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Review

Cellular functions of Transient Receptor Potential channels

Daniela Dadon, Baruch Minke*

Department of Medical Neurobiology, The Institute of Medical Research Israel-Canada and the Kühne Minerva Center, for Studies of Visual Transduction, Faculty of Medicine, The Hebrew University, Jerusalem 91120, Israel

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ABSTRACT

Transient Receptor Potential channels are polymodal cellular sensors involved in a wide variety of cellular processes, mainly by increasing cellular Ca^{2+}. In this review we focus on the roles of these channels in: (i) cell death (ii) proliferation and differentiation and (iii) transmitter release. *Cell death*: Ca^{2+} influx participates in apoptotic and necrotic cell death. The Ca^{2+} permeability and high sensitivity of part of these channels to oxidative/metabolic stress make them important participants in cell death. Several examples are given. Transient Receptor Potential Melastatin 2 is activated by H_2O_2, inducing cell death through an increase in cellular Ca^{2+} and activation of Poly ADP-Ribose Polymerase. Exposure of cultured cortical neurons to oxygen–glucose deprivation, in vitro, causes cell death via cation influx, mediated by Transient Receptor Potential Melastatin 7. Metabolic stress constitutively activates the Ca^{2+} permeable Transient Receptor Potential channels of *Drosophila* photoreceptor in the dark, potentially leading to retinal degeneration. Similar sensitivity to metabolic stress characterizes several mammalian Transient Receptor Potential Canonical channels. *Proliferation and differentiation*: The rise in cytosolic Ca^{2+} induces cell growth, differentiation and proliferation via activation of several transcription factors. Activating a variety of store operated and Transient Receptor Potential channels cause a rise in cytosolic Ca^{2+}, making these channels components involved in proliferation and differentiation. *Transmitter release*: Transient Receptor Potential Melastatin 7 channels reside in synaptic vesicles and regulate neurotransmitter release by a mechanism that is not entirely clear. All the above features of Transient Receptor Potential channels make them crucial components in important, sometimes conflicting, cellular processes that still need to be explored.

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Abbreviations: TRP, transient receptor potential; ADPR, ADP ribose; ROS, reactive oxygen/nitrogen species; PARP, poly ADP-ribose polymerase; SOC, store operated channel; SOCE, store operated calcium entry; CCE, capacitative calcium entry; TNF-α, tumor necrosis factor-α; PLC, phopholipase C; PIP_2, phosphatidylinositol 4,5-bisphosphate; OGD, oxygen–glucose deprivation; DAG, diacylglycerol; EST, Expressed Sequence Tag; GPCR, G protein coupled receptor; IP_3R, inositol trisphosphate receptor; STIM1, stromal interaction molecule 1; PMN, post mitotic neurons; bFGF, Basic Fibroblast Growth Factor; NSC, neural stem cells; PASMC, pulmonary artery smooth muscle cells; CREB, cAMP response element binding protein; NFAT, nuclear factor of activated T cells; PDGF, platelet-derived growth factor; α1-AR, α1-adrenergic receptor; Cav1, caveolin-1; RB, retinoblastoma; EPSP, excitatory postsynaptic potential; SCG, superior cervical ganglion; shRNA, short hairpin RNA; VEGF, vascular endothelial growth factor; SNARE, soluble NSF attachment protein receptors; RGS, regulators of G protein signaling.

* Corresponding author. Tel.: +972 2 6758407; fax: +972 2 6439736.
E-mail address: baruchm@ekmd.huji.ac.il (B. Minke).

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1. Introduction

The TRP channel superfamily is a large and diverse group of cation channels. The founding member of the family was discovered due to a *Drosophila* mutant, which has a defect in its response to light (Cosens and Manning, 1969). This spontaneously formed mutant fly has a transient, rather than a sustained response to prolonged illumination, hence designated "TRP"—Transient Receptor Potential (Minke et al., 1975). After the cloning of the *trp* gene (Montell and Rubin, 1989), the missing protein in the *trp* mutant was found to be the main route of Ca^{2+} entry (Hardie and Minke, 1992; Peretz et al., 1994) and the channel which produces the voltage light response (Hardie and Minke, 1992). A second member of the family was discovered and designated "TRP-like" (TRPL; Phillips et al., 1992), and these channels were established as a new type of cation channel (Hardie and Minke, 1993; Phillips et al., 1992). TRP and TRPL channels are expressed in the *Drosophila* photoreceptor cells and both constitute the light activated channels (Niemeyer et al., 1996).

