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The Effect of Aquaporins on Disease Pathophysiology

Hastalık Fizyopatololerinde Aquaporinlerin Etkisi

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Abstract

Water and its transport are vital for the survival of living organisms. Cell membranes possess a complex structure that regulates this transport process. Aquaporins are integral membrane proteins located on cell membranes and are centrally responsible for facilitating the selective and rapid passage of water. They regulate cell water balance, thereby maintaining osmotic balance, cell volume, and homeostasis. Many different types of aquaporins have been identified, each serving distinct functions in specific tissues. Physiologically, these proteins are expressed in normal tissues and organs and contribute to bodily homeostasis. However, their abnormal expression or mutations in disease-related conditions can lead to various health problems, leading to increased or decreased expression. Therefore, aquaporins are important biomarkers in the pathogenesis of many diseases. This study provides an overview of the pathophysiological roles of aquaporins in disorders of other systems, particularly cancer, urinary, neurological, and ophthalmic diseases. In addition, whether these proteins have therapeutic effects in diseases and where they can be used in the future are discussed.

Key words: Aquaporin, disease, Physiology, pathology

Özet

Su ve suyun taşınması canlılarda temel yaşamlarını sürdürebilmesi için hayati bir öneme sahiptir. Hücre zarları, bu taşıma olayını düzenleyen karmaşık bir yapıya sahiptir. Aquaporinler, hücre zarları üzerinde yer alan ve suyun seçici ve hızlı bir şekilde geçişini kolaylaştıran merkezi sorumluluğu olan integral membran proteinleridir. Bunlar hücrelerin su dengesini düzenlerler ve bu sayede ozmotik denge, hücre hacmi ve homeostaz korunur. Şu ana kadar birçok farklı aquaporin tipi tanımlanmış olup, bunların her biri belirli dokularda farklı görevler üstlenir. Fizyolojik olarak normal doku ve organlarda eksprese olan ve vücut hemostazının sağlanmasında katkıları bulunan bu proteinler hastalıklarla ilişkili olarak anormal ifadeleri ya da mutasyonları çeşitli sağlık sorunlarına neden olarak ekspresyonlarında artma veya azalma söz konusu olmaktadır. Bu durumdan ötürü aquaporinler bir çok hastalığın patogenezinde

önemli bir biyobelirteç konumuna sahiptir. Yapılan bu araştırmada aquaporinlerin, kanser, üriner, nörolojik ve göz hastalıkları başta olmak üzere diğer sistemlerdeki bozukluklardaki fizyopatolojik rollerine genel bir bakış sunmaktadır. Ayrıca bu proteinlerin hastalıklarda terapötik etkilerinin olup olmadığı da gelecekte nerelerde kullanılabileceği sorularını tartışılmaktadır.

Anahtar kelimeler: Fizyoloji, hastalık, patoloji, aquaporin

1. Introduction

Aquaporins (AQPs) are integral membrane proteins found in the cell membrane that enable the selective permeability of water. First discovered in 1992, these proteins have now been identified with more than 13 isoforms (AQP0–AQP12) expressed in different tissues. Aquaporins primarily facilitate the rapid and controlled transport of water into and out of cells; some types also function in the transport of small solutes such as glycerol and urea (e.g., aquaglyceroporins). With these properties, they play a critical role in maintaining cellular osmotic balance, volume regulation, and secretion and absorption processes (Verkman, 2012; Magouliotis et al., 2020). Recent studies have revealed that aquaporins are not only responsible for physiological water transport but also play important roles in pathophysiological processes. The expression and functions of aquaporins vary, particularly in conditions such as cell injury and damage response. For example, overexpression of aquaporins during ischemic injury, traumatic brain injury, or inflammatory processes can exacerbate tissue damage by increasing edema formation. The role of AQP4 in the central nervous system is particularly noteworthy in this context. Similarly, decreased expression of certain aquaporin types can lead to disruption of water balance and cellular functions. Therefore, aquaporins are thought to be important molecular targets in the development and progression of various diseases. This review aims to provide a comprehensive overview of the roles of aquaporins in diseases, focusing particularly on mechanisms related to cell injury (Azad et al., 2021; Meli et al., 2021; Mannan et al., 2024).

