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Transient receptor potential channels: current perspectives on evolution, structure, function and nomenclature

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The transient receptor potential superfamily of ion channels (TRP channels) is widely recognized for the roles its members play in sensory nervous systems. However, the incredible diversity within the TRP superfamily, and the wide range of sensory capacities found therein, has also allowed TRP channels to function beyond sensing an organism's external environment, and TRP channels have thus become broadly critical to (at least) animal life. TRP channels were originally discovered in *Drosophila* and have since been broadly studied in animals; however, thanks to a boom in genomic and transcriptomic data, we now know that TRP channels are present in the genomes of a variety of creatures, including green algae, fungi, choanoflagellates and a number of other eukaryotes. As a result, the organization of the TRP superfamily has changed radically from its original description. Moreover, modern comprehensive phylogenetic analyses have brought to light the vertebrate-centricity of much of the TRP literature; much of the nomenclature has been grounded in vertebrate TRP subfamilies, resulting in a glossing over of TRP channels in other taxa. Here, we provide a comprehensive review of the function, structure and evolutionary history of TRP channels, and put forth a more complete set of non-vertebrate-centric TRP family, subfamily and other subgroup nomenclature.

1. Introduction

Transient receptor potential (TRP) channels typically share six transmembrane segments and form ion channels with varying cation selectivity [1]. TRP channels are gated by a wide variety of mechanisms and stimuli (including thermal, mechanical and chemical), and function in a plethora of systems, chiefly as signal transducers. These proteins have diversified greatly over the course of evolution, acquiring differing domain arrangements, shifting modality specificity, and being recruited into various tissue types, from renal to neural.

The explosion of interest in TRP channels over the last two decades has resulted in a radical restructuring of the superfamily from its original conception. Current evidence supports nine animal TRP families [1–3]: TRPP (polycystin or polycystic kidney disease), TRPML (mucolipin), TRPA (ankyrin), TRPV (vanilloid), TRPVL (vanilloid-like), TRPC (canonical), TRPN (nompC, or no mechanoreceptor potential C), TRPM (melastatin) and TRPS (soromelastatin) (figure 1). TRP channels, however, are widely expressed across eukaryotic taxa [1–11]. Here, we provide an inclusive overview of TRP channels, focusing on their evolution and familial organization.

2. On the early evolution of transient receptor potential channels

At the highest level, TRP channels are divided into two major groups [1,12]: Group 1 (TRPA, TRPM, TRPN, TRPS, TRPV and TRVL) and Group 2 (TRPP and TRML, and possibly TRPY/TRPF). Animals, choanoflagellates, apusozoans,
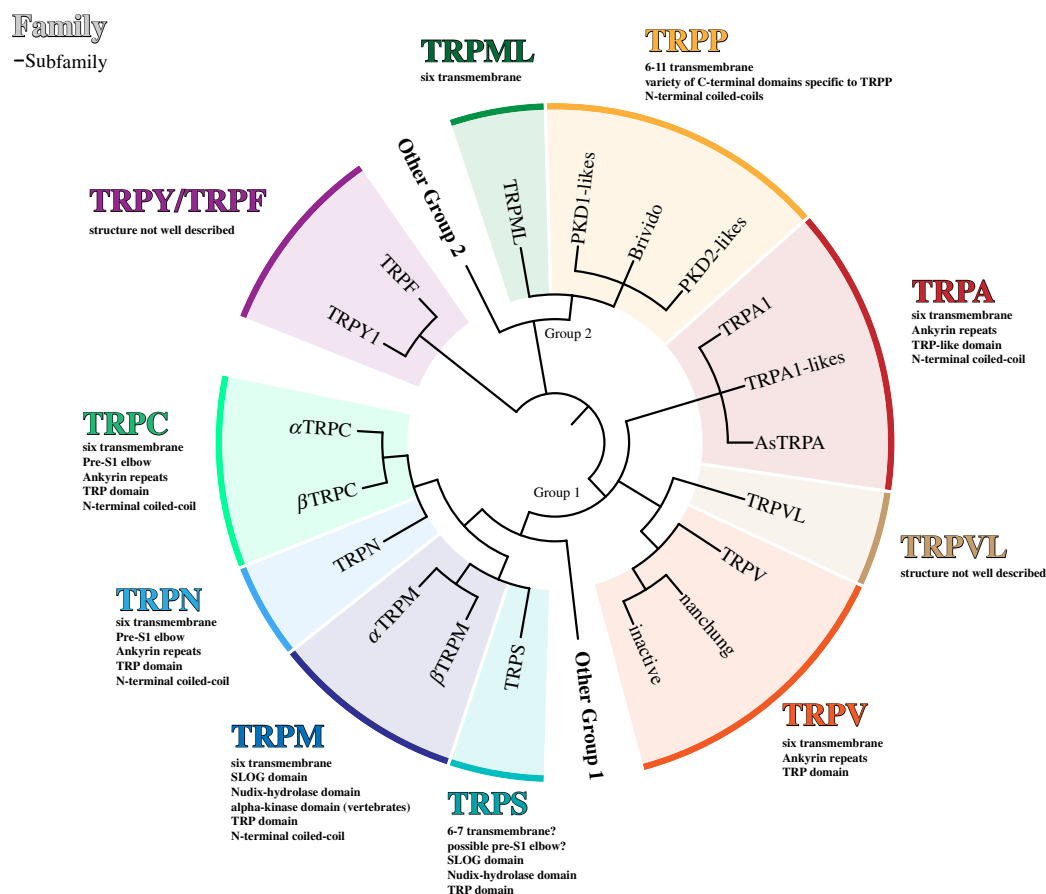
Figure 1. Current view of the relationship between TRP families (bold large) and subfamilies (at tree tips). For detailed family/subfamily/subgroup phylogenies and structural models, see electronic supplementary material, figures S1–S9. (Online version in colour.)

