LUPINE PUBLISHERS

Peer Reviewed Journal of Forensic & Genetic Sciences

DOI: 10.32474/PRJFGS.2022.04.000194

ISSN: 2638-6062

Review Article

A Novel Progress of FXYD6 Structure and Functions

Qin Yang[1], Tianxi Zhang[1], Xiaoyu Li[1], Yuma Yang[1], Yuhua Ma[1], Siqin Luo[1], Yu Zhou[1], Hao Zhang[1], Minghai Shan[2]* and Yanhui Yang[1]*

[1]*Ningxia Key Laboratory of Prevention and Control of Common Infectious Diseases, Ningxia Medical University, China*

[2]*The General Hospital of Ningxia Medical University, China*

***Corresponding author:** Yanhui Yang, Ningxia Medical University, Yinchuan, China

Minghai Shan, The General Hospital of Ningxia Medical University, China

Received: September 23, 2022 **Published:** October 04, 2022

Abstract

FXYD domain containing transport regulator 6 (FXYD6) is a member of the FXYD family of transmembrane protein and encodes phosphohippolin, which likely affects the activity of sodium-potassium pump. FXYD6 is associated with some diseases including hypomagnesemia 2, renal and alternating hemiplegia of childhood. In addition, recent studies have also shown that FXYD6 is expressed in some cancer tissues, such as cholangiocarcinoma, liver cancer and pancreatic cancer. Here, we reviewed the protein structure of FXYDs, and the different expression of FXYD6 in various tissues or organs, and the functions of FXYD6 in diverse cancers and other diseases.

Keywords: FXYD gene family protein; FXYD6 gene; tumor

Abbreviations: NKA: Na+/K+-ATPase; CNS: Central Nervous System; ATP: Adenosine Triphosphate; AFP: Alpha-Fetoprotein; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; TNM: Tumor (T), Nodes (N), and Metastases (M)

Introduction

FXYD family are a class of small-molecule single-transmembrane proteins that function as ion channels or ion channel regulators [1]. All FXYD genes are expressed in the early embryo, and widely distribute in tissues and organs of adult mammals, in organs that transport fluid and solutes, such as breast, kidney, prostate gland and pancreas. FXYD genes also express in most electrically excitable tissues, for instance muscle and nervous system. Moreover, the human FXYD protein modulates α1β1 pump isoforms and alters the apparent affinity of cells for Na+, Therefore, FXYDs proteins alter the selectivity of intracellular ion pumps and affect the function of cell. The α and β subunits of Na+, K+ -ATPase (NKA) are minimal functional units, and they can be further modified by FXYD subunit, which shared a PFXYD motif in the N-terminal, extracellular part of the single TM protein [2].

In mammal, Seven FXYD proteins are expressed and may also serve functions as well as modulating NKA function [3]. FXYD1 is exceedingly expressed in the liver, heart, fat, ovary, prostate, endometrium and brain. Protein kinases A and C phosphorylate serine in the intracellular part of FXYD1, which is described as a phosphorylated heart protein [4]. FXYD1 was activated by phosphorylation [5], and knock-out of the subunit increases Na+, K+ -ATPase activity in the heart of mouse [6]. It was firstly found that FXYD2 associated with the Na+, K+ -ATPase in FXYD family [7]. The expression level of FXYD2 is extremely high in kidney, and high in gall bladder and salivary gland. The mice lacking FXYD2 are survivable, however, have reduced reproduction, perhaps owing to a metabolic phenotype where glucose is tolerated [8]. Distinct most FXYDs, FXYD4 is highly expressed in kidney, and increases the pump's sodium affinity. The roles of FXYD3 and FXYD5 are unclear, however, accumulating evidence suggests the biological role of FXYD3 in some cancers. For example, FXYD3 is a hostile prognostic biomarker related with pro-tumor TILs, T cell exhaustion and hypoxia [9]. FXYD3 deficiency conspicuously hampered cell

migration and proliferation while facilitated cell apoptosis in cervical cancer cells [10]. Low expression of FXYD5 reversed the cisplatin resistance of epithelial ovarian cancer cells [11]. FXYD6 and 7 are highly expressed in brain.