2. Structure And Physıology of Aquaporıns

Aquaporins, also known as water channels, are a small family of integral membrane proteins composed of channel proteins that form pores in cell membranes. Their primary function is to selectively permeabilize the transport of water molecules across membranes. They also facilitate the passage of water while preventing the passage of ions such as sodium and

potassium and small molecules. This selective permeability is vital for maintaining electrochemical gradients across cell membranes (Stroud et al. 2003). Aquaglyceroporins (AQP 3, 7, 9, and 10), a member of the aquaporin family, have a structurally larger pore size than other subtypes that are particularly selective for water, enabling the transport of small, uncharged solute molecules such as glycerol, urea, ammonia, and carbon dioxide. Therefore, this integral protein family is not only involved in water transport; their varying permeabilities demonstrate the functional diversity of this family (Beitz et al. 2006). The monomers of aquaporins consist of six membrane-spanning alpha-helical domains with both carboxyl and amino termini on the cytoplasmic side. These helical domains surround a narrow aqueous pore. Short helical domains contain a high concentration of asparagine-proline-alanine motifs and enclose the cytoplasm of the narrow aqueous pores and the extracellular vestibules. In the cell membrane, aquaporin 4 monomers associate as homotetramers, and each of the four monomers functions as an independent water channel (Adeoye et al. 2021).

3. Aquaporın Functıonal Mechanısms

The primary function of aquaporins is to transport water across cell membranes in response to osmotic gradients created by active solute transport. This transport occurs via facilitated diffusion and requires no energy. Water molecules are guided by the local electric field of the aquaporins and move single-file through the narrow part of the pore. Oxygen atoms face forward as they enter and reverse direction halfway through, preventing the flow of protons and allowing water to pass freely. Water selectivity is achieved by steric factors and electrostatic interactions within the pore, particularly the ar/R filter (aromatic/arginine filter), which further restricts the passage of other molecules and ions. The presence of aquaporin channels can increase membrane water permeability up to tenfold compared to diffusion through the phospholipid bilayer. The rate of water transport through a single AQP1 channel can reach up to 3 billion water molecules per second. This precise molecular mechanism ensures highly efficient and selective water transport, which is vital for rapid physiological responses and the maintenance of cellular integrity. Inhibition of proton influx is critical for maintaining membrane potential (Benga 2009; Hub & De Groot, 2008; Fu & Lu, 2007).

4. Aquaporın Types and Classıfıcatıon

Aquaporins (AQPs) are proteins found in the biological membranes of humans, animals, plants, and bacteria throughout the living world. More than 450 of these proteins have been

identified in living organisms, 13 of which are found in vertebrates (AQPs 0-12). Aquaporins 0, 1, 2, 4, 5, 6, and 8 function solely as water channels. Although similar in amino acid sequence to the others, AQP6 functions as an anion channel, and AQP8 functions as a urea channel. AQPs 3, 7, and 9 are aquaglyceroporins. The recently identified AQP11 and AQP12 are superaquaporins (Xu et al. 2023; Gena et al. 2011).

AQP0: AQP0, also known as MIP (Membrane Intrinsic Protein) or MIP26, has been identified as a 26 kDa major intrinsic protein in the eye. It is abundant in tightly packed ocular fibers of epithelial origin. In addition to its water channel activity, AQP0 is thought to have a possible role in cell adhesion. AQP0 mutation results in congenital cataracts (Hall et al. 2019).

