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Review

Schistosome TRP channels: An appraisal

Swarna Bais, Robert M. Greenberg*

Department of Pathobiology, School of Veterinary Medicine, University of Pennsylvania, 3800 Spruce Street, Philadelphia, PA, 19104, USA

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ABSTRACT

Ion channels underlie electrical excitability in cells and are essential for a variety of functions, most notably neuromuscular and sensory activity. They are also validated targets for a preponderance of approved anthelmintic compounds. Transient receptor potential (TRP) channels constitute an ion channel superfamily whose members play important roles in sensory signaling, regulation of ion homeostasis, organellar trafficking, and other key cellular and organismal activities. Unlike most other ion channels, TRP channels are often polymodal, gated by a variety of mechanisms. Furthermore, TRP channels fall into several classes or subtypes based on sequence and structure. Until recently, there had been very little investigation of the properties and functions of TRP channels from parasitic helminths, including schistosomes, but that situation has changed in the past few years. Indeed, it is now clear that at least some schistosome TRP channels exhibit unusual pharmacological properties, and, intriguingly, both a mammalian and a schistosome TRP channel are activated by praziquantel, the current antischistosomal drug of choice. With the latest release of the *Schistosoma mansoni* genome database, several changes in predicted TRP channel sequences appeared, some of which were significant. This review updates and reassesses the TRP channel repertoire in *S. mansoni*, examines recent findings regarding these potential therapeutic targets, and provides guideposts for some of the physiological functions that may be mediated by these channels in schistosomes.

1. Introduction

Schistosomiasis is a water-borne neglected tropical disease caused by blood flukes of the genus *Schistosoma*. Estimates of prevalence range from approximately 140 million to over 250 million people globally, with almost a billion at risk (Colley et al., 2014; McManus et al., 2018; LoVerde, 2019). The three main species infecting humans are *S. mansoni*, *S. haematobium*, and the zoonotic *S. japonicum*, which also infects water buffalo and other bovines.

Schistosome infection occurs through contact with free-swimming larval cercariae released into fresh water by intermediate host snails. Cercariae infect the definitive host percutaneously, losing their tails upon penetration of the skin and transforming into schistosomula. Within the definitive host, worms migrate and mature over the next several weeks, eventually establishing residence within the mesenteric venules that drain the intestine (*S. mansoni*, *S. japonicum*) or the venous plexus of the bladder (*S. haematobium*). There, they deposit large numbers of eggs, which are either excreted from the host, continuing the parasite life cycle and disease transmission, or remain within the host, triggering an immunopathological response that includes production of granulomas around the eggs and associated fibrosis.

Schistosomiasis is associated with morbidity that can result in compromised childhood development, damage to tissues (eg, liver, bladder), greater susceptibility to other infectious agents such as HIV, and, in some cases, death (van der Werf et al., 2003; King and Dangerfield-Cha, 2008; Hotez and Fenwick, 2009; King, 2010; Ndeffo Mbah et al., 2013; Colley et al., 2014; Brodish and Singh, 2016). Additionally, *S. haematobium* is associated with increased incidence of bladder cancer and, like the liver flukes *Clonorchis sinensis* and *Opisthorchis verrini*, is classified as a Group I carcinogen by the International Agency for Research on Cancer (Oh and Wilderpass, 2014). A recent report even suggests that malignant transformation of a cestode, *Hymenolepis nana*, can produce abnormal, proliferating tapeworm cells that invade human tissue and resemble human cancer (Muehlenbachs et al., 2015).

Though there are potential candidates (reviewed by Tebeje et al., 2016; LoVerde, 2019), there is as yet no vaccine for schistosomiasis, and as a disease of poverty, infrastructural improvements that might reduce or eliminate disease transmission are difficult to implement. Chemotherapy therefore remains the principal strategy for treating the disease and controlling its spread. Praziquantel (PZQ), the drug of choice, is effective against all schistosome species but is also essentially

* Corresponding author.
E-mail address: rgree@vet.upenn.edu (R.M. Greenberg).