alveolates and green algae have representatives in both Group 1 and Group 2 (figure 2) [3,4,14,15]. Given that TRP channels have been described in a variety of eukaryotes, and as there is no evidence of TRP channels in either Archaea or Bacteria, TRP channels probably developed into their recognizable form early in eukaryote evolution.

Despite lack of extensive cross-kingdom phylogenetics, much of the literature suggests that the root is between Group 1 and Group 2, where the branch is typically longest [3,11]. Given the distribution of TRP channels across eukaryotic taxa (figure 2), the most parsimonious hypothesis is that this split pre-dates the bikont–unikont split. It is worth noting that others have found the root nearer the TRPP–TRPML split, but not with high branch confidence [16].

(a) Group 1 diversification

The currently recognized Group 1 families (TRPA, TRPC, TRPM, TRPN, TRPS, TRPV and TRPVL) almost certainly pre-date the Cnidaria–Bilateria split (earlier than 750 Ma) [2,3]. Many also probably pre-date the emergence of animals, as choanoflagellate have at least TRPM, TRPC and TRPA [3,6]. Algae also have channels which resemble Group 1 channels, one which is postulated to be a TRPV [14], and others which form a sister clade to the clade containing TRPN, TRPM and TRPC (and TRPS, though this analysis pre-dates the discovery of TRPS; figure 2, Other Group 1) [4]. There is some evidence that TRPM pre-dates the bikont–unikont split, as *Lingulodinium polyedra* (Alveolata) has two channels which are similar to TRPM [9].

(b) Group 2 diversification

In Group 2, evidence supports an early split between TRPML and TRPP, as at least animals, amoebozoans and alveolates express both (other eukaryotes, including fungi, may only express one or the other) [1–11]. There is some evidence of earlier splits which resulted in TRP families that were lost in many taxa but remain present in algae and alveolates (figure 2, Other Group 2) [4,9]. Assuming the evidence supporting Other Group 2 channels is veridical, and assuming the hypothesis that the TRP channel root is between Group 1 and Group 2, evidence currently supports that the Other Group 2-TRPML/ TRPP split, and the subsequent TRPML–TRPP split, occurred in a common eukaryote ancestor.

3. TRP families

(a) TRPA: ankyrin

TRPA (A for ankyrin) channels are named for their characteristic ankyrin repeats, a sequence motif broadly present across proteins of all types [1,2,17]. The TRPA family has been divided into three major subfamilies: TRPA1, TRPA1-like and 'basal' (here called AsTRPA; electronic supplementary material, figure S2A) [3,18–21].