AQP1: Also known as CHIP28, it is an integral membrane protein with a molecular weight of 28 kDa and abundant in human erythrocyte membranes and kidney proximal tubules. Immunohistochemical studies have shown that AQP1 is located on the apical and basolateral surfaces of the kidney proximal tubules. It has also been detected on the apical and basolateral surfaces of the thin limb of the loop of Henle. However, it is absent from other parts of the nephrons. AQP1 is thought to be essential for urine concentration. Studies have shown that AQP1 contributes to more than 85% of the osmotic water permeability of the erythrocyte membrane. Located in blood and lymphatic vessels, AQP1 participates in endothelial water transfer, thus facilitating the passage of water from plasma to lymphatic fluid. AQP1, found in gallbladder epithelial cells, has been shown to be responsible for mercury-sensitive water transport in bile secretion. Its presence in acinar cells and blood vessels in the pancreas suggests that it facilitates the secretion of pancreatic juice (Calamita & Delporte, 2023; Huebert et al. 2011). In the respiratory system, AQP1 is found in the endothelial cells of capillaries and venules. Its role here is to facilitate fluid transfer across the endothelium and increase fluid outflow from the vessel. It is thought to be a determinant of vascular permeability in the lungs. AQP1 has also been shown to be responsible for water movement in peritoneal dialysis. In the male reproductive system, it is found in the efferent ducts and mediates water absorption from the luminal fluid in the reproductive tract. AQP1 functions with other aquaporins in the inner ear to maintain water and ion balance (Sun et al. 2017; Çiçek et al. 2020).

AQP2: AQP2 is a water channel located in the renal collecting duct, its intracellular localization regulated by antidiuretic hormone. It functions in regulating urine concentration. In addition to the kidney, it is also found in the vaso-deferens and, to a lesser extent, in the inner ear. AQP2

is the only aquaporin stored in intracellular vesicles in the absence of ADH stimulation. Nephrogenic diabetes is a disease characterized by the failure to concentrate urine. It causes excessive urine output due to the insensitivity of renal tubule cells to ADH. In congenital, autosomal recessive, drug-induced, or dominant nephrogenic diabetes, AQP2 is observed to lose its water channel activity, its gene expression is impaired, or it fails to transfer to the apical membrane. In the human reproductive system, AQP2 is suggested to play a role in cyclical changes in the endometrium and to reduce uterine secretion and endometrial edema during implantation (Tingskov et al. 2020; Hildenbrand et al., 2006).

AQP3: AQP3 shares homology with GIpF, a molecule that facilitates glycerol transport. Because it mediates the permeability of glycerol as well as water, it is also called glycerol intrinsic protein (GIpF). It is found in the epithelial cells lining the lumens of many organs, including the kidney, reproductive system, respiratory system, epidermis, eye, and brain. In renal collecting duct cells, it is thought to play a key role in concentrating urine, along with AQP2. AQP3, found in the epithelial cells of the digestive system, plays a role in the hydration of epithelial cells directly exposed to the solid environment of the intestinal contents and feces, and helps transfer water to the lamina propria, which facilitates water absorption in the intestine. AQP3 has been detected in the epithelia surrounding the nasal cavity, trachea, and bronchi in the respiratory system. Because the respiratory epithelium is exposed to respiratory air and loses water from its surface through evaporation, AQP3 in epithelial cells is responsible for water transfer from the connective tissue, where water from the capillary bloodstream is abundant, to the surface. It is found in the conjunctiva of the eye and serves a barrier function (Benga, 2009; Hara-Chikuma & Verkman, 2006).

AQP4: Along with AQP3, it is found in the basolateral membranes of the kidney's collecting ducts. It functions as a water channel for water egress from the basolateral membrane to concentrate urine, and this channel is responsible for a significant portion of water transfer. In rapidly contracting skeletal muscles, AQP4 has been shown to play a role in the rapid volume changes associated with muscle contraction and is localized to the sarcolemma. However, it is not found in the neuromuscular junction. It has been suggested that AQP4 is localized in the basolateral membrane of gastric parietal cells and plays a role in the transcellular transfer of water, which accompanies HCl release (Aslesh et al. 2023; Su et al. 2020). AQP4 is also found in lung and respiratory epithelia. It is localized in the basolateral membrane of bronchioles,

