TRP channels at a glance

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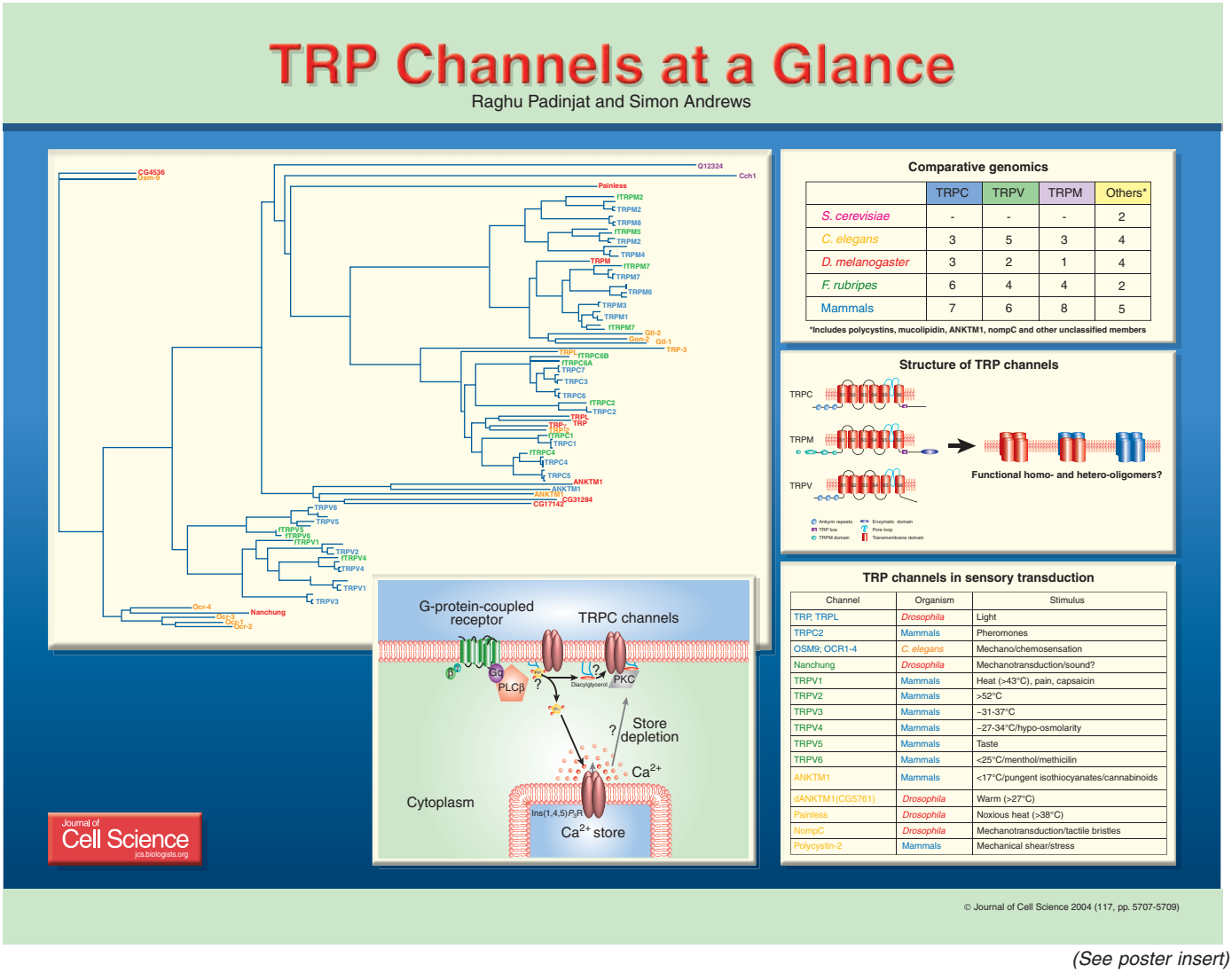
Journal of Cell Science 117, 5707-5709 Published by The Company of Biologists 2004
doi:10.1242/jcs.01343

The *t*ransient *r*eceptor *p*otential (TRP) superfamily consists of a diverse set of proteins whose primary function is to regulate the plasma membrane permeability of animal cells to a variety of ions. They are among the largest family of ion channels known, with representative members in many species right through from yeast to humans. The first member of the family to be identified, *Drosophila melanogaster* TRP, was discovered in the analysis of a mutant fly whose photoreceptors failed to maintain a sustained response to a prolonged stimulus of light (Cosens and Manning, 1969; Hardie and Minke, 1992; Montell and Rubin, 1989).