Other channels, both in mammals and in invertebrates, were found to be part of the TRP superfamily on the basis of similarity to the TRP amino acid sequence, mainly in the transmembrane domain regions. The channels are classified into 7 subfamilies: TRPC, TRPM, TRPV, TRPA, TRPN, TRPML and TRPP (see reviews Clapham, 2003; Montell, 2001, 2005; Nilius and Voets, 2005; Pedersen et al., 2005). The TRPP and TRPML subfamilies form a distinct group in the TRP superfamily since their amino acid sequence have low similarity to the other TRP channels (Montell, 2005). Therefore, we will not discuss these subfamilies in this review. There is a significant variability in the primary amino acid sequence among the different subfamilies. Three features, typically characterizing several types of voltage-gated and CNG channels, are present in all TRPs: the permeability to cations, the basic architecture of six transmembrane segments, S1–S6, with a pore region between S5 and S6 and subunit organization as tetramers. The majority of the TRP channels function both as homotetramers and heterotetramers. Heterotetramers are mostly found within the same subfamily, although there are a few exceptions (Bai et al., 2008; Kottgen et al., 2008; Ma et al., 2010). Other structural characteristics of the TRP channels are: ankyrine repeats, TRP box (WKFQR motif), proline rich region, calmodulin binding site, PDZ-binding motif (amino acid VTTRL), coiled coil domain and partial pleckstrin homology domain (reviewed by Ramsey et al., 2006). These features are present in many but not all TRP channels.

Most of the knowledge on the characteristics of TRP channels was obtained by studying heterologously expressed channels. Therefore, relatively little is known about the physiological role of TRP channels in the native cells. However, additional studies have been recently performed in vivo or in primary cell cultures, and therefore the knowledge and understanding of TRP channels in the physiological relevant context is expanding.

A major difficulty in the study of TRP channels is that most channels do not have specific pharmacological agents which can activate or inhibit the channels. Since most cells express more than one member of the TRP family, the distinction between the characteristics and function of the individual channels is not clear. Thus, there is a need to use a genetic approach rather than a pharmacological one. However, there are several drawbacks to the genetic approach as well. It seems that there are interactions between the regulatory mechanisms underlying the expression of different channels within the same TRP subfamily. In some cases, down-regulation of one TRP family member can result in down- or up-regulation of another TRP member, thus making it difficult to determine which channel is responsible for the specific effect. In addition, compensation by another TRP channel can mask the deficiency in the examined channel. This is illustrated for the TRPC6 knockout mice (TRPC6−/−), in which it was suggested that for some functional processes, TRPC3 up-regulation compensates for TRPC6 loss (Dietrich et al., 2005). Additionally, knocking down one TRP family member may affect the physiological balance between the different TRP channels within a cell, which might result in formation of heteromultimers that do not usually exist, thus masking the isolated effect of one channel. These drawbacks mainly characterize mammalian TRP channels because many mammalian cells express several TRPs of the same subfamily in single cells as exemplified above. This complication is largely reduced in invertebrate species used for genetic dissection of various functions such as *C. elegans* and *Drosophila melanogaster*. In these invertebrate species, the redundancy of TRP channel activity is largely avoided due to the expression of only few members of a specific subfamily in single cells and because of their molecular-genetic power that allows easy separation between the function of different channels.

Like the founding member of the TRP channels, which mediates phototransduction, many TRPs have also been found to participate in sensory transduction pathways, including thermosensation, mechanosensation, taste perception, perception of pungent compounds, pheromone sensing, osmolarity and pain sensation (for reviews see Clapham, 2003; Minke and Cook, 2002; Montell, 2001; Nilius and Voets, 2005). Apart from sensory perception, the involvement of TRP channels was demonstrated in many other processes, including salivary fluid secretion, inflammation, cardiovascular regulation, smooth muscle tone, pressure regulation, Ca^{2+} and Mg^{2+} homeostasis and lysosomal function. In addition, TRP channels were shown to be involved in many cellular functions, including cell adhesion, control of growth and differentiation, proliferation, cell death and cell polarity (Abramowitz and Birnbaumer, 2009; Miller, 2006; Nishida et al., 2006).

Most of the reviews on TRP channels have been focused on their sensory functions and ion transport. In the present review we focus on several cellular functions involving TRP channels, including cell death, proliferation, differentiation and neurotransmitter release. A question arises regarding the specific features of TRP channels, which allow them play important roles in the above cellular functions. Some of these TRP specific properties are described below.

One of the most important properties of TRP channels is their permeability to Ca^{2+}. Ca^{2+} is a ubiquitous intracellular signaling ion, involved in the regulation of many distinct cellular processes. Elevation in intracellular Ca^{2+} concentration is mediated by two main pathways: Ca^{2+} influx from the extracellular medium into the cell and Ca^{2+} release from intracellular stores. Most TRP channels are localized and function at the plasma membrane. Except for the mammalian TRPM4 and TRPM5, almost all TRP channels are Ca^{2+} permeable, although the Ca^{2+} permeability differs from one channel to another.

In addition to their permeability to Ca^{2+}, the *Drosophila* TRP channels have additional important properties, which also characterize several mammalian TRP channels. These proper-

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