Aquaporins in Respiratory System

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Abstract

Aquaporins (AQPs) are water channel proteins supposed to facilitating fluid transport in alveolar space, airway humidification, pleural fluid absorption, and submucosal gland secretion. In this chapter, we mainly focus on the expression of 4 AQPs in the lungs which include AQP1, AQP2, AQP4 and AQP5 in normal and disease status, and the experience of AQPs function from various model and transgenic mice were summarized in detail to improve our understanding of the role of AQPs in fluid balance of respiratory system. It has been suggested that AQPs play important roles in various physiology and pathophysiology conditions of different lung diseases. There still remains unclear the exact role of AQPs in lung diseases, and thus continuous efforts on elucidating the roles of AQPs in lung physiological and pathophysilogical processes are warranted.

Keywords

Aquaporins • Lung disorders • Fluid transport

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7.1 Introduction

Respiratory system by definition includes respiratory center located in brain stem; respiratory muscle including external and internal intercostal muscle, sternocleidomastoid muscle and diaphragm; airways including upper airway and lower airway; alveolus and surrounding pulmonary and systemic circulation. Each part has specific function and mainly carries the function of ventilation and oxygenation with coordination of ventilation and pulmonary circulation that provides adequate oxygen delivery to distal organs. However, the lungs also have metabolism, defending, immune and fluid transport function. The fetus lung is filled with fluid before the fetus is delivered, and the fluid inside of the lungs is absorbed immediately to keep the lungs relatively dry to maintain adequate ventilation and oxygenation after delivery. When the lungs or airways were insulted, it may bring fluid transport disorders, such as airway and lung edema, pleural effusion, etc. However, if there is extra fluid absorption, the airway may become relative dry and induce thick sputum and subsequent airway inflammation. Thus, it is critical to keep fluid balance in alveolus, interstitial space, airway and pleural space to maintain normal respiratory function.

The fluid transport follows few rules: the osmotic fluid transport due to osmotic gradient; the Starling mechanism due to hydrostatic pressure; and the fluid pinocytosis. It has been a long history for the researchers to discover that the cell membrane express a water channel aquaporin (AQP) to control fluid transport [1]. Since the first report of AQP1 in red blood cells, there were numerous publications addressing expression and function of AQPs in various organs including respiratory system. So far, there are 4 AQPs expressed in the lungs, including AQP1 in the vascular endothelium and pleural membrane, AQP3 in epithelium of large airway, AQP4 in epithelium of small airways, and AQP5 in alveolar type I cells and submucosal glands. In this chapter, the expression of above mentioned AQPs in normal and disease status, and the experience of AQPs function from various model and transgenic mice were summarized in detail to improve our understanding of the role of AQPs in fluid balance of respiratory system.

7.2 Expression of AQPs in the Lungs and Airways

There are 4 AQPs expressed in the lungs including AQP1, AQP3, AQP4 and AQP5. AQP1 is expressed in the endothelium of pulmonary capillary, vein and artery [2, 3], the apical and basolateral membrane of the microvascular endothelium within pleural membrane, including inner and out membrane [4]. AQP3 is located in the basolateral membrane of basal cells of the tracheal epithelium and in submucosal gland cell membranes in rodents and in apical membrane of bronchioles and type-II alveolar epithelial cells (ACEs) of adult humans, while AQP4 is expressed in the basolateral membrane of columnar cells in the bronchi and trachea of rats and in type-I AECs in humans [5–8]. AQP5 is expressed in apical membrane of type I ACEs, as well as apical membrane of serous cells of upper airway submucosal glands, it has also been detected in type-II AECs in mice [8, 9]. Some studies show AQP5 is also expressed at apical membrane of ACEs [10].