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the only antischistosomal drug currently available (Danso-Appiah et al., 2013; Kramer et al., 2013; Bergquist et al., 2017; Greenberg and Doenhoff, 2017). Reliance on this single drug for a disease affecting hundreds of millions, combined with reports of PZQ-resistance (Day and Botros, 2006; Doenhoff and Pica-Mattoccia, 2006; Wang et al., 2012; Greenberg, 2013) and the well-known limitations of PZQ (Cioli et al., 2014; Greenberg and Doenhoff, 2017) makes the search for alternative therapeutics especially pressing.

Several strategies have been used and various targets interrogated in the search for new or repurposed antischistosomal drugs. Ion channels, which underlie electrical excitability in cells, are validated targets for many current anthelmintic drugs, and as such represent potentially fertile ground for exploration. Some of the anthelmintics that disrupt normal parasite ion channel activity include ivermectin and other macrocyclic lactones, pyrantel, levamisole, monepantel, emodepside, piperazine, derquantel, tribendimidine, and probably PZQ itself (Wolstenholme, 2011; Epe and Kaminsky, 2013; Greenberg, 2014; Park et al., 2019). Indeed, there is no other class of helminth targets that has been exploited as extensively by current anthelmintics.

Ion channels, protein complexes embedded in plasma and organellar membranes, form gated, ion-selective pores through those membranes. Ions flow down their electrochemical gradients through these pores in a regulated manner, into or out of the cell (or organelle). Ion channels can be activated (or inactivated) by changes in membrane potential (voltage-gated), specific neurotransmitters (ligand-gated), or a variety of factors such as pH, mechanical stress, intracellular messengers and ions, and temperature, among others (Zheng and Trudeau, 2015; Alexander et al., 2017a, 2017b, 2017c). Channel function can also be modulated by toxins, drugs, and intracellular and extracellular signals. Dysfunctional ion channel activity can generate major disruption of an organism's neuromuscular system (as well as of other cells and tissues), a feature exploited by the many pesticides and anthelmintics that target ion channels. Furthermore, a hugely diverse array of some of the most potent natural toxins in existence target ion channels (Kalia et al., 2015). Ion channels are also widely exploited targets in human medicine, particularly for anesthesia and cardiovascular and neurological conditions (Bagal et al., 2013), and dysfunctional ion channels (channelopathies) are associated with several genetic and acquired diseases in humans (Ashcroft, 2006; Imbrici et al., 2016).

Despite the fact that ion channels are validated anthelmintic targets, only a few helminth ion channels have been subjected to any detailed study. One group of helminth ion channels that has recently come under scrutiny, particularly in the platyhelminths, is the transient receptor potential (TRP) channel superfamily. TRP channels form a large, highly diverse branch within the voltage-gated-like “chanome” (Yu and Catterall, 2004). TRP channels are categorized into subfamilies (TRPC, TRPV, TRPA, TRPM, TRPP, TRPN, TRPML) based on structural homology (Venkatachalam and Montell, 2007; Nilius and Owsianik, 2011; Peng et al., 2015). TRP channels are typically non-selective cation channels, and thus permeable to Ca^{2+}, though some mammalian TRP channels (*eg*, Ca^{2+}-activated TRPM4 and TRPM5) are notably Ca^{2+}-impermeable (Launay et al., 2002; Liman, 2014).

Mammals have 25–30 TRP channel isoforms that fall within 6 subfamilies (TRPC, TRPV, TRPA, TRPM, TRPP, TRPML). The different subfamilies contain variable numbers of subtypes. Thus, humans have a single TRPA subtype, but 8 TRPM subtypes. *S. mansoni* contains 15 predicted TRP channel genes representing 5 subfamilies (TRPC, TRPA, TRPM, TRPP, TRPML). Interestingly, neither schistosomes nor other parasitic platyhelminths appear to have genes encoding TRPV channels. In contrast, the genomes of free-living platyhelminths do contain genes predicted to encode TRPV channels (Prole and Taylor, 2011; Wolstenholme et al., 2011; Bais and Greenberg, 2016, 2018). The significance of this difference between the parasitic and free-living platyhelminths is unknown, and whether this disparity is absolute or elastic remains to be determined as more platyhelminth genomes become available.