Estimates of the numbers of TRP channels in fully sequenced genomes vary depending on the inclusion of outlying but related family numbers. More than 100 TRP sequences are present in current non-redundant database sets, including members from *Saccharomyces cerevisiae*, *Dictyostelium discoideum*, *Caenorhabditis elegans*, *Drosophila* and mammals. A phylogenetic tree representing the relatedness of these sequences is presented in the accompanying poster. Recently, a unified nomenclature for these channels has been proposed and accepted by the HUGO gene Nomenclature Committee for all future publications on mammalian TRP channels (Montell et al., 2002). This system defines three broad families of TRP channels: TRPC, TRPV and TRPM. The TRPC family (C is for canonical) is composed of proteins most closely related to the original *Drosophila* TRP channel. The TRPV family is named after the original name of the founding member of this family – the vanilloid receptor VR-1 – and TRPM is named after the founding member of its family – melastatin. Additional but more distantly related families of TRP channels, such as the polycystins, mucolipins and ANKTM have been identified (Clapham, 2003). The estimated numbers of TRP genes of



	TRPC	TRPV	TRPM	Others*
S. cerevisiae	-	-	-	2
C. elegans	3	5	3	4
D. melanogaster	3	2	1	4
F. rubripes	6	4	4	2
Mammals	7	6	8	5

*Includes polycystins, mucolipidin, ANKTM1, nompC and other unclassified members

Channel	Organism	Stimulus
TRP, TRPL	*Drosophila*	Light
TRPC2	Mammals	Pheromones
OSM9; OCR1-4	*C. elegans*	Mechano/chemosensation
Nanchung	*Drosophila*	Mechanotransduction/sound?
TRPV1	Mammals	Heat (>43°C), pain, capsaicin
TRPV2	Mammals	>52°C
TRPV3	Mammals	~31-37°C
TRPV4	Mammals	~27-34°C/hypo-osmolarity
TRPV5	Mammals	Taste
TRPV6	Mammals	<25°C/menthol/methicilin
ANKTM1	Mammals	<17°C/pungent isothiocyanates/cannabinoids
dANKTM1(CG5761)	*Drosophila*	Warm (>27°C)
Painless	*Drosophila*	Noxious heat (>38°C)
NompC	*Drosophila*	Mechanotransduction/tactile bristles
Polycystin-2	Mammals	Mechanical shear/stress

(See poster insert)

different families can be found in the table on the poster.

Structure of TRP channels

The sequence of all TRP channels reveals the presence of six putative transmembrane domains and a pore loop segment between transmembrane segments five and six. Comparison of this pore loop segment with those of bona-fide voltage-gated channels suggests that the residues that contribute to voltage sensitivity are not present within the TRP superfamily. In addition, there are a number of additional domains at the N- and C-termini of different members of this family. Unique among these is the TRP box, a conserved protein sequence following the last transmembrane segment in the TRPC and TRPM but not the TRPV subfamily members (Montell, 2001). Other broadly conserved domains present in these sequences are shown in the poster.

By analogy with the structure of more distantly related channels, such as the K^+ channel KcsA (Doyle et al., 1998) and the cyclic-nucleotide-gated channel (Kaupp and Seifert, 2002), it is expected that TRP channels exist as oligomers. Although evidence has been presented for hetero-oligomers in overexpression systems for both TRPC (Hofmann et al., 2002; Strubing et al., 2001; Strubing et al., 2003; Xu et al., 1997) and TRPV channels (Kedei et al., 2001) the exact composition of the oligomers in vivo, and the functional consequences of oligomerization, if any, remain controversial (Reuss et al., 1997; Xu et al., 1997).

