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Role of Aquaporins in Diseases and Drug Discovery

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ABSTRACT

Aquaporins as water channels in transportation of water in and out of the cells due to their water permeability property play an important role in maintaining water's constancy which result in normal human physiology. Any mutation of the genes encoding them result in causing many diseases which are life threatening and dangerous like hyperinsulinemia, Sjogren's syndrome, vasogenic brain edema, glaucoma, nephrogenic diabetes insipidus, carcinoma,lymph node metastatic carcinoma and tumor growth, etc . Recent studies and discoveries has shown that aquaporins have fundamental role in drug discovery and they serves as attractive targets for different diseases. Several types of aquaporins are discovered which play important role in different types of diseases and drug discovery .In this paper we focused on role of aquaporins, structure- function relationship, types of aquaporins and their related diseases and strategies for identification of modulators of these drug targets for discovery of novel therapies and recent discoveries on different types of aquaporins and introduction of them as attractive targets. These paper showed significant role of aquaporins in normal human physiology and pathophysiology and give insights for deserving attention for them to effectively treat some of life threatening diseases.

Keywords: Aauaporins, Diseases, Drug Discovery, Target, Physiology and Pathophysiology

I. INTRODUCTION

Water as an essential molecule of the body forms major components of body cells and tissues .It is fundamental, supportive basis of all physiological activities of the cells and tissues such as transportation, body temperature regulation, urine control, digestion control, lubrication and cell communication. Circulation and supplement of water as vital life substance should be done using essential elements of the body .Among these elements aquaporins are very important in maintaining water 's constancy and any disturbance in their function causes a pathophysiological state. [1,3] Aquaporins are integral membrane proteins serve as water channels for selectively conducting water in and out of the cells and prevent the passage of ions and other solutes. Aquaporins are formed by intrinsic membrane proteins that forms pores in cells. Aquaporins located in plasma membrane and membrane of intracellular organelles. Aquaporins are mostly present in lens, brain, kidney, lungs,skin, vascular endothelium, gastrointestinal tract, sweat glands, liver, WBC, adipose tissue, salivary, lachrymal and etc.[1,2,3] Aquaporins are formed of six transmembrane alpha helices and their arrangement is in a right-handed pattern,with amino acid and COOH termini present on the cytoplasmic surface of the membrane. The amino acid s and COOH divisions of the arrangement show resemblance to each other like tandem repeat . Extracellular and cytoplasmic vestibules of the aquaporins are formed by five interhelical loop regions (A-E), out of which loops B-E are hydrophobic and consist of highly conserved Asn-Pro-Ala(NPA) motif, which flap the center of lipid bilayer of the membrane, forming a 3-D "sand clock"or" hour –glass" structure where water molecules flow through .This overlap forms one of the two channel constriction sites in the peptide, the first one is Asn-Pro-Ala(NPA) motif and second constriction site which is narrower is called ar/R selectivity filter. Aquaporins by formation of tetramers in the cell membrane, facilitate water transportation and also other small solutes such as CO2,glycerol and urea (uncharged molecules) across the membrane .[1,3] .Size of pores in aquaporins are different and depend upon the type of molecule that are passed through the pore. These pores are not permeable to charged molecules like protons. The movement of

water molecules through the narrow channel is in a single align by orientation themselves in the local electrical field generated by the atoms of the channel wall. Upon entering, the water molecules face with their oxygen atom down the water channel. At the middle time,they reversely oriented facing with the oxygen atom up. This rotation of molecules of water in the pore is due to the interaction of H-bonds between the oxygen of water and the asparagines in the two NPA motifs .This mode of movement for entering and leaving of the water molecules during passing through the channel means entering face down and leaving face up is normal passage of the molecules and essential in normal physiology of the body and any disruption in this normal transportation mechanism result in development of diseases. [3,2]. So far aquaporins are classified into 13 types which are implicated in different diseases, such as brain oedema,cataract, cancer, nephrogenic diabetes insipidus and gallostone, obesity development and polycystic kidney diseases . Most of aquaporins are exclusively water channels and will not permit other small molecules and ions pass through .Some of them are called as aquaglyceroporins which perform transportation of water and glycerol, and a few other small molecules. Aquaporins 1,2,4, and 5 are selectively passage channel of water, whereas AQPs,3,8 and 9 perform transportation of glycerine and larger solutes .AQP3,7 and 9 have permeability property towards urea and glycerol . Cloning of human genes encoding aquaporins identified associated disturbances with abnormal functioning of them. So they have played important role in several related disorders and drug discovery. In this paper we listed types of aquaporins and their contributed tissues where they distributed and their association diseases .[1,2,3].

II. METHODS AND MATERIAL

Aquaporins's association with diseases and their selection as potential drug targets

Aquaporin-0 (AQP0), also called as major intrinsic protein, is a type of the ubiquitous aquaporin family. This type of AQPs is highly expressed in the fiber cells of lens . Main function of AQP0 is lens clarity. This protein consist of 4 identical monomer so is tetrameric protein and each monomer has its own water pore but under specific condition these pores function cooperatively. Any mutation in the coding genes and disturbance result in development of hereditary cataract . So this protein can be a potential target in drug discovery projects. [3,4].