Analysis the expression of different FXYD protein subsets using RT-qPCR techniques, indicated that FXYD5 were expressed in various tissues [12]. In addition, an important paralog of this gene is FXYD1. As one of the components of the FXYD protein family, FXYD6 is expressed in a variety of tissues, and is highly expressed in the brain tissue, it is especially expressed in prefrontal cortex, amygdala, hypothalamus, and so on. It is involved in the excitability of nerve. For these reasons, the FXYD gene family has been implicated in a variety of human diseases, such as taste disorders [13], atherosclerosis [14] and heart failure, and so on. FXYD6 was originally named phosphohippolin because it was discovered in the hippocampus [15,16]. According to research, FXYD6 is not only related to the balance function of the inner ear auditory nerve, but also highly expressed in the brain, it is also closely related to the susceptibility to psychosis [17]. From what has been discussed above, studying on the structure, biological characteristics, physiological function, and regulation of FXYD6 gene and protein will help to further understand the function of FXYD6 [18].

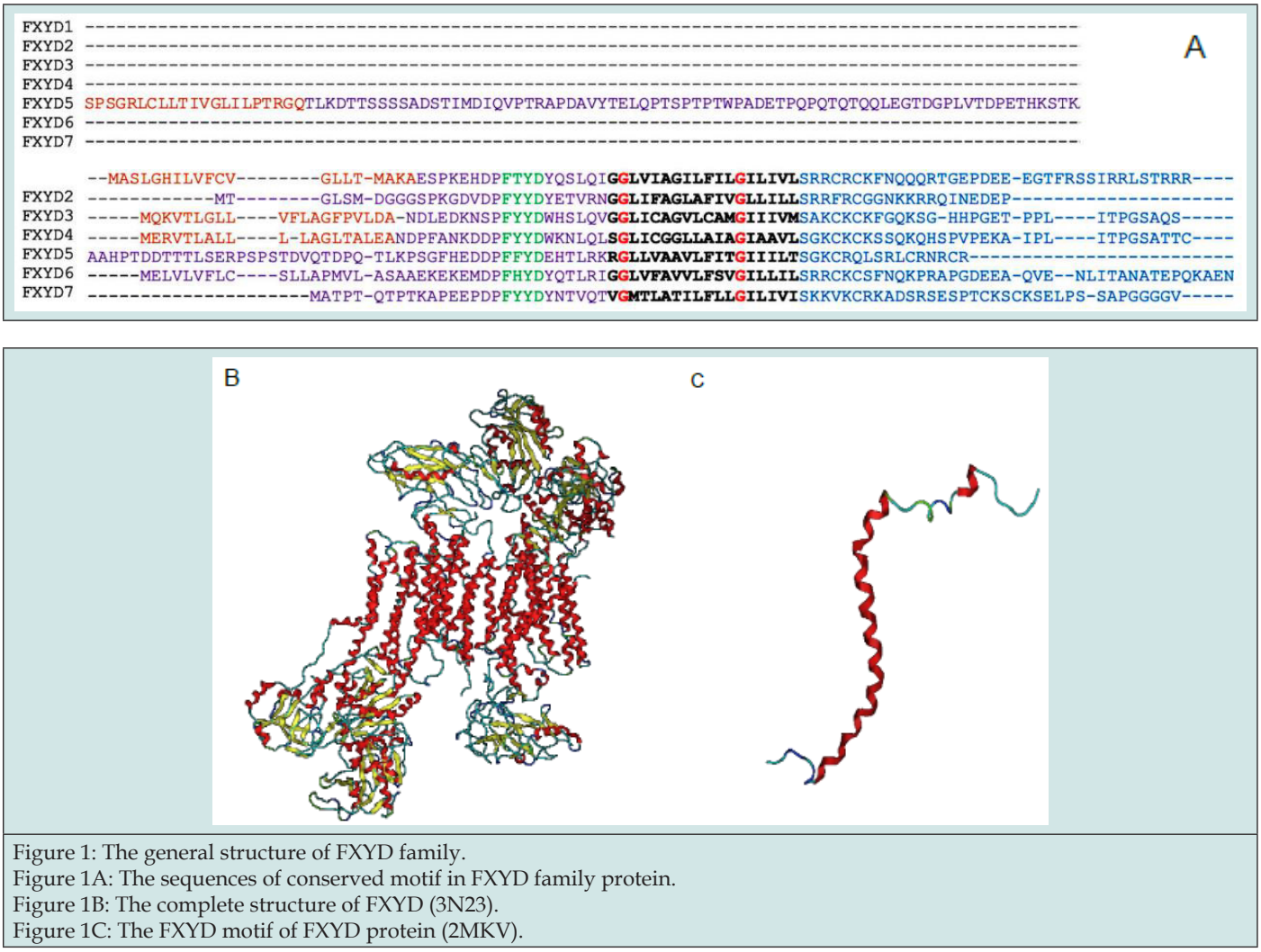

Figure 1: The general structure of FXYD family.
Figure 1A: The sequences of conserved motif in FXYD family protein.
Figure 1B: The complete structure of FXYD (3N23).
Figure 1C: The FXYD motif of FXYD protein (2MKV).