TRP channels play key physiological roles in a wide variety of critical functions, most notably sensory signaling. Thus, they act as transducers for a broad range of cellular and environmental cues. These include cellular messengers (Ca^{2+}, cyclic nucleotides, membrane lipids, osmotic pressure, phosphorylation) and environmental signals such as heat, light, stretch, and chemical compounds, including nociceptive and inflammatory compounds (Venkatachalam and Montell, 2007; Gees et al., 2010; Zheng, 2013; Hoffstaetter et al., 2018). Unlike most other ion channels, TRP channels are often polymodal, meaning that they are activated by a diverse set of different, seemingly unrelated inputs. Accordingly, a single TRP channel can sense and respond to temperature, stretch, pH, voltage, and specific chemical signals, either directly or indirectly (Hilton et al., 2015).

Interestingly, changes in TRP channel expression are associated with cancer and some TRP channels appear to have oncogenic properties when expression or function is dysregulated (Lehhen'kyi and Prevarskaya, 2011; Nilius and Szallasi, 2014; Shapovalov et al., 2016; Prevarskaya et al., 2018; Canales et al., 2019; Wong et al., 2019). Thus, in addition to some TRP channels exhibiting altered expression in cancer cells (and perhaps being able to serve as markers of the transformed state), there is accumulating evidence that aberrant Ca^{2+} signaling through TRP channels or altered Ca^{2+}-independent TRP channel function (eg, interaction with cytoskeletal components), can modify cell survival, proliferation, and migration, and may influence tumor initiation and progression (Vrenken et al., 2016; Fliniaux et al., 2018; Canales et al., 2019; Petho et al., 2019). Furthermore, various studies have revealed an association between TRP channel expression levels and clinical outcomes of various cancers (Park et al., 2016; Fels et al., 2018), and several miRNA/TRP channel pairs appear to play important roles in tumor biology (reviewed by Santoni et al., 2020).

Schistosomes and other helminth parasites themselves exhibit properties in common with cancer cells (Ashall, 1986; Doenhoff et al., 1990; Oliveira, 2014; Narasimhan et al., 2018). Thus, like cancer cells, schistosomes and other parasites act as “selfish” entities, hijacking and manipulating the regulatory signaling mechanisms of their hosts. They evade host immune responses, rely on simple methods of energy uptake, are dependent on proteases to facilitate migration, survival, and growth, and exploit host machinery for their own growth and development. Indeed, drugs developed against cancer can show antiparasitic activities, and vice-versa (Oliveira, 2014). It is tempting to speculate that parasite TRP channels may have unusual characteristics that could provide insights into the role of these channels in cancer cells and perhaps normal development as well.

TRP channels are also considered promising targets for treatment of several other diseases and syndromes (Nilius and Szallasi, 2014). These include pain and inflammation, itch, cough, asthma, pulmonary edema, central nervous system disorders, and cardiovascular disorders (Yue et al., 2014; Moran, 2018). TRP channels have also been proposed as candidate targets for drugs that act against helminth and other parasitic infections (Wolstenholme et al., 2011; Prole and Taylor, 2013; Bais and Greenberg, 2016, 2018). Indeed, a *S. mansoni* TRP channel ($SmTRPM_{PZQ}$) has recently been shown (Park et al., 2019) to be activated stereoselectively by PZQ (see below).

The release of an updated version (v.7) of the *S. mansoni* genome database (https://parasite.wormbase.org) improved the assembly and annotation of the genome over previous versions. In so doing, it also generated many changes in predicted *S. mansoni* genes and gene products, including TRP channel genes. Some of these changes were minor or relatively trivial, but others produced major alterations in TRP channel amino acid sequences, new TRP channel variants, and revised accession numbers. As a consequence, the lists and phylogenetic analyses of predicted *S. mansoni* TRP channels in previous reviews (Prole and Taylor, 2011; Wolstenholme et al., 2011; Bais and Greenberg, 2016, 2018) are no longer accurate. Furthermore, published conclusions based on functional studies of then-current predicted sequences (Bais et al., 2018) need to be reassessed.

