular carcinoma have suggested that this type of cancer is linked to the *GLIS3-CLPTM1L* gene fusion. So far, the mechanism by which mutation in Glis3 drives tumorigenesis remains unclear. Furthermore, the mutant Glis3 has also been identified in both congenital hypothyroidism and polycystic kidney disease. Further investigation of Glis3-related signaling pathways might provide another opportunity for improving the treatment of diabetes, cancer, thyroid, and kidney-related diseases in the future.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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