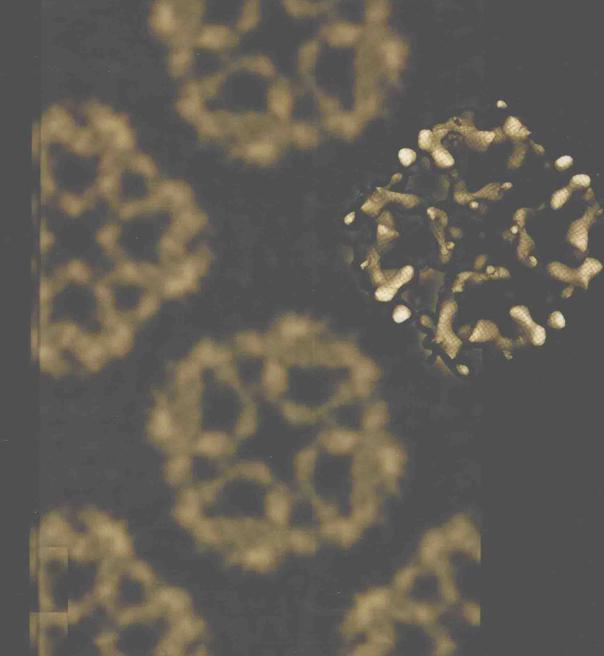
MOLECULAR BIOLOGY AND PHYSIOLOGY OF WATER AND SOLUTE TRANSPORT



Edited by Stefan Hohmann and Søren Nielsen

Molecular Biology and Physiology of Water and Solute Transport

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Front cover: The three-dimensional structure of GlpF (*E. coli*) tetramer is shown as seen from the cytoplasmic side. The structure was reconstructed at a resolution of 6.5 Å (z:12 Å) from tilted images, recorded with a Jeol 3000 SFF (MPI Frankfurt) helium-cooled microscope at 1 Kelvin. The map in the background is the GlpF projection map at 3.7-Å resolution. The image was created using the program *DlNO* (http://www.bioz.unibas.ch~xray/dino). (See also Braun, Philippsen, Wirtz, Borgnia, Agre, Kühlbrandt, Engel, and Stahlberg, Chapter 1.2, this volume).

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PREFACE

Biophysical studies in the 1950's and 1960's led to the realization that the water permeability of certain biological membranes must be due to the presence of water transporting proteins. This hypothesis was confirmed in 1991 and 1992 with the pioneering discovery of the first molecular membrane water channel, CHIP28, by Agre and coworkers. This integral membrane protein, which is abundant in the erythrocyte membrane and in many epithelial cells, is now called aquaporin-1 or AQP1. Thus, the terms water channel or aquaporin are synonymous.

Already at that time several known proteins showed topological and sequence similarity to AQP1: MIP (now AQP0), the major intrinsic protein from mammalian lens fiber, Nod26 and TIP, two plant proteins, as well as the *Escherichia coli* glycerol facilitator GlpF. The existence of homologous proteins from completely different organisms suggested that those were members of an ancient family, the MIP family. Indeed, all eukaryotes and most bacterial or archeal organisms studied so far posses MIP channels.

Human and rat have at least 10 aquaporins that are expressed in different tissues, most prominently in the kidney. Kidney aquaporins play distinct and crucial roles in kidney function for tight regulation of body water balance. Analysis of knockout rat models is now providing further insights into the physiological roles of mammalian aquaporins. Present knowledge suggests that aquaporins are targets for novel drugs, which could be used in the treatment of imbalanced water homeostasis. Such imbalances are the consequence of various kidney, heart, liver and endocrine diseases.

Plants appear to have a large number of MIP channels; the present estimate for the model plant *Arabidospsis* some 30 different proteins expressed in different cell types, developmental stages and environmental conditions. Genetic analysis of the physiological roles is only starting but

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plant aquaporins are expected to play central roles in transcellular and intracellular water partitioning. Hence, plant aquaporins may be a key to understanding the delicate control of plant water homeostasis, which in turn is crucial for the engineering of numerous crop properties.

Unicellular organisms, i.e., bacteria and fungi, appear to have only few MIP channels. Glycerol facilitators are common in bacteria and mediate the uptake of glycerol and related compounds for catabolism. A yeast glycerol facilitator has been shown to mediate glycerol export in osmoregulation. Many microorganisms also posses aquaporins. Their exact physiological roles are still poorly understood although some evidence suggests that they may play roles in the control of cell expansion during growth.

Presently more than 200 MIP channels are known. Those have a common topology of six transmembrane domains. The two halves of the protein are similar suggesting an internal duplication during evolution. Sequences in loops 2 and 5, the NPA boxes, are well conserved and seem to be part of the aqueous pore through the membrane. Phylogenetic analysis and functional studies have separated MIP channels into two major subfamilies, water channels and glycerol facilitators. These subfamilies are characterized by specific conserved amino acid residues thought to determine substrate specificity. The structural analysis of MIP channels is advancing now to atomic resolution, which will be essential to understand and probe the interesting transport specificity: the fact that certain MIP channels transport glycerol but not water excludes size selection as a simple explanation.

In July 2000 more than 200 researchers came together in Gothenburg, Sweden, for the "3rd International Conference on the Molecular Biology and Physiology of Water and Solute Transport" to discuss progress in this emerging research field. 58 different presentations from this conference are the basis for this book. Cumulatively, these 58 short chapters provide a balanced overview complementing numerous recent reviews in this field. We have organized the chapters into different sections, i.e. structure function analysis, mammalian physiology, pathophysiology, plant biology and microbiology. The section titles illustrate the multidisciplinary character of the research area of water and solute transport and aquaporin function, where researchers studying very different biological systems communicate with each other. We hope that this volume will be a milestone in this exciting and rapidly emerging field with major breakthroughs in the understanding of MIP channel structure, function and physiological/pathophysiological roles just ahead of us.

Stefan Hohmann and Søren Nielsen, Göteborg and Århus

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STRUCTURE FUNCTION ANALYSIS OF AQUAPORINS AND GLYCEROL FACILITATORS



1.1 Structure function analysis

FUNCTIONAL ANALYSIS OF THE UNUSUAL SIGNATURE MOTIFS OF THE YEAST MIP CHANNEL, Fps1p

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1. INTRODUCTION

Major Intrinsic Protein (MIP) channels - aquaporins and glycerol facilitators – occur in all types of organisms ranging from bacteria to humans and facilitate the diffusion of water, glycerol and other uncharged compounds across biological membranes. To date, more than 200 MIPs have been identified comprising an amazing number of isoforms expressed in subcellular compartments and tissues. under different environmental conditions or during different developmental stages. For example, ten genes encoding MIP channels are currently known in humans (Borgnia et al., 1999), 30 have been described in the plant Arabidopsis thaliana (Kjellbom et al., 1999) and the nematode Caenorhabditis elegans has nine (Kuwahara et al., 1998). These channel proteins are involved in biological processes as diverse as urine concentration in the mammalian kidney, (Deen and Knoers 1998) root development in Arabidopsis thaliana (Kaldenhoff et al., 1998; Kjellbom et al., 1999) and osmoregulation in Saccharomyces cerevisiae (Luyten et al., 1995; Tamás et al., 1999).

The central importance of Fps1p in yeast osmoregulation is well known. Although it is closely related to bacterial glycerol facilitators such as $E.\ coli$ GlpF, it is - so far - unique in the MIP family for a number of reasons (Hohmann $et\ al.$, 2000). For example, it has long amino- and carboxy-terminal hydrophilic extensions, resulting in a protein of 669 amino acids,

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