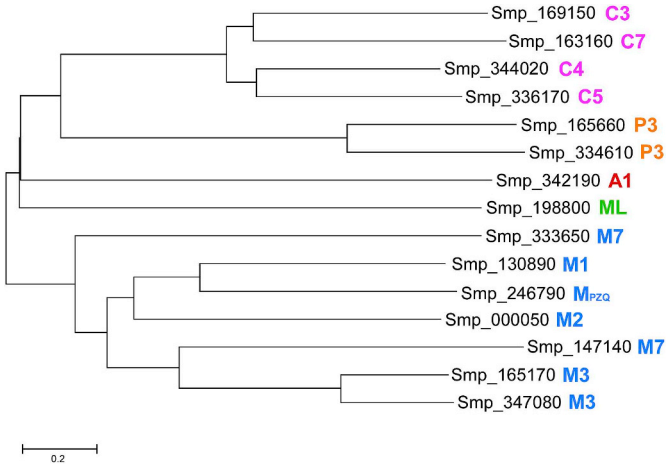

Fig. 1. Phylogenetic tree of predicted *S. mansoni* TRP channels. Neighbor-joining tree of predicted *S. mansoni* TRP channel protein sequences, shown with closest human TRP channel subtype (color coded by subfamily). As in previous analyses, there are no predicted TRPV-like sequences. Smp_246790 (*Sm*.TRPM$_{PZQ}$) clusters more closely with TRPM1 channels, although it has been shown to be homologous to TRPM2 channels (Park et al., 2019), highlighting the uncertainty of the subtype classifications. For the sake of simplicity, only a single predicted splice variant is shown for genes predicted to contain multiple variants (see Table 1). Tree was derived using alignment and tree building software as implemented in MEGA X (Kumar et al., 2018). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

2. Changes in predicted TRP channel representatives and TRP channel sequences in *Schistosoma mansoni*

An updated examination of *S. mansoni* genes predicted to encode TRP channels is presented in Fig. 1. These results were obtained by interrogating the current *S. mansoni* database (https://parasite.wormbase.org/Schistosoma_mansoni_prjea36577/Info/Index/; https://www.genedb.org/#/species/Smansoni) with text terms ("TRP" and "transient receptor potential") and by using BLAST searches with either mammalian TRP channel sequences or previous versions of predicted *S. mansoni* TRP channel sequences as queries. In order to assign the *S. mansoni* TRP-like sequences into sub-families and subtypes, hits were used as queries against the protein databases of mammals, and specifically *Homo sapiens*, with the designation for the *S. mansoni* sequences based on the highest scoring hits. Although the predicted *S. mansoni* TRP channel sequences separate clearly into TRP channel sub-family designations (*eg.*, TRPC, TRPA, etc.), subtype designations within each sub-family (*eg.*, TRPM1, TRPM2, etc.) are less robust, and should be viewed with circumspection. Indeed, the only functional studies reported for schistosome TRP channels are for two TRPA1-like sequences (Bais et al., 2018), one from *S. mansoni* (SmTRPA; Smp_342190, previously known as Smp_125690, KT266713) and one from *S. haematobium* (ShTRPA; KGB35426.1), and for the *S. mansoni* PZQ-responsive SmTRPM$_{PZQ}$ (Smp_246790) sequence (Park et al., 2019). Nonetheless, as the phylogenetic analysis of the *S. mansoni* TRP channel sequences shows (Fig. 1), those channels designated as particular subtypes largely tend to cluster together.

As Fig. 1 and Table 1 show, we again identified 15 predicted *S. mansoni* TRP channel genes in the revised genome database. Though the number of genes is the same as previously reported (Bais and Greenberg, 2016), two former TRPM2-like genes (Smp_161630, Smp_161640) are now consolidated into the single SmTRPM$_{PZQ}$ gene (Smp_246790), which appears to cluster with TRPM1-and TRPM2-like genes (Fig. 1). That net loss of one gene is offset by the identification of a second, previously unreported, SmTRPP3 (polycystic kidney disease 2-like 1 protein)-like sequence (Smp_334610), which brings the total back up to 15.

Prior to the release of version 7 of the *S. mansoni* genome, we reported that SmTRPA exhibits novel pharmacological sensitivities that appear to be a mixture of those found for mammalian TRPA and TRPV1 channels (Bais et al., 2018; Bais and Greenberg, 2018). Given that schistosomes and other parasitic platyhelminths lack genes for TRPV-like channels, which are found in free-living platyhelminths, we speculated that schistosome TRPA channels may have coopted functional and pharmacological properties normally associated with TRPV channels. The SmTRPA sequence predicted in the newer version of the genome (Smp_342190) adds ~200 amino acids to the N-terminus of the sequence we characterized previously (Bais et al., 2018); otherwise it is identical. Using RT-PCR, we have confirmed that a mRNA with this new sequence information is indeed expressed in *S. mansoni* adults (though that does not preclude the possibility that the shorter version is also expressed). As a consequence, we have reassessed the functional and pharmacological properties of the revised, longer SmTRPA channel cDNA sequence (Bais and Greenberg, unpublished) and find that it retains the pharmacological sensitivities found in our experiments using the original cDNA we isolated (NCBI accession number KT266713). Thus, when expressed in CHO cells, it responds robustly to the TRPV1 activator capsaicin as well as to mammalian TRPA1 activators such as allyl isothiocyanate (AITC) and the inflammatory compound 4-hydroxynonenal (4-HNE), which is known to be produced in host organisms in response to oxidative stress.