The Structures of FXYD Family

The name of FXYD family is derived from the conserved PFXYD motif which is located in the extracellular N-terminal domain. The structure of the FXYD gene protein family refers to the ion transport regulator factor containing the FXYD structure, which belongs to the water-insoluble small molecule (66~178 amino acids) type I membrane protein with a single transmembrane α-helix flanked by intracellular C-termini and extracellular N-terminal domains [19]. The signal sequence encoded by the FXYD gene family contains 35 amino acids, including 7 unchanged amino acids and 6 highly conserved amino acid sequences [20]. To date, there were 7 subpopulation members of the FXYD family have been found in mammals. A small number of conserved residues supposed to be vital for NKA binding and regulation are focused on the middle of the primary sequence. In the transmembrane domain, two glycines and a serine are also conserved in all proteins. Then followed by a pattern of basic residues and cysteines in the variable cytoplasmic

domain. After the conserved serine, at least one cysteine is always present, this suggests that they are essential for the regulation of NKA. The crystal structure of several important FXYD proteins has uncovered by nuclear magnetic resonance (Figures 1A-1C) shows structures of the high affinity complex between ouabain and the e2p form of the sodium-potassium pump (PDB ID 3N23 and 2MKV) and highlights crucial structural features of FXYD proteins [21].

The Basic Function and Localization of FXYD6

In 2001, FXYD6 was described and cloned [22]. FXYD6 gene is located on the long arm of chromosome 11 (11q23.3) in human. FXYD6 protein is an ion transport regulator 6 containing an FXYD domain, and its transmembrane protein contains 35 invariant amino acid conserved sequences. The fragmented FXYD6 protein contains 95 amino acids. FXYD6 is also highly expressed in different regions of the cerebellum, CNS, hypothalamus, and cerebral cortex. FXYD6 association with α1β1 resulted in a 30% reduction in apparent affinity for intracellular Na+ with no change in the apparent affinity for extracellular K+ [23]. Furthermore, FXYD6 drastically decreased plasma membrane functional expression of α1β1 in *Xenopus oocytes*, suggesting FXYD6 may function as a regulator of NKA localization in plasma membrane. In the brain, FXYD6 is exclusively discovered in neurons and may participate in neuronal excitability. FXYD6 is colocalized in plasma membrane by immunofluorescence microscopy in primary auditory neurons and in differentiated PC12 cells [24]. Nonetheless, the distribution in non-differentiated PC12 cells shows to be largely perinuclear. FXYD6 expression in the cerebellum, hippocampus, and forebrain proliferates during the first 3 week of life, after which expression gradually reduces. FXYD6 appears to participate in the development of multiple brain structures. Dynamic expression of FXYD6 is also observed in the inner ear and cerebellum.

FXYD6 could be comprised in the development in these cells in specific cerebellar lobules. In 2001, *Saito et al*. showed that FXYD6 expression is increased in the cerebellum between the second and third postnatal weeks coincides [25]. FXYD6 also reduces α1β1 pump sodium affinity that is necessary for extrusion of sodium in type II taste cells relative to type III. Remarkably, FXYD6 expression does not relate to α1β1 expression in all structures, indicating FXYD6 may have other interacting partners. Some other reports suggest that FXYD6 may regulate synaptic transmission. FXYD6 was enriched in synaptosomes and plasma membrane fractions containing the vesicular Na+ -dependent transporter VGLUT1by proteomics study, and was discovered in all brain regions, such as somatic, axonal, dendritic, and presynaptic plasma membrane [26]. FXYD6 is also collocated with synaptic protein PSD95 [27].

Protein Interactions

According to the affinity, Protein interactions are mainly divided into the following several types: they can be classified as specificity and non-specificity interaction. Non specificity interaction can be classified according to their formation of the complex of stability, whether permanent or transient, transient interaction is weak or strong [28]. Most of the specific interaction is permanent, most of the non-specific mutual use is temporary. To further analysis FXYD6-binding proteins, we obtained a total of 10 FXYD6-binding proteins by the STRING tool in Figure 2.