TRPA1 and the related genes described here encode six-transmembrane segment spanning ion channels which assemble as homotetramers (electronic supplementary material, figure S2B). A number of highly conserved ankyrin repeats make up the bulk of the N-terminal domain, while
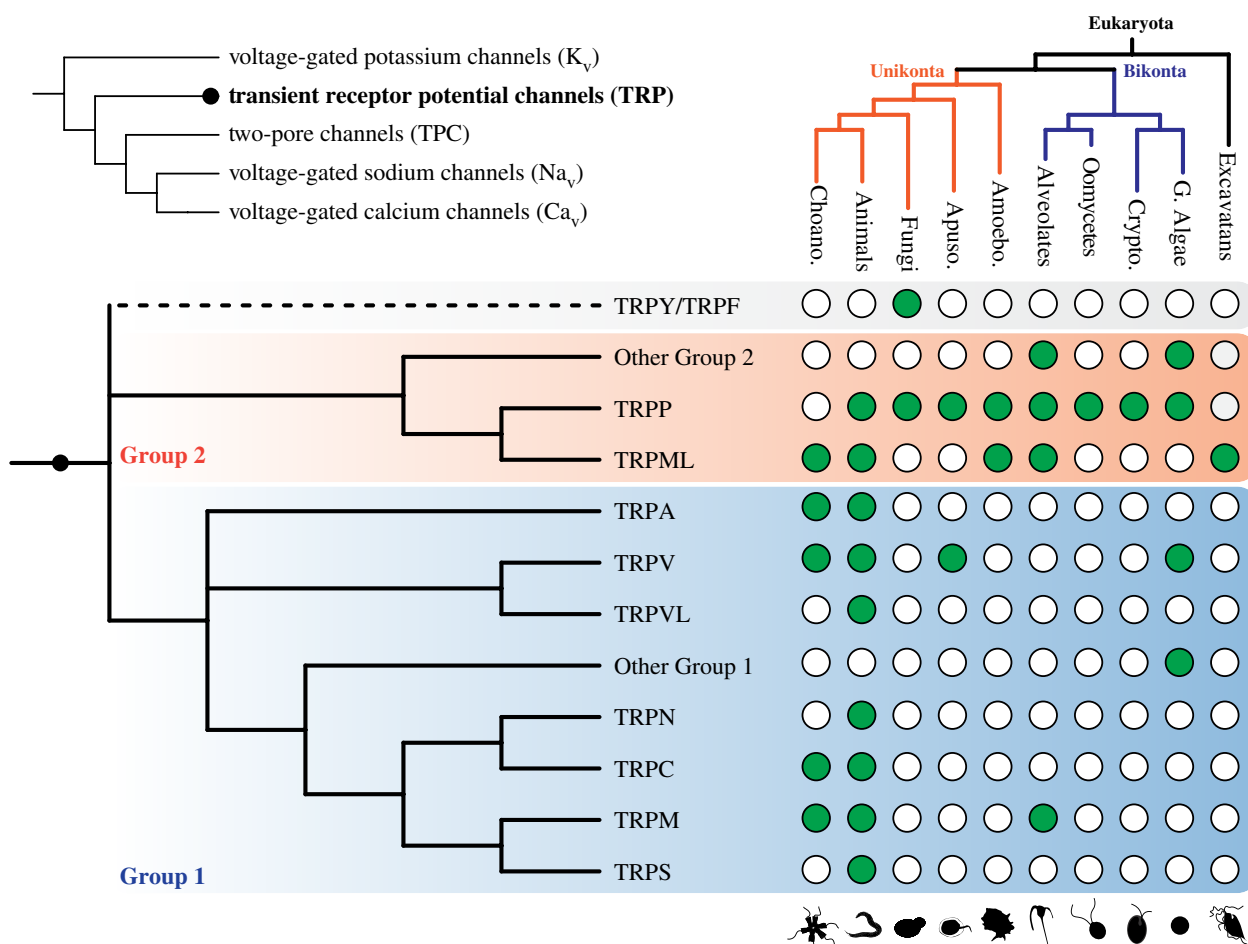
Figure 2. Consensus phylogeny and distribution of the TRP superfamily. Top left shows TRP in the voltage-gated ion channel clade [13]. Taxa shown here: animals, choanoflagellates (Choano.; unicellular flagellates closely related to animals), fungi, apusozoans (Apuso.; flagellate eukaryotes), amoebozoans (Amoebo.; amoeboid eukaryotes), alveolates (including dinoflagellates), oomycetes (fungus-like eukaryotes), cryptophyte and green algae (Crypto. and G. Algae) and excavatans (basal eukaryotes). Filled circles indicate that the family to the left has been proposed to be present in the taxon above; blank circles indicate no evidence for that family in the indicated taxon [1–11]. The dashed line for TRPY/TRPF indicates that its placement is especially uncertain. (Online version in colour.)

the C-terminal domain (CTD) contains a coiled-coil, and a so-called TRP-like domain critical to ligand binding [22].

