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RELATIONSHIP BETWEEN BICAUDAL-C AND PKD

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ABSTRACT

Translational activation and repression play an important role in the spatial-temporal regulation of gene expression in embryonic development. Bicaudal-C of Drosophila is an RNA-binding molecule believed to function at this post-transcriptional level. Loss-of-function mutants in *Drosophila* affects anterior-posterior patterning, producing abnormal embryos lacking head formation and with duplicate posterior segments. Mouse *Bic-C* gene(*Bicc1*) is localized to a C1 region located on Chromosome 10. Bicaudal-C contains several conserved N-terminal KH domains and a conserved C-terminal SAM domain. The KH domains have been shown to bind RNA, and the SAM domain is thought to play a role in protein-protein interactions. There are three mouse mutant models for *Bicc1*,*jcpk*,*bpk*and 67*Gso*. Mutations in different sites of *Bicc1* in these models produce the cystic phenotypes in the kidney and affect the normal formation/functions of other organs(liver, pancreas etc.), which are very similar to human polycystic kidney disease(PKD). Moreover, mutation of Bicaudal-C in other species also causes polycystic kidney disease-like phenotypes.Furthermore, emerging evidence also indicates thatnormal Bicc1 expression requires ADPKD causal gene expression. In this review, we outline the recent progress in Bicaudal-C research and its relationship with polycystic kidney disease.

INTRODUCTION

Molecular Characteristics of Bicaudal-C

The establishment of germline cells and embryonic axes in *Drosophila* involves the asymmetric localization of multiple RNAs and protein molecules within the cell[1]. *Bicaudal-C* gene (*dBic-C*) of *Drosophila* is required for proper migration of head follicular cells and localization in the head segment. *dBic-C*plays an important role in the formation of follicular cells in the head of oocytes and the formation of embryonic head segments. Therefore, *dBic-C* is an essential gene for studying specific cell migration and head-tail body axis specificity during embryonic development [2].

Subsequently, the homologous gene of *dBic-C* was found in several species. The *Bic-C* gene of *Drosophila* was located in the 35E2 region on chromosome 2; the *Bic-C* gene of *Canis* was located on chromosome 4; *Bic-C* of *Rattus norvegicus*is located in the p11 region of chromosome 20; *Bic-C* of *Gallus*is on chromosome 6; mouse *Bic-C* gene is located in C1 region of chromosome 10; and humans *Bic-C* gene are located in the region of 10q21.2. Their protein products are highly conserved among different species. In addition, the orthologs of *dBic-C* are also found in species such as *C. elegans*, *Gambiae* and *Xenopus*. The high conservation of these gene products also indicates that *Bic-C* plays an important role in the organogenesis and development of different species, and for these species *Bic-C* is likely to be an essential gene in its growth and development.

Expression and distribution of Bicaudal-C gene and its product

Northern blot and RT-PCR analysis of *Bicaudal-C* (*Bicc1*) RNA in mice revealed that *Bicc1* RNA was expressed in a series of tissues, including kidney, heart, lung, liver, brain and spleen, testis and skeletal muscle, which are most prominent in the kidneys and heart[3]. During mouse embryonic development, *Bicc1* mRNA expression is first detected at the rostral tip of the primitive streak around E7.5 and in neural tissues at E8.5. At E13.5, strong *Bicc1* mRNA labeling is detected in the bone, heart, and lung tissues. In mouse kidney development, *Bicc1* mRNA is detected at the mesonephros and the first branch of the ureteric bud tree at E11.5, and then at the metanephros and the comma- and S-shaped bodies at E13.5. At birth, *Bicc1* mRNA is mainly seen in the proximal tubules of the mouse kidney[4].

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According to molecular biological analysis, the primary transcript of *Bicc1* mRNA is about 5.9 kb and consists of 22 exons. RT-PCR expression profiling revealed two splicing variants in mouse *Bicc1*: transcript A and transcript B. In normal mouse tissues, transcript A contains exons 1-20 and exon 22. This transcript encodes a 105 kDa protein containing 977 amino acids. Transcript B contains exons 1-22, and encodes a 102 kDa protein of 951 amino acid. The shorter protein encoded by Transcript B due to the presence of a stop codon in exon 21 of the coding region[5].

Functional Domain of Bicaudal-Cprotein

Several KH domains are arranged in the N-terminal sequence of the Bic-C protein. The KH domain is an evolutionarily conserved domain of approximately 70 amino acids that was first identified in human hnRNP K protein [6]. Proteins containing the KH domain can bind RNA or single-stranded DNA *in vitro*, and even the KH domain alone can bind to RNA. The most conserved sequence in the KH domain is VIGXXGXXI, where X represents any amino acid. This conserved sequence is usually located in the middle of the KH domain and mediates binding of the KH domain to RNA. In addition, in the different KH-containing proteins, the spatial conformations of the KH domains are very similar, and they are all folded into a structure containing α-helices on both sides with a 100°-120° rotation angle. This folding is important for the function of the KH domain. Wessely et al. reported that the mouse gene *Bicc1* product contains five KH domains, but the PFAM analysis (pfam.wustl.edu) identified only three of the KH domains. In other species, there are different reports about the number of KH domains of Bic-C protein [7, 8].