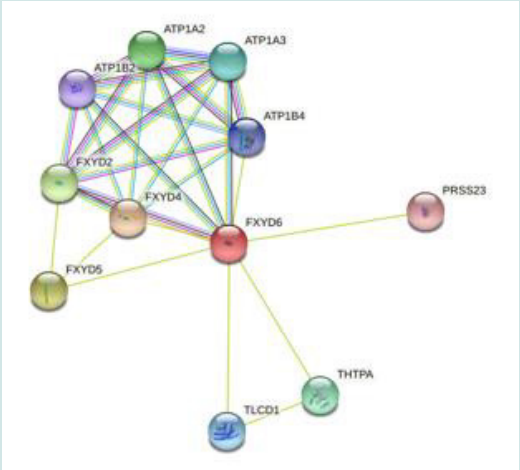

Figure 2: FXYD6-binding proteins using the STRING tool.

The Expression Level of FXYD6 in Various Tissues and Organs

In the context of mature development of gene therapy, we focus on FXYD gene family proteins, and it is known that all FXYD genes are expressed in early embryos and are widely distributed in mammalian. In tissues, it is mainly expressed in tissues and organs that transport fluid and solutes in adults, such as kidney, breast, pancreas, anterior prostate, colon, liver, lung, and placenta; also expressed in electrically excitable tissues such as nervous system

and muscle [29]. As showed in Figure 3, FXYD6 is expressed in many human tissues or organs. The expression level of FXYD6 gene was highest in brain than that of other organs, followed in ovary, then in endometrium and spleen. However, researchers mainly explored the role of FXYD6 gene in cholangiocarcinoma, and the current research mainly focuses on mental health sexual diseases and cholangiocarcinoma. Although the expression level is lower in other tissues, it also has a certain effect and influence on the human body, so it needs special attention and in-depth research the function of FXYD6.

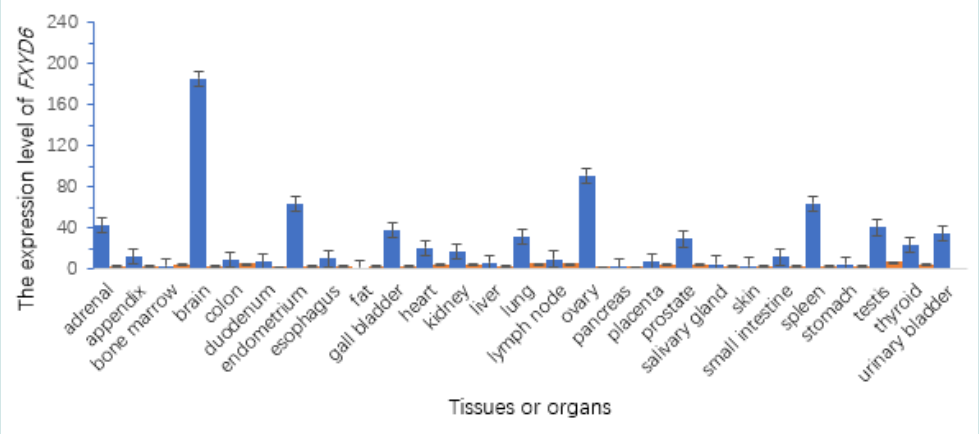

Figure 3: The expression level of FXYD6 in various tissues and organs.

The Functions of FXYD6 in Cancers

Progressively evidence showed that FXYD6 is abnormally expressed in some tumor, such as cholangiocarcinoma, osteosarcoma, and hepatocellular carcinoma, pancreatic cancer and rectal cancer. In either case, it may prove a clinically useful biomarker.

Cholangiocarcinoma

The human FXYD6 gene may play an essential role in the transformation and evolution of cholangiocarcinoma. FXYD6 expression is inversely correlated with the degree of differentiation of cholangiocarcinoma. In situ testing showed that human FXYD6 gene was localized in the cytoplasm of bile duct carcinoma epithelial cells and was significantly higher in tumor cells than in normal bile duct cells [30]. Studies suggest that human FXYD6 antisense nucleic acid inhibits the proliferative activity of qb939 cells in human cholangiocarcinoma in vitro but has no significant effect on its ability to invade. FXYD6 has a clear expression in human pancreatic cancer tissue with a clear pathological diagnosis [31].

