SYMPOSIUM REVIEW

TRPM2: a multifunctional ion channel for calcium signalling

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The transient potential receptor melastatin-2 (TRPM2) channel has emerged as an important Ca^{2+} signalling mechanism in a variety of cells, contributing to cellular functions that include cytokine production, insulin release, cell motility and cell death. Its ability to respond to reactive oxygen species has made TRPM2 a potential therapeutic target for chronic inflammation, neurodegenerative diseases, and oxidative stress-related pathologies. TRPM2 is a non-selective, calcium (Ca^{2+})-permeable cation channel of the melastatin-related transient receptor potential (TRPM) ion channel subfamily. It is activated by intracellular adenosine diphosphate ribose (ADPR) through a diphosphoribose hydrolase domain in its C-terminus and regulated through a variety of factors, including synergistic facilitation by $[Ca^{2+}]_i$, cyclic ADPR, H_2O_2, NAADP, and negative feedback regulation by AMP and permeating protons (pH). In addition to its role mediating Ca^{2+} influx into the cells, TRPM2 can also function as a lysosomal Ca^{2+} release channel, contributing to cell death. The physiological and pathophysiological context of ROS-mediated events makes TRPM2 a promising target for the development of therapeutic tools of inflammatory and degenerative diseases.

(Received 31 October 2010; accepted after revision 29 November 2010; first published online 6 December 2010)
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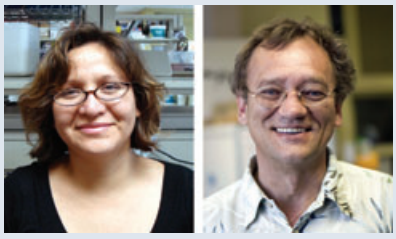
Introduction

Transient receptor potential (TRP) proteins represent a large superfamily of six-transmembrane (6TM) monovalent and divalent cation-permeable ion channels that are homologues of the *Drosophila melanogaster* TRP protein, a Ca^{2+}-permeable channel that is essential for phototransduction (Ramsey *et al.* 2006; Nilius, 2007;



Adriana Sumoza-Toledo, PhD (left) is a Scientist at the Queen's Medical Center and adjunct Assistant Professor at the University of Hawaii in Honolulu, HI. She earned her Ph.D. in Molecular Biomedicine from CINVESTAV, Mexico and received post-doctoral training in Immunology and Biophysics at Nationwide Children's Hospital, Columbus, OH and The Queen's Medical Center, Honolulu, HI, respectively. Her research background includes cell cytoskeleton, cell signaling, immunology, biochemistry, and electrophysiology. Her research interests focus on TRPM2 channels in innate immune cell function and cancer biology. **Reinhold Penner, MD, PhD (right)** is the Director of Research at The Center for Biomedical Research at The Queen's Medical Center in Honolulu, Hawaii. He worked at the Max-Planck-Institute for Biophysical Chemistry in Göttingen, Germany for 12 years and relocated to Honolulu in 1997 to establish the Laboratory of Cell and Molecular Signaling at The Queen's Medical Center. His work has contributed to the understanding of store-operated calcium entry and led to the discovery the Calcium Release-Activated Calcium (CRAC) channels. His laboratory also contributed to the discovery and characterization of several TRP channels, including TRPM2, TRPM4, TRPM5, and TRPM7. His group is now involved in drug discovery efforts for a range of ion channels involved in inflammation, autoimmune diseases, diabetes, and cancer.

This review was presented at the TRP 2010 symposium *TRP channels: from structure to disease*, which took place in Leuven, Belgium, 22–24 September 2010, celebrating the 65th birthday of Professor Bernd Nilius. It was commissioned by the Editorial Board and reflects the views of the authors.

DOI: 10.1113/jphysiol.2010.201855