Initially associated with human fibroblasts [23], TRPA1 was soon identified as a temperature-activated TRP channel [24,25]. It is now known to be polymodal, sensing hot and cold [25,26], mechanical perturbations [27], hypoxic water [28], electrophilic chemicals [29–31], cinnamaldehyde [32], cannabinoids [31], menthol [33], icilin [34], reactive oxygen species [35] and endogenous molecules associated with tissue damage [36], among many others [37].

Some of these functions are conserved across species, and therefore may be inherited from a common TRPA1 ancestor [18,19]. For example, cysteines critical to AITC sensing are thought to be conserved from such an ancestor [19]. By contrast, TRPA1 is required for menthol-evoked behaviour in *Drosophila*, but it is not directly gated by it, nor are amino acids critical to mammalian TRPA1 menthol sensitivity well conserved [18,38].

A variety of other channels phylogenetically similar to TRPA1—here referred to as TRPA1-like—have been found in cnidarians, ecdysozoans (protostomes which notably grow by molting), and lophotrocozoans (a major spiralian clade) [18,39]. The function of these channels is less well understood.

The 'basal' subfamily includes several subgroups restricted to arthropods (painless, pyrexia, water witch, HsTRPA, TRPA5 and TRPApw) [40–44]. We suggest that the use of

'basal' is uninformative, as arthropods are not informatively basal with respect to say, vertebrates, nor is this subfamily obviously basal in the TRPA family. Given that this clade and the subgroups therein appear to be restricted to arthropods, here they will be referred to as arthropod-specific TRPAs (AsTRPA). AsTRPA channels participate in similar processes as TRPA1. For example, painless, pyrexia and HsTRPA participate in high-temperature sensing, pointing to a shared ancestral function [40,41,44], while water witch functions in hygro- and sound detection [42,45].

(b) TRPC: canonical

Drosophila trp, the namesake of the TRP channel family, was first described by Cosens & Manning in 1969 when they observed that *trp* mutant flies behaved in a T-maze as if they were blind [46]. *trp* was eventually characterized as an ion channel critical to phototransduction by Montell & Rubin in 1989 [47], and independently shortly thereafter by Wong *et al.* [48]. This was undoubtedly the beginning of the modern study of TRP channels.

trp now belongs to the TRPC family (C for canonical). Here, we propose that the metazoan TRPC family is subdivided into two distinct subfamilies, αTRPC and βTRPC (electronic supplementary material, figure S3A). Although TRPC channels have been phylogenetically well characterized, this does not

extend to non-arthropod protostomes nor non-protostome invertebrates [2,3,20,21], and thus here, only vertebrate paralogues and a broad protostome clade are shown (electronic supplementary material, figure S3B). The proposed α-β distinction is phylogenetically well supported in the literature cited above, but has not been explicitly named. Here, this distinction only serves to illustrate that vertebrate and non-vertebrate TRPCs are not all orthologous.

TRPC channels have a relatively archetypal TRP structure (electronic supplementary material, figure S3B) with the addition of a hydrophobic segment called the Pre-S1 elbow. The Pre-S1 elbow spans only half the plasma membrane, allowing the protein to curl back intracellularly, and is thought to participate in lipid binding [49–51]. The general features of TRPC channels also include a C-terminal TRP domain, a coiled-coil and N-terminal ankyrin repeats [49–51]. Put relatively broadly, TRPC channels typically function as part of the phospholipase C signal transduction pathway (reviewed recently and extensively by Wang *et al.* [52]).

(c) TRPM: melastatin

TRPM (M for melastatin) was named after melastatin/MLSN1 (now known as TRPM1), a transcript correlated with melanoma aggressiveness [53,54]. TRPM channels typically form archetypal six-transmembrane ion channels with a highly conserved N-terminal SLOG domain (of relatively unknown function), a C-terminal TRP domain (shared with TRPN, TRPC, TRPS and TRPV), and a variable CTD, which may include a Nudix-hydrolase-like domain and/or an alpha kinase (electronic supplementary material, figure S4B) [1,2,55–57].