Hepatocarcinoma

A key feature of cancer cells is cells divided and multiplied uncontrollably. FXYD6 is overexpressed in hepatocellular carcinoma, the transmission of cell proliferation signals is maintained. FXYD6 expression is related to clinicopathological characteristics, early postoperative recurrence and survival time of patients with hepatocellular carcinoma [32]. FXYD6 expression is associated with gender, age and tumor differentiation and tumor size in hepatocellular carcinoma. However, there was no correlation between tumor maximum diameter, tumor number, preoperative AFP level, and HBV or HCV infection. In addition, membrane integrity, microvascular invasion and TNM stage were all correlated. The rate of early recurrence in FXYD6 overexpression group is higher than that of normal group [33]. Furthermore, FXYD6 is also related to the differentiation of liver cancer, from normal liver tissue, liver cirrhosis tissue to liver cancer tissue, FXYD6 The protein expression levels increased significantly in turn. FXYD6 antibody can inhibit HepG2 hepatoma cells cultured in vitro at appropriate concentrations Inhibition of the proliferation and growth of liver cancer cells [34]. However, this inhibitory effect has no dose-response relationship [35]. Anti-human FXYD6 Antibodies can inhibit the growth of HepG2 cells. FXYD6 antibody may affect the growth of HepG2 hepatoma cells in vitro in terms of gene transcription and translation [36].

With the gradual development of liver cirrhosis into hepatocellular carcinoma [37], the intensity of FXYD6 protein immune response has a tendency to gradually increase, reminding that in tissues with high expression of FXYD6 protein, the differentiation degree of tumor cells has a tendency to deteriorate, and the degree of malignancy is higher, which indicates that the liver cancer cases with high expression of FXYD6 protein should be aware of the high risk of its clinical prognosis, and be alert to the occurrence of hematologic or lymphatic disease [38]. FXYD6 protein is highly expressed in hepatocellular carcinoma tissues and may be involved in the carcinogenesis of hepatocytes and its effects. Progression may be a poor prognostic factor in patients with hepatocellular carcinoma.

Pancreatic Cancer

FXYD6 plays a key role in the pathogenesis of pancreatic cancer, and with the degree of pancreatic cancer differentiation from high to low, the intensity of FXYD6 protein immune response gradually

increased. In pancreatic cancer tissues with lymphatic metastasis, FXYD6 protein expression was also significantly enhanced. The above results indicate that high expression FXYD6 has poor differentiation degree of tumor cells, high degree of malignancy, and are prone to lymph node metastasis. For pancreatic cancer cases with high expression of FXYD6 protein in the clinic, even if there is no obvious lymphatic metastasis during surgery, extended surgery is required [39]. Furthermore, FXYD6 expression is significantly different in various TNM stages, specifically, in stage II-IV pancreatic cancer tissue FXYD6 expression is significantly higher than that in stage I-II, so intraoperative detection determining the expression level of FXYD6 protein is helpful for the correct staging of intraoperative pancreatic cancer and has guiding significance for the operation method and scope. Given that FXYD6 It is a tissue-specific regulatory protein of NKA, and it is speculated that FXYD6 may regulate NKA by regulating the differentiation and proliferation of tumor cells, and its specific mechanism of action remains to be further explored. In conclusion, FXYD6 protein is closely related to the occurrence and development of pancreatic cancer and may be a potential tumor-related protein.

Rectal Cancer

FXYD6 regulates chemosensitivity by mediating the expression of NKA α1 and affecting cell autophagy and apoptosis in colorectal cancer. FXYD6 was depressed in chemo-resistant colorectal cancer and related to chemoresistance. FXYD6 expression is higher in tumor tissue than that in normal tissue, and also has a higher expression in the cytoplasm of rectal cancer cells than that in the normal cell membrane, because FXYD6 is tissue-specific for NKA. FXYD6 may serve as a potential non-specific tumor-associated protein, in addition to up-regulation of NKA activity affecting tumor cell differentiation and proliferation, there may be many other unknown mechanisms of action that need to be further explored.

FXYD6 in Other Diseases

FXYD6 may be essential for several pathological mechanism, such as the sense of taste, atherosclerosis, psychosis, and inner ear hearing. The polymorphisms of FXYD6 gene have been associated with schizophrenia. Nevertheless, other research has not detected such an association [40].