tracheal, and nasopharyngeal columnar epithelial cells. AQP4, found in these epithelia, is thought to function in the clearance of alveolar fluid in adult and neonatal lungs and to play a role in the formation of edema after lung injury. AQP4 is abundant in the brain. While AQP4 is not found in neurons, it is concentrated at the tips of astrocyte processes and in the membranes bordering glial cells. Due to its abundance and localization, it has been suggested that AQP4 may play a role in the formation of edema in the brain. These results suggest that AQP4 plays a key role in regulating brain water transport and that AQP4 inhibitors may be used to reduce brain edema in cerebral injuries. It is known to have important functions in the eye and inner ear, such as physiological fluid movement, regulating the ionic environment, and maintaining volume, along with other aquaporins (Papadopoulos & Verkman, 2007; Beall et al. 2007).

AQP5: Immunohistochemical studies have shown that AQP5 is present in the submandibular, parotid, and sublingual salivary glands, as well as in the minor submucosal salivary glands of the tongue. In the gastrointestinal system, AQP5 is found in some of the mucus-secreting glands. Immunohistochemical studies have identified its presence in pyloric gland cells in the stomach, duodenal gland cells in the intestine, and the pancreas. AQP5 is suggested to play an important role in water transfer during pancreatic secretion in the pancreas (Liao et al. 2021; Hosoi, 2016). In the respiratory system, it is found in the apical membranes of submucosal gland cells, in extrapulmonary bronchioles in humans and mice, and in the apical membranes of columnar epithelial cells in the trachea and bronchi. In the lung, it is localized in type I pneumocytes lining the lung alveoli. Experimental studies have revealed that AQP5 mediates osmotic water permeability in type I alveolar cells but is not essential for normal lung function. Due to the bronchoconstrictive effects of AQP5, further studies are needed to establish its relationship with asthma. In the eye, AQP5, found in the plasma membrane of the stratified corneal epithelium, plays a role in maintaining the transparency of the corneal epithelium lining the underlying stroma. A defect in AQP5 in the salivary glands results in impaired saliva production (Hosoi, 2016; Hansel et al. 2010).

AQP6: A homolog of aquaporins was cloned from human and rat kidney cDNA and named WCH3 or hKID. It has been shown to exhibit mercury-sensitive osmotic water permeability and exhibit the properties of gated ion channels activated by low pH and HgCl2. AQP6 has been shown to localize in intracellular vesicles of epithelial cells of the collecting ducts in the kidney (Adeoye et al. 2021; Rodríguez et al. 2010).

AQP7: It was identified in rat testes and shares a high homology with AQP3. It has been shown to localize around spermatids in the seminiferous tubules. AQP7 plays a role in reducing fluid volume during spermatid development. It is also called adipose aquaporin (AQPap or AQPL) because it is most concentrated in adipose tissue. Its role in this process is thought to be related to the regulation of plasma glycerol levels (Yeste et al. 2017).

AQP8: AQP8 is a 28 kDa protein with a long N-terminus and a short C-terminus. It has been detected in many organs and tissues, including the pancreas, liver, colon, salivary gland, kidney, testis, epididymis duct, stomach, duodenum, jejunum, lung, trachea, and placenta. In the kidney, AQP8 is located in intracellular membrane vesicles in the proximal tubules and the collecting ducts of the cortex and medulla. In the salivary gland, it is localized in myoepithelial cells, not acinar cells. In the liver, the transfer of AQP8 from intracellular vesicles to canalicular membranes suggests that it may play an important role in glucagon-induced bile secretion. In the respiratory system, it is found in the myoepithelial cells surrounding the bronchial and tracheal glands, as well as in the salivary glands. AQP8 has been detected at all stages of spermatogenesis in the testes. Immunohistochemical studies have also shown its presence in Sertoli cells. It is thought to play a role in the liquefaction of the cytoplasm during the differentiation of spermatids into spermatozoa (Rato et al. 2010; Zhu et al. 2017).