Canonically, TRPM had been said to have eight distinct subfamilies: TRPM1–TRPM8. However, more recent phylogenetic analyses have made it clear that TRPM1–8 are restricted to vertebrates, and that the 1–8 identifiers do not accurately reflect the makeup of the TRPM family in other organisms [2,18,58]. The recently reorganized TRPM family is divided into the αTRPM and βTRPM subfamilies (electronic supplementary material, figure S4A), their split having occurred sometime before the Cnidaria–Bilateria split (greater than 750 Ma). Most bilaterian taxa studied, except Tardigrada, have TRPM channels, typically within both subfamilies [2].

At least among mammals, most TRPMs serve as Ca^{2+}-permeable sensors of various stimuli [59]. There is some evidence that TRPM channels share functional capacity across the α-β divide. For example, both vertebrate TRPM8 (a βTRPM) and *Drosophila* Trpm (αTRPM) function in cold and menthol sensing [18,60–65]. In vertebrates, the αTRPMs TRPM6 and TRPM7 evolved so-called chanzyme activity, by which they function as both Mg^{2+} channels and protein kinases; there is also evidence that cnidarian and choanoflagellate TRPMs function as chanzymes via their linked Nudix domains, and it has thus been suggested that this is an ancestral function of TRPM proteins [66,67].

A third putative subfamily, TRPMc (formerly called TRPMm), has been found in some arthropods and possibly cnidarians; however, its presence and position are inconsistent and phylogenetically unstable [2,20,21].

(d) TRPML: mucolipin

The TRPML family (ML for mucolipin; originally called MCOLN) is named due to its causative role in mucolipidosis type IV, a neurodegenerative disorder [68,69]. Most invertebrates have a single TRPML, whereas vertebrate TRPML expanded into TRPML1–3 (electronic supplementary material, figure S5) [3,70]. Cnidarians, sponges, placozoans and choanoflagellates also have TRPMLs, but their phylogenetic position has been less well described [3].

In mammals and insects, TRPML1 and trpml, respectively, are thought to be localized to late-endosomes and lysosomes [71–73]. By contrast, mammalian TRPML2 and TRPML3 are thought to localize to the cell plasma membrane, much like other canonical TRP channels, where they function in regulation of the endosomal pathway and innate immunity [74–80]. TRPML structure and physiology is best understood in mammals [81] and remains otherwise understudied.

(e) TRPN: No mechanoreceptor potential C

TRPN (N for nompC, short for no mechanoreceptor potential C) was named after the mutant phenotype in *Drosophila*, which consists of defects in mechanosensory transduction [82]. Despite the occurrence of several independent whole-genome duplications across bilaterian taxa, only a single TRPN is predicted to be present in bilaterian genomes [17]. There is no evidence of TRPN in placozoans, comb jellies, or choanoflagellates, leading to the suggestion that TRPN emerged in a common cnidarian–bilaterian ancestor after animals emerged [3,17]. However, the most closely related TRP family is typically thought to be TRPC, and choanoflagellates are thought to have a TRPC [2,3,17]; this would suggest that TRPC and TRPN split before animals emerged, and that TRPN was lost in the taxa indicated above.

TRPNs form archetypal TRP channels–six-transmembrane spanning units, with a Pre-S1 elbow, which organize as homotetramers (electronic supplementary material, figure S6) [83]. TRPN channels have remained remarkably unchanged over the course of evolution, typically containing 28–29 ankyrin repeats and a TRP domain, leading to the hypothesis that these structures are critical to protein function [17]. It has since been demonstrated that ankyrin repeat-microtubule tethering is critical to TRPN function [84]. TRPNs primarily participate in mechanosensation [82,85–90]. *Drosophila nompC* is also required for larval cold nociception, although its mechanisms are unknown [65].

(f) TRPP: polycystin

TRPP (P for polycystin) is named due to the causative role of *PKD1* and *PKD2* in polycystic kidney disease [91,92]. TRPP channels are organized into three subfamilies: PKD1-like, PKD2-like and the brividos (electronic supplementary material, figure S7A) [93,94]. PKD1-likes are relatively unique in that they do not encode canonical 6-transmembrane ion channels (electronic supplementary material, figure S7B) [95]. Although they share sequence homology in their transmembrane segments, PKD1-likes are large genes encoding proteins with 11 transmembrane domains and many extracellular domains, including so-called PKD repeats of unknown function [93,96–98].