Physiological functions of TRP channels

Roles in cell physiology

TRP channels are cation influx channels that show a diverse range of biophysical properties. These have been compiled on David Clapham's website (http://clapham.tch.harvard.edu/trps/). Most eukaryotic cells show Ca^{2+} influx from the extracellular compartment in response to cell surface receptor activation. This influx, typically following an initial release from intracellular stores, is a prominent feature in most non-neuronal cell types and is referred to as capacitative calcium entry (CCE) or store-operated calcium entry (SOCE) (Putney and McKay, 1999). The molecular identities of the ion channels that underlie most SOCE remain unknown. Despite intense interest in the possibility that TRPC channels might represent the molecular correlate of CCE and numerous studies examining this hypothesis, conclusive evidence to back this idea remains elusive. *Drosophila* phototransduction is the only in vivo signalling cascade in which the role of store depletion, mediated by activation of inositol 1,4,5-trisphosphate [Ins(1,4,5)P_3] receptors by the second messenger Ins(1,4,5)P_3 in TRP channel activation, has been rigorously tested and, in this case, TRP and TRPL do not appear to be activated by store depletion (Acharya et al., 1997; Raghu et al., 2000). More recent evidence suggests that second messengers other than Ins(1,4,5)P_3 that are generated by receptor activation might play a role in TRPC channel activation (Hardie, 2003). The signalling mechanisms involved in TRPC channel activation are depicted. The problems and complexities of addressing this issue have been discussed in detail elsewhere (Clapham, 2003; Zitt et al., 2002). Independently of their role in regulating levels of calcium as a second messenger, TRP channels may also be involved in the regulation of intracellular ion homeostasis. TRPV5 and TRPV6 are thought to be involved in the re-absorption of calcium in the renal tubules and intestine (den Dekker et al., 2003). In addition, TRPM7 channels have been implicated in the regulation of intracellular levels of trace elements such as Zn^{2+}, Cu^{2+}, Mn^{2+} and Co^{2+} (Monteilh-Zoller et al., 2002).

Sensory transduction

Drosophila TRP is the major component of the light-activated conductance in *Drosophila* photoreceptors (Hardie and Minke, 1992). Since then a number of other TRP channels from all three subfamilies have been implicated in sensory transduction processes in vivo and in heterologous systems. It is clear from these studies that TRP channels respond to a wide range of sensory stimuli in a number of different organisms. A summary of these is given in the poster.

Development

TRP channels have been shown to function or have been implicated in a number of developmental process. The cell divisions required for gonad development in *C. elegans* require GON-2, a TRPM channel (West et al., 2001). Fertilization is thought to be mediated by a series of sperm-egg interactions. TRPC channels have been shown to play a role in this process both in mouse (TRPC2) (West et al., 2001) and in *C. elegans* (TRP-3) (Xu and Sternberg, 2003). Recent studies have suggested that Ca^{2+} signalling mediated by polycystin 2, a distant member of the TRP superfamily, might be one of the primary events in the establishment of left-right asymmetry in early vertebrate embryogenesis (McGrath et al., 2003). In cell culture experiments, TRPV2 channels are known to undergo translocation to the plasma membrane from an intracellular pool, following stimulation with insulin-like growth factor 1 (Kanzaki et al., 1999), which suggests a role for Ca^{2+} influx through TRP channels during development.

TRP channels and human disease

Four members of the TRPM family have been implicated in human diseases, although in no case is the functional link between channel activity and the disease process clearly known. Transcript levels of TRPM1 have been inversely correlated with the metastatic potential of cutaneous neoplastic lesions (Duncan et al., 2001) and TRPM8 levels are elevated in a number of different primary tumour tissues (Tsavaler et al., 2001). However, it is unclear whether TRPM protein levels or TRPM function are altered in these scenarios or whether changes in TRPM1 transcripts are a secondary downstream effect of other primary factors contributing to metastatic potential. Recent work has shown that the gene affected in mucolipidosis type IV, a developmental neurodegenerative disorder, is a distantly related member of the TRP superfamily (Sun et al., 2000). Mutations in polycystin 2 and polycystin 1, a protein required for the function of PKD2, result in polycystic kidney disease(Mochizuki et al., 1996).

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