Levels of AQPs expression depend on timing of lung development and pathological conditions. There is a dramatic difference of AQPs expression in airway and alveolar epithelium before and after birth delivery. The underlying mechanism might be the accommodation of fluid transport because airway epithelium and alveolar epithelium play an important role in fetal lung fluid secretion before delivery and turn to absorption function after delivery to clear lung fluid for oxygenation. Most of the studies about AQPs in fetal lungs are derived from animal experiments. Fetal sheep have been used as an important animal model for lung developmental studies, particularly of factors regulating the physiological development of the fetal lung [11, 12]. Sheep fetal lungs can express AQP1, AQP3, AQP4 or AQP5 in mRNA and protein levels during midterm gestation [13]. Rat fetal lungs express very

little AQPs before birth, and only AQP1 and AQP4 in rats has been detected at present before birth [14–16]. Although AQP1 expression in mRNA and protein levels in the lungs of fetal and neonatal rats is increased when treated with synthetic glucocorticoids [7, 15], little is known about the physiological factors to control its expression before birth. Besides, Ya sui et al. [15] found that AQP4 could be induced to increase by corticosteroids and β-adrenergic agents. However, AQP5 mRNA expression in very low level was detected before birth in mice [13].

The deletion of one or more AQP genes in the studies of mice suggested that AQPs are not essential for neonatal survival [17]. However, what is true in mice may not be true for all species, including humans [18]. Because the expression and distributions of different AQPs in the lungs are varied from the different species, it is difficult to make a consistent conclusion about the physiological role of AQPs in fetal lung development and the transition to extra-uterine life at birth, especially in the species with long-gestation such as humans.

7.3 AQPs and Lung Fluid Transport

Besides ventilation and oxygenation, the lungs exert other biological functions such as lung fluid transport, metabolism, immune defense, etc. Herein, lung fluid transport refers to the alveolar fluid balance, airway hydration, pleural fluid transport and submucosal glands secretion.

7.3.1 AQPs and Alveolar Fluid Balance

Fluid transport between alveolar and capillary endothelium presents with several forms including the osmotic fluid transport, blood-gas barrier disruption induced fluid leakage and hydrostatic fluid transport. AQP1 and AQP5 are mainly expressed at apical membrane of capillary endothelial cells and type I AECs [8, 9, 19] (Fig. 7.1). The location of these two AQPs suggests possible roles in facilitating water transport. As stated before, AQP expression varies during gestation time, 45 min immediately after delivery do not shown difference of lung wet/dry weight ratio between wild-type and AQP1, 4, 5 knockout mice [21], suggesting slow fluid absorption does not require AQP facilitation, plus these AQPs do not have full expression at the time point of experiment. Several studies have showed that knockout AQP1 and AQP5 could significantly reduce osmotic fluid transport [17, 22]. However, deletion of AQP1 or AQP5 did not alter lung edema formation and resolution difference in acute lung injury model [23, 24], in which increased capillary permeability leads to the fluid accumulation in interstitial and alveolar tissue. This might be explained that AQP-mediated fluid transport is slower than fluid transport through enlarged capillary leakage, and fluid transport through cell membrane is little [23, 24]. Similarly, to study the effects of AQP5 on hydrostatic pressure-induced lung edema, high pressure infusion plus blockage of outflow from left atrium are designed to mimic left heart failure induced lung edema. Deletion of AQP5 did not affect lung edema induced by high pulmonary pressure infusion [22]. These studies further indicate that AQP1 and AQP5 mainly facilitate osmotic fluid transport through the apical membrane of capillary endothelial cells and AECs, but they may not participate in fluid transport driven by capillary permeability and hydrostatic pressure changes.

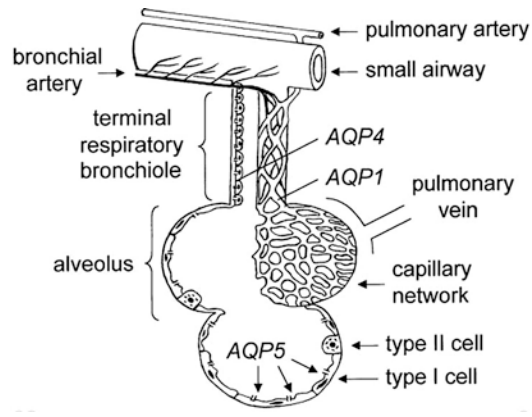

Fig. 7.1 Expression of AQP1, AQP4 and AQP5 in distal airway and alveolar space [20]