AQP9: It is also found in human leukocytes and, to a lesser extent, in the liver, lung, and spleen. It has been detected in the liver, testes, and brain of rats. In the male reproductive system, it is located in the apical membranes of non-ciliated cells in the efferent duct, vas deferens, and epididymis. Its expression level is controlled by androgen and it functions in sperm maturation and storage. In the female reproductive system, it plays a role in oocyte maturation and facilitates the passage of water and small solutes across the placental barrier. AQP9, expressed in the brain, has been found in astrocytes and helps regulate post-ischemic edema. In the digestive system, it participates in the synthesis and secretion of mucus in mucus-secreting goblet cells. AQP9, localized in the sinusoidal membrane of the liver, facilitates glycerol uptake into hepatocytes during gluconeogenesis (Abdel-Sater, 2018; Li & Wang, 2014).

AQP10: AQP10, cloned in humans, has been found to have a sequence similar to aquaglycerophorins such as AQP3, AQP7, and AQP9 and exhibits mercury-sensitive osmotic water permeability. It functions as a channel for neutral solutes. It has been found to localize in epithelial cells in the small intestine, which function as absorbers. It has been identified in the

apical membranes of ciliated and non-ciliated cells of the efferent ducts in the male reproductive system (Ishibashi et al. 2009).

AQP11: AQP11 is known to be expressed in the brain, kidney, and liver, but its functions are not fully understood (Koike et al. 2016).

AQP12: It is not known which structures and substances are permeable to AQP12 expressed in the pancreas (Itoh et al. 2005).

5. Roles Of Aquaporıns in Dıseases

5.1. Aquaporins in Cancer Diseases

Excessively increased expression levels of AQP1 have been observed in brain tumors, lung cancer, breast cancer, and colorectal cancer, and this increase is reported to be related to angiogenesis and metastasis. Therefore, inhibition of AQP1 is thought to inhibit cancer cell proliferation by reducing tumor growth and angiogenesis (Mobasheri et al. 2005). AQP3 is known to be overexpressed in breast, colon, liver, lung, esophagus, cervix, and head and neck cancers, and it facilitates cell migration and invasion, thereby increasing tumor progression and worsening prognosis (Marlar et al. 2017). Studies have shown that AQP4 is upregulated in gliomas and causes tumor invasion, migration, and brain edema (Behnam et al. 2022). AQP5 is overexpressed in lung, salivary gland, kidney, ovarian, cervix, esophagus, and hepatocellular carcinomas, and has been suggested to be associated with tumor metastasis and angiogenesis (Moosavi & Elham, 2020). There are hypotheses that AQP7 may increase resistance to oxidative stress in breast cancer, while AQP8 may reduce colorectal cancer growth but increase proliferation in other cancers. AQP11 expression is associated with favorable survival in ovarian cancer (Milković et al. 2023; Chetry et al. 2018). The consistent overexpression of aquaporins across these various cancer types suggests that these channels play critical roles in facilitating key features of cancer, such as tumor growth, metastasis, and angiogenesis. Targeting specific aquaporins may offer new therapeutic strategies (Moon et al. 2022).

5.2. Aquaporins in Kidney Disease

Mutations in the AQP2 gene cause nephrogenic diabetes insipidus, which leads to impaired water reabsorption in the collecting ducts and excessive urine production. AQP1 deficiency in mice causes severe urine concentration defects. AQP3 knockout mice exhibit polyuria and impaired urine concentration. Altered expression of AQP1, AQP2, AQP3, and AQP11 has been

observed in polycystic kidney disease (PDKD), potentially leading to cyst formation and growth. AQP1 is known to delay kidney cyst development by inhibiting Wnt signaling. Aquaporins are central to kidney function, and their dysfunction due to genetic mutations or altered expression in response to disease directly leads to significant water balance disturbances (Lan et al. 2024; Bockenhauer & Bichet, 2015; Wang et al. 2015).