The Sense of Taste

The NKA regulated gene FXYD6 is expressed in type II taste cells of mouse taste buds, and specific expression in type II taste cells, and taste cells frequently co-express FXYD6 and NKA1. Simultaneously, FXYD6 is co-expressed with transient receptor potential ion channel M subfamily member 5, which is a key component of sweet, bitter, and umami-taste signal transduction pathway. Therefore, FXYD6 also has a certain effect on human taste.

Atherosclerosis

Related studies have shown that the expression of FXYD6 is up-regulated in atherosclerotic plaques. Lentivirus-induced overexpression of FXYD6 in cultured monocyte-derived macrophages resulted in higher Na+ adenosine triphosphatase activity, intracellular cholesterol accumulation, and increased secretion of proinflammatory cytokines, thereby enhancing atherosclerotic lesions.

Psychosis

Human FXYD6 shares 48.1% homology with rat transmembrane protein FXYD1, and FXYD6 expression in rats is increased at 3 weeks after birth. highest in the brain and continued into adult rats, suggesting that FXYD6 is responsible for neuronal excitation in postnatal and mature rat brains and, sex also plays a key role [41]. According to a study of 496 patients and 488 normal subjects at the University of London, it was found that in FXYD6 seven microsatellites or single nucleotide polymorphism markers in or beside the gene are associated with susceptibility to psychosis. The allele is related to the occurrence of psychosis, and it is reported that there is a susceptibility gene region for psychosis in the chromosome 11q22-q24 region. It is believed that the base pair change of the FXYD6 gene or the change of the promoter control subregion of the gene causes the abnormal function of the FXYD6 protein, Increased susceptibility to psychosis [42]. In childhood psychosis, the FXYD gene encodes a protein that regulates ATP-dependent pump function and stratifies complex conditions according to age of onset to identify deleterious variants.

The Inner Ear Hearing

FXYD6 colocalizes with NKA in stria vascularis and can coimmunoprecipitate with NKA and is preferentially expressed in different regions of the inner ear [43]. NKA are also key proteins in maintaining the electrochemical composition of endolymph. Endolymph greatly affects the sensitivity of the cochlea. The results suggest a unique role for FXYD6 in endolymphatic composition.

Conclusion

At present, a general understanding of the FXYD protein family, especially the development of FXYD6 for biomarker for human diseases. Here, we have reviewed the structure of FXYD family proteins in mammal, and FXYD6 functions, colocalization, protein interactions, and expression levels in cancer and other disease. FXYD6 is highly expressed in most pathological conditions. Notably, while inhibitors of NKA, FXYD6 is also expressed in the heart muscle, and the expression and dimerization of FXYD6 increase in heart failure, which may reveal the cause pathophysiology of NKA dysregulation in heart failure. In conclusion, although we have reviewed the up-to-date functions of FXYD6, the comprehensive roles of FXYD6 in human is uncovered, in the future, more in-depth research on FXYD6 and FXYDs family proteins will help to provide novel biomarkers for diagnosis or treatment related diseases.

Disclosure Statement

All the authors declare that there is no potential conflict of interest.

Funding

This work was supported by the Ningxia Natural Science Foundation (No.2020AAC03161) and Research Projects for Social Development of Ningxia Hui Autonomous Region (No.2021BEG03072).