Peri-bronchial edema formation was found to decrease in AQP1 mutation patients after bonus saline infusion, for capillary network formation defects after AQP1 mutation, and thus it is unlikely that AQP1 could contribute to hydrostatic pressure induced fluid accumulation [25]. Besides, deletion of AQP4, which is expressed on the epithelium of small airways close to alveolar spaces, does not significantly affect fluid transport compared to wild-type mice. However, AQP4 deletion displays a more decrease in osmotic fluid transport compared with AQP1 knockout in mice, suggesting AQP4 acts as the main role in facilitating fluid transport through small airway epithelium [25]. The potential effect of AQP4 is under covered by AQP1, because function of AQP4 appeared more significant when AQP1 is deleted.

7.3.2 AQPs and Airway Fluid Balance

Airway must keep high humidity to protect airway epithelial cells that work together with submucosal glands to secret fluid to facilitate cilliary movement to expel inhaled exopathogens. Although AQP3 and AQP4 has been found to be expressed on apical membrane of ciliated epithelial cells [26] (Fig. 7.2) and studies showed that AQPs play minor role in airway humidification, ASL hydration, and isosmolar fluid absorption in AQP3 and AQP4 knockout mice [27]. By calculating fluid transport rate, the fluid movement across airway epithelium challenged by dry air is relatively slower compared to salivary gland secretion where AQP5 facilitates fluid transport. Furthermore, the minor effect of AQP3 and AQP4 in airway physiology suggests slow fluid movement does not rely on water channel necessarily unless it is challenged by osmotic fluid movement [27].

A recent study showed AQP3 deletion reduce airway re-epitheliulization [28], the possible role is reduced epithelial cell migration due to water and glycerol transport reduction [29]. The role of AQP3 in airway epithelial growth provide potential role of AQP in tissue repair.

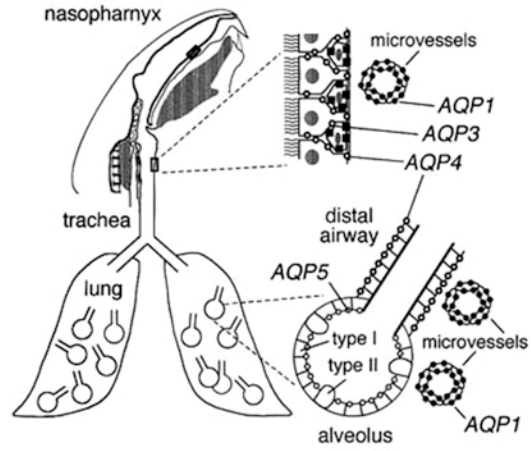

Fig. 7.2 AQP1, AQP3, AQP4 and AQP5 expression in capillary, airway, and alveolar space [26]

7.3.3 AQPs and Pleural Fluid Balance

The pleural space plays an important role in pleural fluid secretion and absorption and lubricating visceral and parietals membrane of pleural space to facilitate lung extension. The fluid is filtered through capillary within visceral membrane and reabsorbed by parietal lymphatic duct located on parietal membrane. In some malignancy, these lymphatic can be blocked to result in fluid accumulation within pleural space. AQP1 is expressed at apical membrane of visceral and parietal pleura, and apical membrane of endothelial cell within visceral membrane [4] (Fig. 7.3). Our group found that AQP1 could facilitate the osmotic fluid transport within pleural space, and deletion of AQP1 could significantly reduce osmotic fluid transport. However, AQP1 did not take part in pleural isosmolar fluid clearance [30, 31]. Similarly, there is no relationship of AQP1 with clinically relevant mechanisms of pleural fluid accumulation or clearance [4].