5.3. Aquaporins in Neurological Disorders

AQP4 is the most abundant water channel in the brain and plays a critical role in the development and resolution of brain edema (cytotoxic and vasogenic) following stroke, traumatic brain injury, and other events. Inhibiting AQP4 expression may be protective in cytotoxic edema but detrimental in vasogenic edema. In Alzheimer's disease, AQP4 plays a role in the glymphatic system, which clears beta-amyloid (Aβ) and tau. Dysfunction of AQP4 can impair waste clearance. AQP4 is the primary autoantigen in neuromyelitis optica spectrum disorder (NMOSD), in which autoantibodies targeting AQP4 in astrocytes lead to neuroinflammation and demyelination in the central nervous system. Aquaporins, especially AQP4, are key regulators of cerebral fluid dynamics and their dysfunction contributes to various neurological pathologies (Silverglate et al. 2023; Graber et al. 2008).

5.4. Aquaporins in Eye Diseases

Mutations in AQP0 cause congenital cataracts and play a key role in maintaining lens transparency. Altered expression of AQP1, AQP2, AQP7, and AQP9 has been observed in the iris and retina of glaucoma patients, suggesting a potential role in intraocular pressure regulation and retinal ganglion cell function. AQP1 deficiency has been reported to accelerate cataract formation in mouse models. Aquaporins are critical for maintaining the delicate fluid balance and transparency required for proper eye function, and their dysfunction is directly implicated in major eye diseases (Tran et al. 2017; Schey et al. 2014).

5.5. Aquaporins in Digestive System Diseases

The pathology of many intestinal diseases is associated with alterations in the location and expression of aquaporins, such as intestinal infection, which can alter the expression and distribution of AQPs in intestinal tissues/cells by affecting cytokines and chemokines. Dysregulation of various AQPs (AQP1, AQP3, AQP4, AQP5, AQP8, AQP9, AQP10) in gastrointestinal diseases is associated with conditions such as diarrhea, constipation,

inflammatory bowel disease, and gastric cancer, affecting intestinal fluid absorption and secretion (Ye et al. 2023; Aykoç & Yıldırım 2022).

5.6. Aquaporins in Other Diseases

Altered expression of AQP1, AQP3, AQP4, and AQP5 has been reported in lung diseases (such as COPD and asthma), potentially affecting mucus production, airway inflammation, and fluid balance. AQP1 has been proposed as a prognostic marker for malignant mesothelioma. AQP3 and AQP7 are known to be important in the pathogenesis of skin tumor growth and inflammatory skin diseases, and AQP3 deficiency can lead to dry skin. Studies have linked AQP7 deficiency to adult-onset obesity in mice. Aquaporins play a role in a wide variety of diseases affecting various organ systems, highlighting their essential role in maintaining fluid homeostasis and cellular function throughout the body (Kao et al. 2012; Osorio et al. 2019; Zhang et al. 2015).

6. Therapeutic Approaches Targeting Aquaporins

6.1. Aquaporin Inhibitors

Several small molecule inhibitors, such as acetazolamide, bumetanide, TGN-020, and AuPhen, have shown promise in preclinical studies for their ability to inhibit specific aquaporin isoforms. These inhibitors target conditions such as cerebral edema, cancer metastasis, and glaucoma. Metal-based inhibitors, such as mercuric chloride, can block aquaporin function but are generally too toxic and nonselective for therapeutic use. The development of selective and nontoxic aquaporin inhibitors offers significant therapeutic potential for a wide variety of diseases characterized by abnormal fluid transport (Wang et al. 2023; Abir-Awan et al. 2019).

