Advances in Experimental Medicine and Biology 969

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Aquaporins

Springer

Advances in Experimental Medicine and Biology

Advances in Internal Medicine

Volume 969

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ISSN 0065-2598 ISSN 2214-8019 (electronic)
Advances in Experimental Medicine and Biology
ISBN 978-94-024-1055-6 ISBN 978-94-024-1057-0 (eBook)
DOI 10.1007/978-94-024-1057-0

Library of Congress Control Number: 2017932281

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer Science+Business Media B.V.
The registered company address is: Van Godewijckstraat 30, 3311 GX Dordrecht, The Netherlands

Preface

The mechanisms and physiological functions of water transport across biological membranes are subjects of long-standing interest. Recent advances in the molecular biology and physiology of water transport have yielded new insights into how and why water moves across cell membranes. Aquaporins (AQPs) are a group of water channel proteins that are specifically permeable to water and some other small molecules, such as glycerol, urea, etc. Thirteen water channel proteins (AQP0–AQP12) have been cloned, and gene organization, protein crystal structure, expression localization, and physiological functions of some AQPs have been studied and determined. In recent years, the studies in AQP knockout mouse models suggest that AQPs may be involved in some disease development and be useful targets for drug discovery of selective inhibitors. Our aim in writing this book is to stimulate further research in new directions by providing novel provocative insights into further mechanisms and physiological significance of water and some small molecule transport in mammals.

This book provides a state-of-the-art report on what has been learned recently about AQPs and where the field is going. Although some older work is cited, the main focus of this book is on advances made over the past 30 years on the biophysics, genetics, protein structure, molecular biology, physiology, pathophysiology, and pharmacology of AQPs in mammalian cell membranes. It is likely that advances in understanding molecular biology and physiology of AQPs will yield new insights into biology and medicine.

In listing names, one always lives in fear of having forgotten someone. I thank all authors and colleagues for their contribution to this book.

Beijing, China — Baoxue Yang

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Molecular Biology of Aquaporins

1

Chunling Li and Weidong Wang

Abstract

Aquaporins (AQPs) are a family of membrane water channels that basically function as regulators of intracellular and intercellular water flow. To date, thirteen AQPs, which are distributed widely in specific cell types in various organs and tissues, have been characterized in humans. Four AQP monomers, each of which consists of six membrane-spanning alpha-helices that have a central water-transporting pore, assemble to form tetramers, forming the functional units in the membrane. AQP facilitates osmotic water transport across plasma membranes and thus transcellular fluid movement. The cellular functions of aquaporins are regulated by posttranslational modifications, e.g. phosphorylation, ubiquitination, glycosylation, subcellular distribution, degradation, and protein interactions. Insight into the molecular mechanisms responsible for regulated aquaporin trafficking and synthesis is proving to be fundamental for development of novel therapeutic targets or reliable diagnostic and prognostic biomarkers.

Keywords

Aquaporin • Posttranslational modification • Endocytosis • Exocytosis

1.1 Classification of Aquaporins (AQPs)

1.1.1 Discovery of the First Water Channel

The existence of a water channel protein had been predicted for a long time. In early 1980s last century, people believed that a protein migrating as band 3 on the electrophoretogram of red blood

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B. Yang (ed.), *Aquaporins*, Advances in Experimental Medicine and Biology 969,
DOI 10.1007/978-94-024-1057-0_1

cell membrane was a common pore for water and electrolytes [214]. The membrane water channel was not identified until the pioneering discovery of AQP1 by Peter Agre and colleagues around late 1980s and early 1990s. During that period, Agre and coworkers had purified by chance a novel protein from the red blood cell membrane [47], with a non-glycosylated component of 28 kDa and a glycosylated component migrating as a diffuse band of 35~60 kDa, which displayed a number of biochemical characteristics. The 28-kDa polypeptide was found to exist as an oligomeric protein with the physical characteristics of a tetramer. The amino acid sequence was later identified [213] and cDNA was subsequently cloned [190]. The new protein was initially called CHIP28 (CHannel-like Integral Protein of 28 kDa), but was later redubbed aquaporin-1 or AQP1 [2].

The AQP1 was identified by injecting its cRNA into *Xenopus laevis* oocytes, which exhibited remarkably high osmotic water permeability causing the cells to swell rapidly and explode in hypotonic buffer [190]. To test the role of AQP1 as a molecular water channel, highly purified AQP1 protein from human red blood cells was reconstituted with pure phospholipid into proteoliposomes and were compared with liposomes without AQP1 [260, 261]. The unit water permeability (conductance per monomeric AQP1) was extremely high in the liposomes with AQP1 when compared with controls, in addition, AQP1 proteoliposomes were not permeable to various small solutes or protons, thus suggesting that AQP1 was water selective (although later studies found that AQP1 is indeed gas permeable). These results confirmed that AQP1 is a molecular water channel and strongly suggested that AQP1 water channels were of fundamental importance for transmembrane or transcellular water transport in tissues where it is expressed. The discovery of AQP1 also laid the ground for the identification of other water channel family members by homology cloning and other means, which has led to the understanding that aquaporins play essential roles in water transport in tissues.

1.1.2 Classification of AQPs

A large number of evidences have shown an unexpected diversity of AQPs in both prokaryotic and eukaryotic organisms [1, 58] since the discovery of AQP1. More than 300 different aquaporins have been discovered so far in which thirteen isoforms have been identified (AQP0–AQP12) in human. AQPs are integral, hydrophobic, transmembrane proteins that primarily facilitate the passive transport of water depending on the osmotic pressure on both sides of membrane. Subsequent studies showed that AQPs can transport not only water molecules but also other small, uncharged molecules, i.e., glycerol, urea, down their concentration gradients.