3. Praziquantel

PZQ has been the drug of choice against schistosomiasis since the 1980s. The many advantages of PZQ over other antischistosomals are significant enough for it to have become the only antischistosomal available commercially. The molecular target(s) and mode of PZQ action remained undefined decades following the introduction of the drug, limiting rational design of new antischistosomals and obscuring strategies for overcoming resistance should it emerge (Greenberg and Doenhoff, 2017; Thomson and Timson, 2018). Recent results, however, point to TRP channels perhaps playing a key role in PZQ action (Park and Marchant, 2020).

Shortly following its discovery, PZQ was shown to produce a contractile paralysis of schistosomes and disruption of the worm's tegument, both of which are Ca^{2+}-dependent (reviewed by Doenhoff et al., 2008; Cioli et al., 2014; Greenberg and Doenhoff, 2017). These effects on the worms provided clues to a mode of action, and several molecular targets for PZQ have been proposed over the years, with uneven degrees of validation (Angelucci et al., 2011). Multiple lines of evidence point to a key role for components of parasite voltage gated Ca^{2+} (Ca_v) channels (Greenberg, 2005; Chan et al., 2013), which would be consistent with the clinical effects of the drug. Nonetheless, rigorous proof for schistosome Ca_v channels as direct, primary targets of PZQ is lacking.

More recently, Chan et al. (2017) showed that the (*R*)-enantiomer of PZQ can act as a partial agonist of a host serotonergic G protein-coupled mammalian 5-HT$_{2B}$ receptor to elicit constriction of mesenteric vessels, which are the predilection site for adult *S. mansoni* and *S. japonicum* parasites. PZQ may therefore depend in part on a combination of effects on the host that promote parasite clearance, along with the more "selective" deleterious effects (paralysis, tegumental disruption) on the parasite (Chan et al., 2017). Thus, paradoxically, part of what may make PZQ (and perhaps other successful antiparasitics) particularly effective is its lack of specificity; rational design to achieve maximal selectivity against parasite receptors may in some cases be counterproductive (Chan et al., 2018).

4. Praziquantel and TRP channels

In line with this demonstration of PZQ effects on a host receptor, two independent groups subsequently found that PZQ acts as a partial

Table 1
Comparison of predicted TRP channels in current and previous *S. mansoni* genome databases.

Subtype	Previous accession number	Current accession number	Changes from prior version and other notes
C3	Smp_169150	**Smp_169150**	Two predicted splice variants; no change in predicted protein sequence of Smp_169150.1.
C7	Smp_163160	**Smp_163160**	No change in predicted protein sequence.
C5	Smp_147860	**Smp_344020***	Major changes in predicted protein sequence.
C5	Smp_151880	**Smp_336170***	Major changes in predicted protein sequence.
P3	Smp_165660	**Smp_165660**	~75 amino acid insert at N-terminus.
P3	none	**Smp_334610****	Not previously reported.
A1	Smp_125690	**Smp_342190***	Major changes from previous genomic sequence at 3′ and 5′ ends; additional ~200 amino acids at N-terminus compared to cDNA sequence reported by Bais et al. (2018).
ML	Smp_198800	**Smp_198800**	Two predicted splice variants that differ by a 12 amino acid insert (in Smp_198800.2), plus a K335E change immediately following the insert. Previous sequence was the same as Smp_198800.1, which was used for phylogenetic analysis here.
M1	Smp_130890	**Smp_130890**	Two predicted splice variants that vary at the 3′ end (the larger Smp_130890.1 was used in this analysis). Changes throughout the sequence from previous version.
M_{PZQ}	Smp_161630, Smp_161640	**Smp_246790**	Shown by Park et al. (2019) to respond to PZQ; 7 predicted splice variants; Smp_246790.5 was analyzed by Park et al. (2019) and used in the phylogenetic analysis here.
M2	Smp_000050	**Smp_000050**	Two predicted splice variants that differ by a single amino acid insert. Changes from previous sequence throughout.
M7	Smp_035140	**Smp_333650***	Approximately 250 amino acid addition to N-terminus.
M7	Smp_147140	**Smp_147140**	Previously classified as M3 (Bais and Greenberg, 2016).
M3	Smp_165170	**Smp_165170**	Small insert at N-terminus.
M3	Smp_199590	**Smp_347080***	Large insert (238 amino acids) at start of transmembrane domains.

