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Regulation and transport mechanisms of eukaryotic aquaporins

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Abstract

Aquaporins are found in all kingdoms of life where they are involved in water homeostasis. They are small transmembrane water conducting channels that belong to the ancient protein family Major Intrinsic Proteins (MIP). Early on in the evolution, a gene duplication event took place that divided the aquaporin family into two subgroups; orthodox aquaporins, which are strict water facilitators, and aquaglyceroporins that except for water also transport small uncharged solutes.

The main questions that I have tried to address in this thesis are which regulatory mechanisms that are involved in aquaporin gating and to investigate transport differences in solute permeation. Specifically, we have investigated yeast and human aquaporins. To find answers to our questions, we have attempted to combine structural knowledge with functional analysis.

A high resolution structure of *P. pastoris* orthodox Aqy1 to 1.15Å generated new knowledge of regulatory mechanisms and functions of the long N-terminus that is common among fungi. We suggest that Aqy1 is gated by phosphorylation and by mechanosensation. An important functional role of Aqy1 in rapid freeze thaw cycles could be demonstrated. During this work, a single deletion strain was generated that now serves as the primary aquaporin expression platform in our laboratory.

Fps1 is a regulated glycerol facilitator that is important for yeast osmo-regulation. The regulatory mechanism is still not known but here we show that a suppressor mutation within the transmembrane region restrict glycerol by its transmembrane core. Thereby, we suggest that post translational modifications in the regulatory domains of N- and C-termini fine tunes glycerol flux through Fps1.

The aquaglyceroporins are classified as having a dual transport function, namely being capable of facilitating the movement of both water and glycerol over the plasma membrane. In this study, we can clearly show that there are major differences in the substrate specificity and efficiency between the different aquaglyceroporins and that small changes affect the transport efficiency and specificity of the channels.

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