Within the PKD2-likes, the PKD2, PKD2L1 and PKD2L2 subdivisions are not representative of all eukaryotes. For example, *Drosophila* [99], *C. elegans* [100] and cnidarian [3,17,101] PKD2-likes phylogenetically sort independent of vertebrate PKD2, PKD2L1 and PKD2L2 [93]. This is also the case for channels from non-vertebrate chordate taxa, including but not limited to the tunicate *Ciona intestinalis*; as such, PKD2,

PKD2L1 and PKD2L2 likely differentiated specifically in vertebrates [5].

Insects have three additional TRPP family members, referred to as the brividos, which sort independently [94,102,103]. In current phylogenetic analyses, the brividos form a sister clade to all other PKD2-likes, yet brividos have only been noted in insects [102,103]. Given that insects also have PKD2-likes, it follows that the brivido-PKD2 split occurred before the protostome–deuterostome split (approx. 550 Ma) and was lost in most bilaterian taxa except insects. This, however, has not been formally explored in the literature. Moreover, neither non-animal PKDs nor non-bilaterian PKDs have been phylogenetically characterized alongside the brividos.

With respect to function, and like many of their cousins, TRPPs are multimodal and most well understood in mammals [81]. Together, mammalian PKD2- and PKD1-like proteins interact via their shared coiled-coil and tetragonal opening for polycystin (TOP) domains, forming heteromeric mechanosensory units [104,105]. This mechanosensitive unit most notably functions in cilia-dependent mechanosensation in mammalian renal tissues [106]. This mechanosensory function extends to other species as well, although it remains less studied [5,65]. In Drosophila, Pkd2 and the brividos also function in cold sensing [65,94,107]. Yeast likely encode 2 TRPPs, called pkd2 and Pkd2p, which function to regulate cell shape, cell wall synthesis, and cell separation during cytokinesis [108,109].

(g) TRPS: soromelastatin

TRPS (S for soromelastatin; soro-, sister) is the most recently discovered TRP family, and was named due to its position as a sister group to TRPM [2]. TRPS is relatively widely expressed among bilaterians, yet is among the most under-studied of the TRP families, perhaps because it is not present in vertebrates or insects. While there is only a single major TRPS clade when considering metazoans as a unit (electronic supplementary material, figure S8A), TRPS has independently expanded among molluscs, nematodes, tardigrades, myriapods (including centipedes) and chelicerates (including arachnids) [2]. The function of TRPS, however, remains mostly mysterious. Only a single member has been functionally characterized: C. elegans ced-11, which encodes a Ca^{2+} channel which participates in apoptosis [110].

Outside of domain identification via sequence homology, the structure of TRPS channels has not yet been elucidated (and thus is shown here via a simplified model; electronic supplementary material, figure S8b) [2]. Transmembrane predictions of ced-11 indicate that there are seven transmembrane domains; one might, therefore, hypothesize that they are similar in structure to TRPN and TRPC, in that the 'extra' hydrophobic cluster may be a pre-S1 elbow-like structure (perhaps indicating this is a conserved feature from a common N/C/M/S ancestor). Like TRPM channels, TRPS channels have SLOG, Nudix-hydrolase and TRP domains.

(h) TRPV and TRVL: vanilloid and vanilloid-like

TRPV (V for vanilloid) is named due to TRPV1's sensitivity to two vanilloid compounds, capsaicin and resiniferatoxin. TRPV genes encode canonical 6-transmembrane segment spanning ion channels characterized by N-terminal ankyrin repeats and a C-terminal TRP domain (electronic supplementary material, figure S9B) [111,112], their structure and gating mechanisms most well understood in mammals [113].

One of two Drosophila TRPV gene loci was first described in 1977 by W. D. Kaplan, via the inactive (iav) mutation [114]. Over the course of the next two decades, the iav mutation was associated with courtship and locomotion abnormalities [115–117], and an aberrant response to cocaine [118]. Nearly 30 years later, iav was characterized as one of two Drosophila TRPV channels, alongside nanchung [119,120]. TRPVs, however, were first described as channels in 1997: in mammals (VR1, now TRPV1) [121], and in C. elegans (OSM-9) [122].