7.3.4 AQPs and Submucosal Gland Secretion

Submucosal glands are located at upper and lower airway submucosal area, where capillary

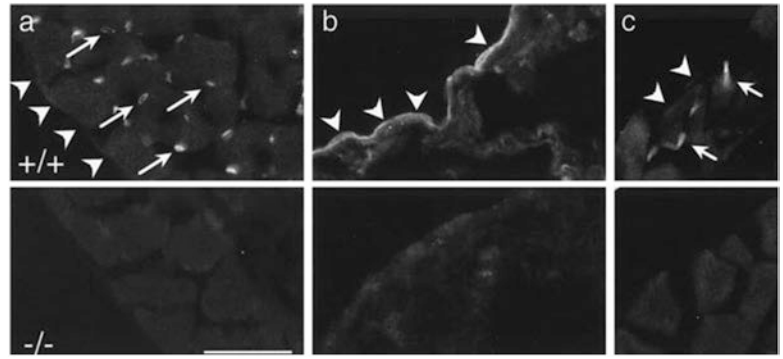

Fig. 7.3 AQP1 expression in parietal and visceral membrane of pleural space [4]

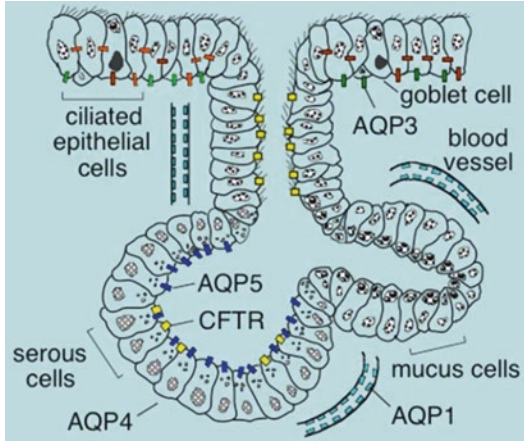

Fig. 7.4 AQP1, AQP3, AQP4 and AQP5 expression in airway submucosla glands [33]

and nerves are surrounded to keep normal function for gland secretion. In general, when glands are stimulated with nerve or chemical through muscarinic receptors, increased cytosolic cAMP level will activate CFTR function, to induce chloride secretion, and sodium will increase in cell to follow the electronic neutralization through intracellular and paracellular pathway, and then water will come out of the cells following the ionic osmotic gradient mainly through AQP5 water channel. This phenomenon was evidenced in airway submucosal glands and salivary glands [32] (Fig. 7.4). Deletion of AQP5 significantly reduced gland fluid secretion and thus made the secreted fluid more viscous [33]. There are few studies showing that dry mouth due to salivary glands radiation or sojoren syndrome are associated with abnormal distribution of AQP5 [34, 35], suggesting AQP5 modulation may potentially improve dry moth syndrome through correction of saliva secretion. It is therefore interesting to test whether AQP5 modulation could be useful to promote airway mucus clearance in COPD or bronchiectasis patients.

7.4 AQPs and Lung Cancer Development

Several studied found that AQP1, AQP3, AQP4 and AQP5 are over-expressed in lung cancer [36–39]. The expression of AQP1 is higher in lung adenocarcinoma (ADCs) and bronchoalveolar carcinoma than that in lung squamous cell carcinoma and normal lung tissue [37]. AQP1 is located in the endothelial cells of capillaries within lung cancer tissue and responsible for tumor angiogenesis [40, 41]. AQP1 is also involved in invasion of lung cancer cells, and reducing AQP1 expression by AQP1-shRNA could inhibit lung cancer cell invasion and migration [41]. Moreover, AQP1 expression is correlated with high postoperative metastasis ratios and low disease-free survival rates in ADCs, especially with micropapillary ADC components [36]. These studies suggest that AQP1 could be a significant prognostic index for stage and histologic differentiation of lung cancer.

AQP3 is over-expressed in non-small cell carcinoma (NSCLC), especially ADCs, well-differentiated bronchioloalveolar carcinomas and papillary subtypes. Some studies found that AQP3 might regulate biological functions of lung cancer cells, in the early stage of lung ADC [36], and even involve in angiogenesis of lung cancer

through HIF-2α-VEGF pathway and lung cancer cell invasion partly by the AKT-MMPs pathway, mitochondrial ATP formation and cellular glycerol uptake [42]. The anticancer effect of shRNA-targeting AQP3 is confirmed in experimental NSCLC models, and further is confirmed in preclinnical studies [42]. Beside, AQP4 wis involved in the invasion of lung cancer cells [41]. Higher transcript and protein levels of AQP4 in well-differentiated lung ADCs suggest an association with a better prognosis [38].