There is also a SAM (Sterile alpha motif) domain at the C-terminus of the Bic-C protein. It is generally believed that the function of this domain is mostly to mediate the interaction between proteins and promote protein homology/heterodimer dimerization [9]. In almost all tested species,the SAM domain contains a conserved tyrosine (Tyr) at its 19 position. Phosphorylation analysis of the conserved tyrosine (Tyr) residues in SAM revealed that this structure also interacts with proteins containing the SH2 domain[10]. The SH2 domain specifically recognizes the phosphorylation site of the Tyr residue and thus recruits the SH2-containing protein localizing to the Tyr phosphorylation site of the SAM domain [11]. This acts as the regulation pathway of intracellular signal cascade.

Relationship between Bicc1 and Polycystic kidney disease (PKD)

Polycystic kidney disease (PKD)

Polycystic kidney disease (PKD) is an inherited disorder in which the renal tubules become structurally abnormal, resulting in the development and growth of multiple cysts within the kidney [12]. These cysts may begin to develop before birth or in infancy, in childhood, or in adulthood [13]. Cysts are non-functioning tubules filled with fluid pumped into them, which range in size from microscopic to enormous, crushing adjacent normal tubules and eventually rendering them non-functional also. The two main types of polycystic kidney disease are: autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD).

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disorders characterized by progressive cyst development and various extrarenal manifestations [14, 15]. Cystogenesis in human kidneys progressively occupy the normal parenchyma of the kidney and lead to renal failure, which usually occurs in mid-to-late adulthood. This disease is the fourth most common single cause of end-stage renal failure worldwide [16, 17].

ADPKD is caused by mutations in the *PKD1* or *PKD2* genes, which encode the proteins polycystin-1 (PC1) and polycystin-2 (PC2), respectively. Approximately 85% of ADPKD patients have mutations in *PKD1*, and the remaining 15% have mutations in *PKD2*[18-21]. The most common extrarenal manifestation of ADPKD is the formation of bile-duct-derived cysts in the liver [15, 22]. Liver cysts occur in 83% of all ADPKD patients, and 94% of the patients with liver cysts are over 35 years old [23, 24]. Other ADPKD phenotypes include pancreatic cysts [25, 26], aneurysms [27-30], and aortic root/thoracic aorta abnormalities [31-33].

Autosomal recessive polycystic kidney disease (ARPKD) is one of the most common hereditary renal cystic diseases in infants and children, with an estimated incidence of ~1 in 20,000 live births and a prevalence of heterozygous carriers of ~1 in 70 [34-36]. The disease is caused by mutations in *PKHD1*, which encodes a 16-kb transcript, contains at least 86 exons, and spans 470 kb on chromosome 6p12 [37]. The longest ORF is predicted to be 66 exons and yields a 4074-amino acid membrane-associated receptor-like protein, fibrocystin/polyductin (FPC) [38-42]. Its major clinical manifestations include fusiform ectasia of the renal collecting and hepatic biliary ducts and fibrosis of the liver and kidneys [43-45] , although the renal lesions predominate at the time of diagnosis [45, 46]. Approximately 50% of ARPKD patients present as neonates [47] when they are born with dramatically enlarged, symmetric kidneys and ectasia of the collecting duct [48, 49]. The mortality rate is 30-50% for neonates due to respiratory and/or renal dysfunction [50].

Bicc1 mutation and Polycystic kidney disease

Currently, there are at least three mouse models of *Bicc1* gene mutations, *jcpk*, *bpk* and 67*Gso*having been reported. All these models exhibit a phenotype of polycystic kidney disease. Studying and analyzing these mouse models will conducive to clarify the biological function of the mouse Bicc1 gene product in polycystic kidney disease.

jcpk(juvenile congenital polycystic kidney disease) mouse model

Jcpk is an ARPKD mouse model. An abnormal splicing caused by apoint mutation (G→A) on exon 3 results in the deletion of exon 3of the *jcpk* mouse model. This mutation leads a frameshift mutation in the reading frame in *jcpk*, and a stop codon was generated in the exon 4 reading frame. The transcripts A and B produced by the *jcpk* mutant were identical. The protein product was only 93 amino acids.

