

The structural basis of an exceptional protein kinase TRPM6

Clinical relevance

Mutations in the *TRPM6* gene have been shown to cause familial hypomagnesemia with secondary hypocalcemia. This finding, together with its apical expression on Mg²⁺ reabsorbing epithelia in the kidney and its identification as a Mg²⁺-permeable channel, emphasizes TRPM6's critical role in controlling Mg²⁺ homeostasis. Disturbances in the Mg²⁺ balance have been associated with diabetes mellitus type 2, osteoporosis, asthma, and heart and vascular diseases. Furthermore, hypomagnesemia is a commonly occurring problem in hospitalized patients (~11%), which may lead to muscle cramps, tetany, seizures and in more pronounced cases to cardiac arrhythmias. Therefore, in-depth understanding of the molecular regulation of TRPM6 can be exploited to develop better treatments of hypomagnesemia and increase our understanding for the management of other electrolyte abnormalities in human diseases.

Background

The kidney is the most important organ for maintaining the total body Mg²⁺ homeostasis as fine-tuning of the renal Mg²⁺ reabsorption in the DCT preserves a constant Mg²⁺ concentration in blood. The epithelial magnesium channel transient receptor potential melastatin subtype 6 (TRPM6) was identified as the magnesium entry pathway in the distal convoluted tubule (DCT) of the kidney, where it functions as key player in controlling the body's magnesium balance. This is of central importance for various physiological processes. Together with TRPM7, TRPM6 is unique among the ion channel field as it consists of an ion channel merged with a kinase domain. Protein kinases are enzymes that phosphorylate target proteins to modulate their function. The function of the kinase domain is not well understood.

Goals

In this internship we want to answer the following questions:

- Which proteins are phosphorylated by TRPM6?
- Does TRPM6 get degraded via the ubiquitin pathway?
- Which TRPM6 domain structures are important for this signaling?
- What signals for TRPM6 activation and degradation?

Techniques:

This internship will allow you to learn and apply several techniques such as:

- Cloning
- Real Time PCR
- Western Blot
- Protein purification

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