References

1. Meyer DJ, S Bijlani, M de Sautu, K Spontarelli, VC Young, et al. (2020) FXYD protein isoforms differentially modulate human Na/K pump function. J Gen Physiol 152(12): e202012660.
2. Ren S, N Zhou (2009) Research status of FXYD gene protein family and FXYD6 protein. Journal of Binzhou Medical University 32(2): 134-136.
3. Geering K (2005) Function of FXYD proteins, regulators of Na, K-ATPase. J Bioenerg Biomembr 37(6): 387-392.
4. Cuomo M, E Florio, R Della Monica, D Costabile, M Buonaiuto, et al. (2022) Epigenetic remodelling of Fxyd1 promoters in developing heart and brain tissues. Sci Rep 12(1): 6471.
5. Mishra NK, M Habeck, C Kirchner, H Haviv, Y Peleg, et al. (2015) Molecular Mechanisms and Kinetic Effects of FXYD1 and Phosphomimetic Mutants on Purified Human Na,K-ATPase. J Biol Chem 290(48): 28746-28759.
6. Bell JR, E Kennington, W Fuller, K Dighe, P Donoghue, et al. (2008) Characterization of the phospholemman knockout mouse heart: depressed left ventricular function with increased Na-K-ATPase activity. Am J Physiol Heart Circ Physiol 294(2): H613-621.
7. Forbush B 3rd, JH Kaplan, JF Hoffman (1978) Characterization of a new photoaffinity derivative of ouabain: labeling of the large polypeptide and of a proteolipid component of the Na, K-ATPase. Biochemistry 17(17): 3667-3676.
8. Arystarkhova E, YB Liu, C Salazar, V Stanojevic, RJ Clifford, et al. (2013) Hyperplasia of pancreatic beta cells and improved glucose tolerance in mice deficient in the FXYD2 subunit of Na, K-ATPase. J Biol Chem 288(10): 7077-7085.
9. Yonekura S, K Ueda (2022) FXYD3 Expression Predicts Poor Prognosis in Renal Cell Carcinoma with Immunosuppressive Tumor Microenvironment. Cancers (Basel) 14(15): 3596.
10. Peng X, J Gao, C Cai, Y Zhang (2020) LncRNA LINC01503 aggravates the progression of cervical cancer through sponging miR-342-3p to mediate FXYD3 expression. Biosci Rep 40(6): BSR20193371.
11. Liu YK, YJ Jia, SH Liu, HJ Shi, J Ma (2021) Low expression of FXYD5 reverses the cisplatin resistance of epithelial ovarian cancer cells. Histol Histopathol 36(5): 535-545.
12. Chen X, L Ding, D Kong, X Zhao, L Liao, et al. (2020) FXYD6 overexpression in HBV-related hepatocellular carcinoma with cirrhosis. Open Life Sci 15(1): 259-266.
13. Shindo Y, K Morishita, E Kotake, H Miura, P Carninci, et al. (2011) FXYD6, a Na, K-ATPase regulator, is expressed in type II taste cells. Biosci Biotechnol Biochem 75(6): 1061-1066.
14. Dong XH, ZF Lu, CM Kang, XH Li, KE Haworth, et al. (2021) The Long Noncoding RNA RP11-728F11.4 Promotes Atherosclerosis. Arterioscler Thromb Vasc Biol 41(3): 1191-1204.
15. Kadowaki K, K Sugimoto, F Yamaguchi, T Song, Y Watanabe, K, et al. (2004) Phosphohippolin expression in the rat central nervous system. Brain Res Mol Brain Res 125(1-2): 105-112.
16. Ito Y, Y Nakamura, N Takahashi, S Saito, B Aleksic, et al. (2008) A genetic association study of the FXYD domain containing ion transport regulator 6 (FXYD6) gene, encoding phosphohippolin, in susceptibility to schizophrenia in a Japanese population. Neurosci Lett 438(1): 70-75.
17. Choudhury K, A McQuillin, V Puri, J Pimm, S Datta, et al. (2007) A genetic association study of chromosome 11q22-24 in two different samples implicates the FXYD6 gene, encoding phosphohippolin, in susceptibility to schizophrenia. Am J Hum Genet 80(4): 664-672.
18. Chen X, M Sun, Y Hu, H Zhang, Z Wang, et al. (2014) FXYD6 is a new biomarker of cholangiocarcinoma. Oncol Lett 7(2): 393-398.
19. Franzin CM, XM Gong, P Teriete, FM Marassi (2007) Structures of the FXYD regulatory proteins in lipid micelles and membranes. J Bioenerg Biomembr 39(5-6): 379-383.
20. Wang PJ, CH Lin, HH Hwang, TH Lee (2008) Branchial FXYD protein expression in response to salinity change and its interaction with Na+/K+-ATPase of the euryhaline teleost Tetraodon nigroviridis. J Exp Biol 211(23): 3750-3758.
21. Yatime L, M Laursen, JP Morth, M Esmann, P Nissen, et al. (2011) Structural insights into the high affinity binding of cardiotonic steroids to the Na+, K+-ATPase. J Struct Biol 174(2): 296-306.
22. Yamaguchi F, K Yamaguchi, Y Tai, K Sugimoto, M Tokuda (2001) Molecular cloning and characterization of a novel phospholemman-like protein from rat hippocampus. Brain Res Mol Brain Res 86(1-2): 189-192.
23. Meyer DJ, S Bijlani, M de Sautu, K Spontarelli, VC Young, et al. (2020) FXYD protein isoforms differentially modulate human Na/K pump function. J Gen Physiol 152(12): e202012660.
24. Delprat B, JL Puel, K Geering (2007) Dynamic expression of FXYD6 in the inner ear suggests a role of the protein in endolymph homeostasis and neuronal activity. Dev Dyn 236(9): 2534-2540.
25. Saito S, R Matoba, K Kato, K Matsubara (2001) Expression of a novel member of the ATP1G1/PLM/MAT8 family, phospholemman-like protein (PLP) gene, in the developmental process of mouse cerebellum. Gene 279(2): 149-155.
26. Biesemann C, M Gronborg, E Luquet, SP Wichert, V Bernard, et al. (2014) Proteomic screening of glutamatergic mouse brain synaptosomes isolated by fluorescence activated sorting. EMBO J 33(2): 157-170.
27. Shiina N, K Yamaguchi, M Tokunaga (2010) RNG105 deficiency impairs the dendritic localization of mRNAs for Na+/K+ ATPase subunit isoforms and leads to the degeneration of neuronal networks. J Neurosci 30(38): 12816-12830.
28. Cornelius F, YA Mahmmoud (2007) Modulation of FXYD interaction with Na, K-ATPase by anionic phospholipids and protein kinase phosphorylation. Biochemistry 46(9): 2371-2379.
29. Blagosklonny MV (2022) Hallmarks of cancer and hallmarks of aging. Aging (Albany NY) 14(9): 4176-4187.
30. Jiao LZ, B Wang, XR Niu, XD Ma, JP Li, et al. (2011) A family-based association study of FXYD6 gene polymorphisms and schizophrenia. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 28(5): 539-542.
31. Y Z (2007) Effects of HFXYD6 antisense nucleic acid on cholangiocarcinoma cell lines. World Chinese journal of digestion 15(10): 929-935.
32. Sweadner KJ, E Rael (2000) The FXYD gene family of small ion transport regulators or channels: cDNA sequence, protein signature sequence, and expression. Genomics 68(1): 41-56.
33. Xu SY, PF Xu, TT Gao (2018) MiR-372-3p inhibits the growth and metastasis of osteosarcoma cells by targeting FXYD6. Eur Rev Med Pharmacol Sci 22(1): 62-69.
34. Li ZM, HY Zhang, YX Wang, WB Wang (2016) MicroRNA-137 is downregulated in human osteosarcoma and regulates cell proliferation and migration through targeting FXYD6. J Drug Target 24(2): 102-110.