Jcpk homozygous mutant mice exhibit severe polycystic kidney disease phenotype and abnormalities of extrarenal tissues and certain organs, including gallbladder enlargement and dilation of bile ducts and pancreatic ducts, which are usually present in newborn mice. The pathological phenotype

is very obvious in postnatal Day 3. The *jcpk* heterozygous mice had no abnormal phenotype at birth, but 30% of these mice showed abnormal phenotype at10 months old, mainly as glomerular renal cysts[51].

bpk(BALB/c polycystic kidney disease) mouse model

bpk is an autosomal recessive mouse model established by mutations in BALB/c mice during self-intersection [3]. Due to the insertion of two bases (-GC-) into exon 22, the reading frame of transcript A of *Bicc1* was changed, which extends transcript A by 149 amino acids. Transcript B is not affected.

bpk/*bpk* homozygous mutant mice generally survive no more than four weeks due to severe renal dilation. At the time of birth, cysts were formed only at the primary tubules, and after 21 days, the cystic sites were transferred to the renal collecting duct. The *bpk* homozygous mutant exhibits the disease phenotype that is not as severe as the *jcpk* homozygous mutant, and its phenotype is more similar to human ARPKD [52].

67Gso(t(2;10))67Gso)mouse model

The 67Gso mutant mouse model was established in a high-dose chemical mutagen-induced mutation screen. This mutation is a translocation mutation caused by fragmentation of chromosome 2 and chromosome 10. FISH analysis revealed that *Bicc1* gene was involved in the shift region of 67Gso on chromosome 10. Neonatal mice with homozygous mutant *67Gso* are small and weak. The kidneys of these mice exhibit many narrow and elongated cysts extending from the glomerulus and the nephron of the collection tube to the extrarenal cortex. In the liver, the number of bile ducts significantly increases and dilates [53]. The survival rate of these homozygous mice is very low, some mice die at birth, and the remains survive no more that 3-4 days.

Mutation of Bicaudal-C in other species

Mutation of *Bicaudal-C* in other species also causes polycystic kidney disease-like phenotypes. In *Drosophila*, Gamberi et al. have demonstrated that *Drosophila* mutants lacking the translational regulator Bicaudal C exhibited progressive cystic degeneration of the renal tubules (so called "Malpighian" tubules) and reduced renal function. The BicC protein was shown to bind to *Drosophila* (d-) myc mRNA in tubules. Elevation of d-Myc protein levels was a cause of tubular degeneration in BicC mutants. Activation of the Target of Rapamycin (TOR) kinase pathway, another common feature of PKD, was found in BicC mutant flies. This result presented new mechanistic insight on BicC function and propose that *Drosophila* may serve as a genetically tractable model for dissecting the evolutionarily-conserved molecular mechanisms of renal cystogenesis [54].

In zebrafish, Bouvrette et al. found that knockdown of zebrafish Bicc1 expression resulted in the formation of kidney cysts and expression of mouse Bicc1 rescues the cystic phenotype of the morphants. These results demonstrate that the function of Bicc1 in the kidney is evolutionarily conserved[55]. In *Xenopus*, *Bicaudal-C* mRNA was present in the epithelial structures of the Xenopus pronephros, the tubules and the duct, but not the glomus. Inhibition of the translation of endogenous *Bicaudal-C* led to a PKD-like phenotype. Embryos lacking Bicaudal-C developed generalized edemas and dilated pronephric tubules and ducts. This phenotype was caused by impaired differentiation of the pronephros[56].

Molecular link between Bicc1 and PKD

Study has demonstrated that the absence ofBicc1 in cells promotes miR-17's binding to the 3'UTR of *Pkd2*and disrupts the stability of the *Pkd2* mRNA [57]. This finding indicates that Bicc1 acts as a posttranscriptional factor upstream of*Pkd2* and reveals the molecular relationship between *Bicc1* and*Pkd2*, a causal gene of human ADPKD. Our result also indicated that lack of Bicc1 leads to disruption of normal cell-cell junctions, which in turn impedes establishment of epithelial polarity. These cellular defects initiated abnormal tubulomorphogenesis and cystogenesis of IMCD cells grown *in vitro*. The observation of aberrant cellular behaviors in Bicc1-silenced IMCD cells reveal functions for Bicc1 in renal epithelial cells and provides insight into a potential pathogenic mechanism of polycystic kidney disease[58]. Moreover, our group also demonstrated that another human ADPKD causal gene, *Pkd1*, is involved in the regulation of Bicc1 expression *in vitro* and *in vivo*. Loss of the *Pkd1*gene product, polycystin-1 (PC1) down regulates *Bicc1* expression. This finding indicates that *Bicc1* is not only associated with *Pkd2*,but also with *Pkd1* expression[4]. The association between Bicc1 and polycystins implies that a disruption of Bicc1 induces cystic phenotypes through the polycystin pathway.

Perspective

Recent studies have shown that the *Bicaudal-C* gene is widely present in various species. This high degree of conservation also indicates that Bic-C plays an important role in the growth and development of the entire biological system. The results from various Bic-C biological mutant models indicate that this gene may play an important role in species polycystic kidney disease-like phenotypes.

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