Aquaporin 1 is an integral membrane proteins serve as water channels whose main function in body physiology has been characterized in the kidney. It is also distributed in gastrointestinal tract, sweat glands, red blood cells, vascular endothelium and lungs. Any disturbance in their functioning leads in development of following disease : thichening of corena, defect in the ability for concentration of urine,tumour growth, conjunctivalailment, glaucoma and cotton-null blood antigen transfusion incompatibility. The role of AQP1 in mentioned disorders emphases its role as effective drug target for their treatment.[3,5]

AQP2 report released in 1994 about its mutation in chromosome 12q13 which causes nephrogenic diabetes insipidus, a non –x linked diseases . This mutation is very rare. Since this report, more than 25 mutations in human AQP2 have been identified . The main function of AQP 2 is to reabsorb water from urine during removing it from the blood by the kidney so facilitate production of concentrated urine by the kidney. [3,6].Mutation of arginine vasopressin receptor type 2 (AVPR2) gene required for translocation of AQP2 water channel to the membrane result in Congenital nephrogenic diabetes insipidus (NDI).arginine vasopressin (AVP), antidiuretic hormone (ADH) regulates body's water retention by increasing the water permeability of the renal collecting duct. The AQP 2 has been shown to be the target for this action. Recent studies has been reported that AQP2 is a attractive target for treatment of nephrogenic diabetes insipidus (NDI).[7]

Aquaporin 3 is another member of ubiquitous aquaporin family. This AQP is expressed in the basal lateral cell membrane of collecting duct cells of the kidney and facilitate a route for water to exit these cells. Any disturbance in its function can be result in polyurea.[3]. Recently, scientists discovered the role of AQP3 in Nonmelanoma Skin Cancer(NMSC). In this study using immunohistochemical expression, the skin biopsies of nonmelanoma Skin Cancer, normal and psoriasis samples which were 60,40,and 30 in number respectively,were evaluated and result has demonstrated that AQP3 was expressed in 93.3% of squamous cell carcinoma (SCC) cases and 66.7% of basal cell

carcinoma (BCC) cases . SO AQP3 may play a role in NMSC pathogenesis. This study help in unrevealing g the mechanism involved in development of this cancer type and facilitate conduction of new target discovery projects with focus on AQP3 as new target for treatment of NMSC. [8]. The role of AQP3 also identified in development of the pathogenesis of psoriasis via nuclear factor-κB (NF-κB) signaling .[9].

AQP4 is another type of the aquaporin family of integral membrane proteins for conduction of water through the cell membrane. The protein is distributed in kidney, brain,gastrointestinal tract,lungs and muscles . The related diseases to this proteins are vasogenic brain edema, seizers, hydration of stratum corneum in skin,Devic's autoimmune diseases and glaucoma . [2,3]. Aquaporin 4 also plays important role in cerebral ischemia in association with MicroRNA-29b a therapeutic target. Scientists concluded that miR-29b could potentially anticipate stroke outcomes as a novel biomarker, and overexpression of miR-29b decreased blood-brain barrier disruption after ischemic stroke through downregulation of AQP-4. These studies support the potentiality of AQP4 as therapeutic target for treatment of related diseases. [10] .

AQP5 is another class of aquaporin family of water channel proteins. This protein has significant role in production of tears, saliva and pulmonary secretions .The disturbances associated with its function cause Sjogren's syndrome thickening of cornea and primary carcinoma and lymph node metastatic carcinoma of on-small cell lung cancer (NSCLC) .[1,3]. Regarding its role in primary and lymph node metastatic NSCLCs, scientists analyzed the AQP5 expression using an immunohistochemical labeled streptavidin-biotin method which determined AQP5 expression in 94 NSCLC cases primary carcinoma including 51 cases associated with lymph node metastasis. The results demonstrated that AQP5 expression was notably higher in adenocarcinomas compared with squamous cell carcinomas (P=0.002). Additionally AQP5 in the primary carcinomas with lymph node metastasis significantly showed higher percentage compared with percentage of those without lymph node metastasis (P=0.024). So AQP5 is a potential drug target for treatment of the related diseases.[11].

AQP6 is another type of integral membrane protein which functions as water channel. This type of AQPs are specific for the kidney .The diseases related to this protein are Hyperinsulinemia and decreased plasma glycerol.[3].Recent study on AQP6 demonstrated role of AQP6 in the Mercury-sensitive osmotic lysis of rat parotid secretory granules. The scientists used Hg^{2+} for activation of AQP6 to investigate the properties and characteristics of permeability of solute in rat parotid secretary granule lysis. The result showed permeation of halide group anions which serves as a Hg^{2+}-sensitive anion channel in parotid secretary granule of rat by AQP6. AQP6 can be investigated as drug target for better treatment of kidney diseases. [12,13]

AQP7 is another type of aquaporin family encoded by the AQP7 gene. This protein has significant role in sperm function, facilitation of transportation of water, urea and glycerol. The protein shows similarity in sequence with AQP3 and AQP9 so suggested to be a subfamily. AQP7 and AQP3 located at the same chromosomal locus, The main disease associated with its disturbance is Hyperinsulinemia. [1,3,14].