35. Yang Z, Y Chen, Y Fu, Y Yang, Y Zhang, et al. (2014) Meta-analysis of differentially expressed genes in osteosarcoma based on gene expression data. BMC Med Genet 15: 80.

36. Liu J, N Zhou, X Zhang (2011) A monoclonal antibody against human FXYD6. Hybridoma (Larchmt) 30(5): 487-490.

37. Gao Q, X Chen, H Duan, Z Wang, J Feng, et al. (2014) FXYD6: a novel therapeutic target toward hepatocellular carcinoma. Protein Cell 5(7): 532-543.

38. Luo W, Q Liu, X Chen, H Liu, B Quan, et al. (2021) FXYD6 Regulates Chemosensitivity by Mediating the Expression of Na+/K+-ATPase alpha1 and Affecting Cell Autophagy and Apoptosis in Colorectal Cancer. Biomed Res Int 2021: 9986376.

39. Zhang J, R Che, X Li, W Tang, Q Zhao, et al. (2010) No association between the FXYD6 gene and schizophrenia in the Chinese Han population. J Psychiatr Res 44(6): 409-412.

40. Iwata Y, K Yamada, Y Iwayama, A Anitha, I Thanseem, et al. (2010) Failure to confirm genetic association of the FXYD6 gene with schizophrenia: the Japanese population and meta-analysis. Am J Med Genet B Neuropsychiatr Genet 153B(6): 1221-1227.

41. Miyashita T, K Akiyama, R Inamoto, A Matsubara, T Nakagawa, et al. (2012) Presence of FXYD6 in the endolymphatic sac epithelia. Neurosci Lett 513(1): 47-50.

42. Chaumette B, V Ferrafiat, A Ambalavanan, A Goldenberg, A Dionne-Laporte, et al. (2020) Missense variants in ATP1A3 and FXYD gene family are associated with childhood-onset schizophrenia. Mol Psychiatry 25(4): 821-830.

43. Delprat B, D Schaer, S Roy, J Wang, JL Puel, et al. (2007) FXYD6 is a novel regulator of Na, K-ATPase expressed in the inner ear. J Biol Chem 282(10): 7450-7456.

DOI: 10.32474/PRJFGS.2022.04.000194