Subtype assignments are based on BLAST searches against human and mammalian genomes. * = new accession number. ** = not previously reported.

agonist of the human TRPM8 channel at micromolar concentrations (Babes et al., 2017; Gunaratne et al., 2018). As with the 5-HT_{2B} receptor, the effect is stereoselective, but surprisingly, it is the (*S*)-enantiomer, which is the less active enantiomer against schistosomes themselves, that primarily elicits the response (Gunaratne et al., 2018). The (*S*)-enantiomer also relaxes precontracted mesenteric arteries, similar to the effects of known TRPM8 agonists (Gunaratne et al., 2018), and TRPM8-knockout mice had fewer dorsal root ganglion cells that responded to racemic PZQ, though the responses were not eliminated (Babes et al., 2017). On the other hand, (*S*)-PZQ and TRPM8 agonist-elicited vessel relaxation persist in TRPM8-knockout tissues, suggesting that TRPM8 is not mediating this effect (Gunaratne et al., 2018). Interestingly, the (*S*)-enantiomer of PZQ is associated with the bitter taste of PZQ (Meyer et al., 2009), a challenge in mass administration of the drug, especially to children. Although TRPM8 is not associated directly with taste reception (Roper, 2014), perhaps indirect interactions between it and other host sensory channels contribute to this adverse effect of PZQ.

The discovery that PZQ activates a mammalian TRPM8 channel led the Marchant group to extend these findings by assessing whether PZQ also interacts with any schistosome TRP channels. A recent, particularly exciting report has indeed established that PZQ interacts with a schistosome TRP channel, *Sm*.$TRPM_{PZQ}$ (Smp_246790.5), a member of the *S. mansoni* TRPM channel subfamily (Park et al., 2019). Thus, Ca^{2+} imaging assays revealed a sustained PZQ-elicited Ca^{2+} signal in HEK293 cells expressing *Sm*.$TRPM_{PZQ}$. The Ca^{2+} signal required extracellular Ca^{2+}, indicating Ca^{2+} influx, lasted as long as PZQ was present, and decreased to baseline upon washout of PZQ. The effect of PZQ was also stereoselective, with the (*R*)-enantiomer (EC_{50} ≅ 600 nM) showing ~45-fold higher potency than the (*S*)-enantiomer (EC_{50} ≅ 28 μM) at room temperature. Raising the assay temperature to 37 °C resulted in an approximately four-fold decrease in the EC_{50} (154 nM) for (*R*)-PZQ. Electrophysiological experiments using whole-cell recording confirmed these results, showing a PZQ-evoked, rapidly activating inward current in cells expressing *Sm*.$TRPM_{PZQ}$. The gene encoding *Sm*.$TRPM_{PZQ}$ (Smp_246790) predicts 7 splice variants, of which the longest (Smp_246790.5) was tested; it will be useful to determine the expression patterns and pharmacology of other splice variants, as well as their physiological roles. *Sm*.$TRPM_{PZQ}$ homologs are also found in other platyhelminth genomes, and it will be interesting to compare pharmacological responses (Park et al., 2019).

Rigorously defining *Sm*.$TRPM_{PZQ}$ as the PZQ receptor (as opposed to a PZQ receptor), will require experiments to determine whether disruption of *Sm*.$TRPM_{PZQ}$ expression (*eg*, by RNA interference) or function alters schistosome sensitivity to PZQ *ex vivo* and, more persuasively, *in vivo*. Such experiments may not be trivial in schistosomes but may have better feasibility in a more experimentally amenable platyhelminth, assuming it is also sensitive to PZQ and its *Sm*.$TRPM_{PZQ}$ homolog is PZQ-activated. Regardless, this clear demonstration of a PZQ receptor with characteristics consistent with the clinical properties of the drug is a major tour-de-force and, further, supports schistosome TRP channels as viable therapeutic targets. More details about the path defining $TRPM_{PZQ}$ as a target of PZQ can be found in a recent review (Park and Marchant, 2020).