Structural analysis of several AQPs has established that these protein channels share common structural features. The functional aquaporin unit is a homotetramer, which comprises six α-helix transmembrane domains with two conserved asparagine–proline–alanine (NPA) motifs embedding into the plasma membrane, a signature sequence of water channels, five loops (A-E) and intracellular N- and C-termini. The amino acid sequences of human AQPs are approximately 30–50% identical. Conformational changes of AQP protein permit other molecules passing through plasma membrane, i.e. urea, glycerol, H_2O_2, NH_3, CO_2, etc.

According to their structural and functional similarities, AQPs are initially subdivided into two subfamilies, classical AQPs (water-selective) and aquaglyceroporins (glycerol channel, Glps) aquaporins. However, this viewpoint was challenged by recent evidence revealing that both subfamilies overlap functionally, for examples, some classical AQPs transport water and other small solutes e.g. glycerol. In addition, a new group of AQPs discovered recently showed that their structure is highly deviated from the previous AQPs especially around the AQP NPA box [95, 104, 107]. This subfamily was later named superaquaporin (also called unorthodox aquaporin) as it has very low homology with the previous two subfamilies [104]. This classification is

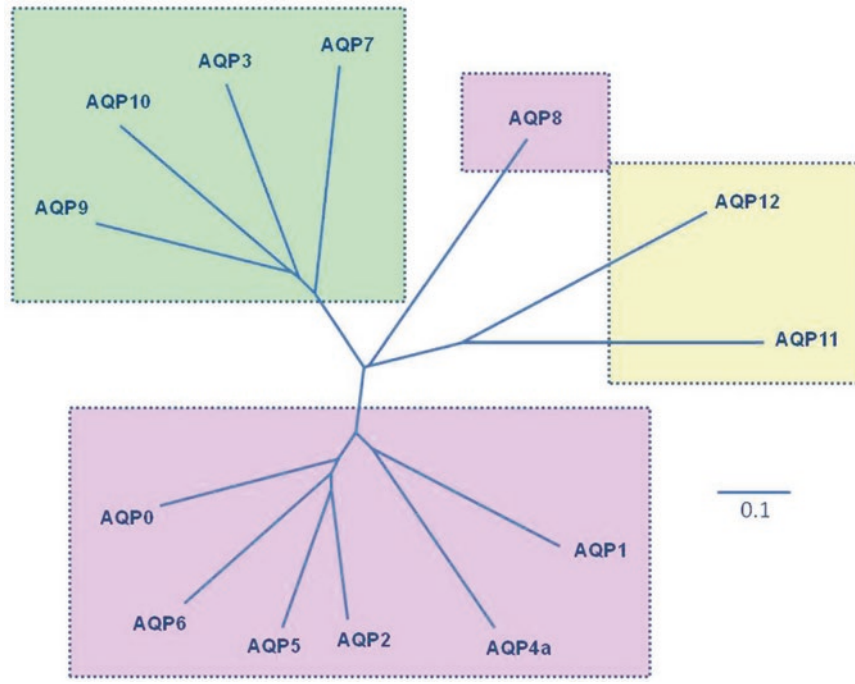

Fig. 1.1 The phylogenetic tree of 13 human AQPs. The tree shows the classical AQPs (AQP0, AQP1, AQP2, AQP4, AQP5, AQP6, AQP8, note that AQP8 is also named as AQP8-related AQPs, as in phylogeny it is different from other classical AQPs, *light pink square*); the aquaglyceroprins (AQP3, AQP7, AQP9, AQP10, *light green square*); and the superaquaporins (AQP11, AQP12, *light yellow square*) (Modified from Ref. [104])

generally accepted and will be discussed in the current review. Aquaporins may also be organized into four categories, classical aquaporins, Aqp8-type aquaammoniaporins, unorthodoxaquaporins, and Glps, according to the phylogenetic tree (Fig. 1.1) or phylogenetic topology inferred from Bayesian inference [58, 104].

The first subfamily is that of aquaporins, the water selective or specific water channels, also named as "orthodox", "classical" aquaporins, including AQP0, AQP1, AQP2, AQP4, AQP5, AQP6 and AQP8. This subfamily of AQPs has been extensively studied, which help us define regulation of AQP expression in the body and their potential roles in physiological and pathophysiological states. Recent literature, however, appears to suggest that AQP6 and AQP8 be classified as unorthodox auquaporins, due to low water permeability of AQP6 [62, 256] and unique, different phylogenetics of AQP8 from others [122, 152].

The second subfamily is represented by aquaglyceroporins that are permeable to water and other small uncharged molecules (ammonia, urea, in particular glycerol). They also facilitate the diffusion of arsenite and antimonite and play a crucial role in metalloid homeostasis [15]. The aquaglyceroporins, including AQP3, AQP7, AQP9 and AQP10, can be distinguished from aquaporins based on amino acid sequence alignments [21]. AQP3 is the first mammalian aquaglyceroporin to be cloned, and it is permeable to glycerol and water [50, 252]. AQP7, AQP9, and AQP10 transport water, glycerol, and urea when expressed in Xenopus oocytes [100, 103, 232]. AQP9 is also permeable to a wide range of other solutes in oocytes [232]. Most aquaglyceroporins which transport glycerol and urea are less understood yet.

The third subfamily of related proteins have low conserved amino acid sequences around the NPA boxes unclassifiable to the first two subfamilies [104]. Mammalian AQP11 and AQP12 are