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Structural studies of aquaporins in human kidney and plant

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Akademisk avhandling för filosofie doktorsexamen i Naturvetenskap, som med tillstånd från Naturvetenskapliga fakulteten kommer att offentligt försvaras fredagen den 12:e april 2013 kl. 9.30 i Ragnar Sandberg, Institutionen för kemi och molekylärbiologi, Medicinaregatan 7A, Göteborg.

ISBN: 978-91-628-8661-5
Online: http://hdl.handle.net/2077/32281

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ABSTRACT

Membrane proteins are key players in our biology and are links between the inside and the outside of the cell, allowing for signal transduction and transport of molecules. Aquaporins are membrane protein channels that allow water to pass in and out of the cell. Since all life depend on water, their function is vital for any type of organism. Although aquaporins are very similar, they have small but important differences in their structure and function. Understanding these subtle dissimilarities helps us understand the fundamentals of our biology and is also essential if aquaporins are to be used as drug targets.

This thesis has investigated the structure and function of two aquaporins from different species; human and spinach. The spinach aquaporin SoPIP2;1 has become the structural model for gated plant aquaporins. In this thesis, structural and functional data is presented that gives further insights into the gating mechanism controlled by the physiological signals phosphorylation, pH and divalent cations. In addition, the mechanism behind the activation of SoPIP2;1 by mercury, commonly regarded as an aquaporin blocker, has been studied.

Human Aquaporin 2 is crucial for the kidneys ability to concentrate primary urine, and its malfunction leads to nephrogenic diabetes insipidus. An X-ray crystallographic structure to 2.95Å is presented, which show that AQP2 is markedly different also from its most closely related homologues. These differences are mainly focused on loop D and the C-terminus and can be related to binding of Cd^{2+} in the structure. We present data that Cd^{2+} could correspond to Ca^{2+} in vivo, and discuss the role of the C-terminal helix as a protein interaction partner. In addition, mutations leading to nephrogenic diabetes insipidus are studied in the structural context.