Aquaporin 8 is water conducting channel expressed in pancreas and colon. The Studies by RT-PCR demonstrated detection of AQP8 mRNA in proximal jejunum, duodenum,, rectum, pancreas, proximal colon and liver and, to a few degree, in stomach and distal colon. Distribution of AQP8 suggested its significant role in the water absorption in the intestine, bile secretion in liver and pancreatic juice in pancreas. Its cytoplasmic localization may also link its participation in intracellular osmoregulation process. So this protein association and function can be promising support for their role in drug discovery as drug target.[3,15]

AQP 9 is another member of aquaporins belonging to the aquaglyceroporin subfamily of aquaporins. The main function of the protein is transportation of water, urea,glycerol, purines and pyrimidines . [3].It plays a role in metabolism of glycerol and differentiation of osteoclast. It also has some roles in immunological response and bactericidal activity.Recent studies has demonstrated association of decreased hepatic AQP9 and glycerol permeability with insulin resistance in non-alcoholic fatty liver disease . In this analysis, scientists observed downregulation of APQ9 together with subsequent decrease in hepatic glycerol permeability in

insulin –resistant cases. Using real-time PCR, western blotting and immunohistochemistry. These studies are fundamental support for their role in drug discovery as drug target for new treatment of related diseases.[1,3,16]
AQP10 is another type of aquaporins family with binary functional characteristics as a channel/carrier for transportation of solute. The studies also showed representation of AQP10 as an alternative pathway for glycerol efflux from human adipocytes. These finding help in providing a new insight into its performance mechanism, which would help further illustrate its physiological role.[17,18].

AQP11 is another type of aquaporins family which shows functional distinction from other proteins of subfamily of aquaporin. The studies have shown its role in the brain but still further studies is required. [19].The studies also demonstrated disruption in AQP11 result in polycystic kidneys following vacuolization of the proximal tubule. This study is done using generation of AQP11-null mice .The mice expressed cyst formation of the proximal tubule and vacuolization .These finding demonstrate that AQP11 has essential role in proximal tubular function.[20]

AQP12 is a novel aquaporin member which expressed in pancreatic acinar cells. Scientists identified this type of protein using BLAST program search. They applied northern blot analysis for revealing expression of AQP12 in pancreas .using other techniques such as in situ hybridization and RT-PCR, selectively localization of AQP12 in the acinar cells of pancreas identified .Additional investigation using expression of AQP12 in Xenopus oocytes, cultured mammalian cells and Immunocytochemistry suggested a role of AQP12 in secretion of digestive enzyme such as exocytosis of secretory granules and maturation. More investigation and analysis is required for supporting selection of these proteins as drug targets for treatment of life threatening disorders.[21].

III. CONCLUSION

Because of significant role of aquaporins in selectively transportation of water and solutes, considerable medical focus has been made in human aquaporins as potential drug targets. Also due to their important role in physiological process such as wound healing, angiogenesis, migration of cells during tumour development and regeneration, these proteins are suggested to be attractive drug targets. The drugs target aquaporins in such a way that can control their role by activation and deactivation of them. Theses activation and deactivations mechanisms of drugs on aquaporins are such as monitoring urine formation for fluid imbalance, cancer treatment by inhibition of tumour growth and prevention of its metastasis, prevention of brain injury, controlling energy production to fight weight gain for obesity, maintaining moisture in dry skin, controlling formation of polycystic kidney, prevention of polyurea and so on. So association of aquaporins with development of different pathological conditions in human, emphases their role as therapeutic targets .Although discovery of drugs that target aquaporins is still in the young stage but this area of research demands attention in order to successfully treat some of these aquaporins related diseases .Although available conventional technologies and methods in biological sciences are used for screening ion channel but these technologies cannot be effectively used for screening of aquaporins. However, some technologies are available for indirectly measuring aquaporins such as confocal and internal reflectance fluorescent microscopy for measurement of quantitative changes of volume of water, radiolabelled auaporins for study of permeability, fluorescent indicators for measurement of water permeability in the cells and so on. Recently application of several recent biological tools such as real-time PCR, western blotting, generation of transgenic aquaporin knockout mice like null mice for AQP1,3,4,5, and 8, in situ hybridization, culturing of the mammalian cells including the tissues having aquaporins like AQP12 and immunohistochemistry and so on helped in understanding the mechanisms, association role and identification of more Aquaporins types. Recent discoveries on aquaporins demonstrated generated medical interest in aquaporins as attractive drug targets. So This attention deserves towards aquaporoins conduction projects for selection of them as drug target for treating life threatening disorders. Identification of pharmacologically effective aquaporins modulators is a challenging area as they have significant role in human physiology and pathophysiology. But this research area is still at nascent stage and demand scientists to focus on the area for generation of new therapy for decreasing suffering and death percentage related to aquaporins disruptions.

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