6.2. Aquaporin Activators and Upregulation Strategies

In conditions such as nephrogenic diabetes insipidus (NDI), which result from AQP2 deficiency, therapeutic strategies aimed at increasing AQP2 expression or its transport to the cell membrane are being investigated. Compounds such as sildenafil and simvastatin show promise. There is research suggesting that gene transfer of aquaporins to the salivary and lacrimal glands in Sjögren's syndrome may be a potential treatment for xerostomia. Enhancing aquaporin function in cases of deficiency or dysfunction is another important therapeutic avenue (Bech et al. 2018).

6.3. Clinical Trials and Current Treatments

Although no aquaporin-targeted drugs are in widespread clinical use, anti-AQP4 antibodies are being used in the treatment of neuromyelitis optica spectrum disorder (NMOSD). Clinical trials are ongoing to evaluate the efficacy of various compounds that may indirectly affect aquaporin function in various diseases. The successful use of anti-AQP4 antibodies in NMOSD demonstrates the clinical importance of targeting aquaporins. Continued research and clinical trials are crucial for translating preclinical findings into effective therapies for other diseases (Jarius & Wildemann, 2010).

7. Challenges and Future Directions in Aquaporin Research

7.1. Current Challenges

Identifying highly specific and potent inhibitors for each of the 13 human aquaporin isoforms remains a significant challenge. Aquaporins have been considered "hard-to-medicate" targets due to their compact structure and the difficulty of effectively modulating their functions with small molecules. Developing robust and reliable high-throughput screening methods to identify novel aquaporin modulators is technically challenging. Understanding the precise molecular mechanisms of water and solute transport through different aquaporin isoforms and how these processes are regulated in various physiological and pathological conditions requires further research. The physiological significance of some aquaporin-mediated solute transport (e.g., gases, ions) remains controversial and requires further clarification. Achieving seamless biomimetic membranes containing aquaporins for applications such as water purification is challenging. The need for aquaporin tetramerization and its significance remain poorly understood.

7.2. Future Research Directions

Focus should be on the development of novel, highly specific, and potent aquaporin inhibitors and activators targeting individual aquaporin isoforms using advanced screening techniques, structural information, and computer modeling. Non-canonical roles of aquaporins beyond water transport, such as cell signaling, cell adhesion, and metabolism, should be further investigated. The role of aquaporins in a broader spectrum of diseases, including infectious diseases, metabolic disorders, and inflammatory conditions, should be explored. Detailed studies on the regulation of aquaporin expression and function by various factors, such as hormones, osmotic stress, pH, phosphorylation, ubiquitination, and non-coding RNAs, should

be conducted. Advances in structural biology techniques, such as cryoelectron microscopy, should be utilized to determine high-resolution structures of aquaporins in complex with inhibitors and other interacting partners. More specialized animal models (e.g., conditional knockouts, knock-ins) should be developed and used to examine the specific roles of individual aquaporins in different disease contexts and to evaluate the efficacy of potential therapeutic interventions. The potential of aquaporins as diagnostic and prognostic biomarkers for various diseases, including cancer and kidney disorders, should be investigated. The development of aquaporin-based biomimetic membranes in water purification and other biotechnological fields should be advanced. The role of aquaporins in the male and female reproductive systems should be further investigated. Progress in clinical trials targeting aquaporins for various diseases should be monitored and supported. Unresolved questions in aquaporin biology, such as gas and ion transport mechanisms, regulation of AQP0, and the importance of tetramerization, should be addressed.

8. Conclusion

Aquaporins play a vital role in maintaining water and small solute homeostasis in various tissues and organs. Dysfunction of aquaporins significantly contributes to the pathogenesis of a wide range of human diseases, including cancer, kidney disease, neurological conditions, and eye diseases. The therapeutic potential of targeting aquaporins with specific inhibitors and activators is promising, and ongoing research and clinical trials in this area promise significant progress. However, significant challenges remain in aquaporin research, particularly in drug development and understanding their precise roles in different disease contexts. Overcoming these challenges and pursuing future research directions will lead to a deeper understanding of these important proteins and new therapeutic strategies for numerous debilitating conditions.

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