The TRPV family is divided into three distinct sub-families (electronic supplementary material, figure S9A), here named the TRPV subfamily, nanchung and inactive. Phylogenetics suggests that placozoans (a basal animal phylum) and cnidarians have both inactive and nanchung, indicating that the TRPV, nanchung, and inactive clades all substantially pre-date the emergence of vertebrates [3]. Moreover, these same analyses indicate that choanoflagellate TRPV channels phylogenetically cluster more closely to mammalian TRPV than to inactive/nanchung [3]. It therefore appears that, in bilaterians, TRPV was lost in an early protostome ancestor, while nanchung and inactive were lost in an early deuterostome ancestor.

With respect to function, TRPV channels diversified greatly over the course of evolution. TRPV channels serve as temperature, chemical and osmotic sensors in vertebrates [121,123–128], chemical and mechanical sensors in nematodes [122], and hygro- and mechanosensors in insects [42,119].

A sister family to TRPV, called TRPVL, was proposed via phylogenetics by Peng et al. in 2015, albeit its presence is restricted to cnidarian and annelid genomes [3].

(i) TRPY and TRPF: the fungus-specific TRP channels

TRPY1 was the first of the fungus-specific TRP channels to be discovered [10], a group that has since been expanded to include TRPF1–5 [8]. While a detailed structure of these channels has not been elucidated, TRPY1 is thought to form an intracellular Ca^{2+} channel which gates in response to cytoplasmic Ca^{2+}, osmotic shock, mechanical deformations and aromatic compounds [10,129–135]. In yeast, TRPY1 is expressed in the vacuole [10]. Like TRPY1, TRPF genes encode intracellular channels. They, however, do not gate Ca^{2+} in response to osmotic shock, and it is unknown what functions TRPFs actively participate in [8].

Early phylogenetic evidence supported TRPY as a distinct group outside the canonical Group 1/Group 2 divide [7]. While recent analyses agree that TRPY may have diversified specifically in fungi, they instead suggest that TRPY is likely to be a sister group to TRPP, which also has yeast constituents [11]. While we have left the position of TRPY/TRPF unresolved with respect to Group 1 and Group 2 (figure 2), the hypothesis that they form a sister group to TRPP is parsimonious with the presence of various non-TRPP channels in non-fungal genomes. The position of TRPF channels in the wider TRP phylogeny has not been well resolved; they are likely to be very closely related to TRPY, and therefore to sort in the same position [8].

4. Future directions

Despite many recent advances in our understanding of TRP evolution, much of the relationships between TRP channels remains to be uncovered. In short, the phylogenetic independence of some major putative families (e.g. TRPV and

TRPVL) and many subfamilies (e.g. TRPMc) continue to be relatively underexplored. Moreover, many subfamilies named herein have not been extensively or explicitly characterized in the literature. Using TRPC as an example, this is true despite the family containing the namesake of TRP channels themselves.

Resolution, however, need not only come via large-scale phylogenetic analyses. Functional and structural studies are also required, as the subdivision of clades absent structural or functional differences would be of more limited use. The ancient nature of many of these subfamilies may in fact be a clue that they are functionally divergent, and we should thus not assume that the characterization of a single family member is necessary generalizable to others. Functional and structural work will also be key to understanding the nature of ancestral TRP channels, and their role in ancient nervous systems. Some have hypothesized, for example, that TRPMs and TRPAs functioned in ancestral bilaterian nervous systems in similar ways to modern nervous systems [18,19]. Short of continued study, these remain hypotheses chiefly grounded in the conservation of critical amino acids.

Continued study is also required to elucidate unique properties TRP channels have as compared to their closest cousins (e.g. voltage-gated Ca^{2+}, K^+ and Na^+ channels) [13] (figure 2)— properties like low voltage sensitivity [136]—which can be used to better understand the evolution and diversification of the broader voltage-gated ion channel clade.

Given how ancient most of these TRP families are, and the widespread nature of their expression patterns and functions, continued study of TRP channels also stands to reveal much more than information relevant to nervous systems. This is in part because TRP channels themselves—and perhaps their sensory capacity—pre-date the nervous system, which is so often credited as the basis for behaviour. It is therefore possible our view should be, in a sense, smaller—that we might consider TRP channels among the basic, necessary components which facilitated the evolution of complex behaviours and physiology; the components which made the nervous system, complex signaling mechanisms in the kidney, and like systems, viable.

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