The expression of AQP5 was also detected to dramatically increase in lung ADCs and correlated with poor prognosis of patients with NSCLC [43]. AQP5-expressed cells exhibited a loss of epithelial cell markers and activation of c-Src through SH3 binding domain to promote epithelial to mesenchymal transition (EMT) which might be responsible for the promote metastasis of lung cancer [43]. Over-expressed AQP5 could facilitate lung cancer cell growth and invasion through the activation of the EGFR/ERK/p38 MAPK pathway [43, 44]. The cAMP-protein kinase (PKA) consensus site in AQP5 is also preferentially phosphorylated and promoted cell proliferation ability in tumor. The phosphorylation S156 in PKA consensus site is demonstrated to play an important role in tumor proliferation and invasion [45]. So, S156 in AQP5 may provide a potential therapeutic target by developing small molecules as an inhibitor. Moreover, developing specific monoclonal antibody targeting AQP5 will also be another approach.

7.5 AQPs and Acute Lung Injury and Lung Infection

Several studies have shown that both AQP1 and AQP5 are down-regulated after lung injury [23, 24, 46]. Deletion of AQP1 does not show significant phenotype changes while AQP5 deletion shows worsened lung injury after *P. aeruginosa* challenge [21, 24]. The mechanism may be that AQP1 was expressed in pulmonary capillary endothelium cells, and deletion of AQP1 impairs osmotic fluid transport but not near isosmolar fluid transport during capillary leaking due to increased permeability changes. AQP1 mutation in human does not cause morphology changes, but results in retarding fluid accumulation around airways [23].The underlying mechanism could be a change in capillary networks. It is believed that hydrostatic force could affect isosmolar fluid transport through water channels. Besides, the worsened lung injury in AQP5 null mice after *P. aeruginosa* challenge could be due to airway surface liquid property changes [24], in which AQP5 deficiency leads to reduced mucin production in lung. Moreover, and declined activation of mitogen-activated protein kinase and nuclear factor-kappa B before and after PA infection.

Considering that AQP 1 and AQP5 are expressed at blood-gas barrier, and both of them facilitate osmotic fluid transport, it has been though that AQP1 and AQP5 may play an important role in acute lung injury, especially in the pulmonary edema. Several studies showed that AQP1 and AQP5 are significantly down-regulated after lung injury [23, 24], and deletion of AQP1 does not show any difference of lung edema formation or resolution in LPS induced acute lung injury, suggesting slow fluid transport or fluid leakage from paracellular pathway may not require AQPs for intracellular fluid transport in acute lung injury. Meanwhile, AQPs may facilitate osmotic fluid transport but not near isosmolar fluid movement.

7.6 AQPs and Asthma

Asthma is featured by increased airway constriction, esionphilic infiltration, hypersecretion of airway mucus and small airway epithelium edema formation. Immunostaining study shows AQP1 expressed not only in alveolar type I and type II cells, as well as in airway epithelium. OVA-induced Asthma animal model shows an increase in expression of AQP1 and AQP5 compared to control group, suggesting AQP1 and AQP5 may participate in airway epithelium edema formation [47]. Bronchial provoke test usually shows hyperactivity and hyper responsiveness to methacholine [48]. AQP5 knockout

mice study shows deletion of AQP5 increased airway reactivity challenged by inhalation of methacholine accompanying with increased airway resistance [10]. It is not clear why deletion of AQP5 decreases airway challenge threshold. Besides, same loci of AQP5 and other asthma gene located at chromosome 12q and mouse chromosome 15 further indicated potential role of AQP5 in asthma development [10].

7.7 Summary

AQPs are water channel proteins supposed to facilitating fluid transport in alveolar space, airway humidification, pleural fluid absorption, and submucosal gland secretion. Previous studies suggested the roles of AQPs in various physiology and pathophysiology condition of different lung disease in vivo or vitro. It still remains unclear the exact role of AQPs in lung diseases, and thus continuous efforts on elucidating the roles of AQPs in lung physiological and pathophysiological processes are warranted.

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