5. Known and potential physiological roles of TRP channels in schistosomes and other platyhelminths

In addition to their potential as candidate drug targets, TRP channels almost certainly play important roles in platyhelminth biology. For example, our results show that schistosome TRP channels are important for regulation of normal parasite neuromuscular activity. Thus, a variety of TRPV1 and TRPA1 activators stimulate motor activity in larval and adult schistosomes, an effect which can be eliminated by knockdown of SmTRPA expression (Bais et al., 2015). Compounds that selectively activate other mammalian TRP channels also affect schistosome motility in a similar manner (our unpublished data). Similarly, icilin, an agonist of mammalian TRPM8 (and TRPA1) evokes a dose-related increase in motility in the free-living planarian *Dugesia dorotocephala* (Rawls et al., 2007).

Platyhelminth TRP channels also appear to play important sensory roles in free-living planarians. A TRPM-like channel transduces thermal signaling in *Dugesia japonica* (Inoue et al., 2014), and knockdown of a *Schmidtea mediterranea* TRPA1-like channel by RNAi disrupts extraocular avoidance responses to near-ultraviolet light, which may in fact be due to channel interaction with reactive oxygen species (ROS) that are byproducts of UV-light exposure (Birkholz and Beane, 2017). The *S. mediterranea* TRPA1 channel rescues noxious heat avoidance in TRPA1-deficient *Drosophila*. However, the *S. mediterranea* TRPA1 channel is not itself activated directly by heat when expressed in a heterologous system, but instead appears to be responding to ROS (and H_2O_2), in this case produced from heat-generated tissue damage. This response to ROS has been hypothesized to represent an early nociceptive TRPA1-mediated signaling system (Arenas et al., 2017). Whether

and how these types of TRPA1 channel functions exploited by free-living planarians might manifest in schistosome free-living (miracidia, cercariae) and parasitic (intramolluscan, intramammalian) stages remains to be determined.

Other than these few examples, much remains unknown about the authentic functions of TRP channels in schistosomes and other platyhelminths. Nonetheless, findings from other organisms can provide important guideposts and predictions. We highlight some persuasive and interesting possibilities below.

TRP channels are known to be widely expressed in male and female reproductive organs and may play important roles in reproductive biology. Thus, several TRP channel types, including TRPV1, TRPM8, TRPC2, TRPM7, and TRPA1, are expressed in and appear to serve key functions in reproductive organs and germ cells of mammals and other vertebrates (reviewed byDorr and Fecher-Trost, 2011; Shukla et al., 2012; DeClercq and Vriens, 2018). Furthermore, along with a voltage gated Ca^{2+} channel ($Ca_v3.2$), two TRP channels (TRPV3 and TRPM7) appear to be essential for generation of Ca^{2+} oscillations required for activating embryonic development in mice (Carvacho et al., 2013; Bernhardt et al., 2018). TRP channels also play important roles in mammalian gonadotrope cells in the anterior pituitary, which secrete gonadotropins regulating gonadal function (Beck et al., 2017).

Perhaps more relevant to schistosomes are analogous studies in other invertebrates, most notably *Caenorhabditis elegans* and *Drosophila melanogaster*. The cell divisions required for gonadal development in *C. elegans* require GON-2, a TRPM6/7-like channel (West et al., 2001) and a *C. elegans* TRPC homolog is required for sperm-egg interactions during fertilization (Xu and Sternberg, 2003). In *Drosophila*, a TRPP2-like channel (Amo) is required for sperm storage and fertilization in females and modulates flagellar beating in sperm (Gao et al., 2003; Watnick et al., 2003; Kottgen et al., 2011), and, as in vertebrates, a TRPM channel mediates Ca^{2+} influx required for egg activation (Hu and Wolfner, 2019). As egg production is key to pathogenesis and disease transmission in schistosomiasis, identifying the roles of TRP channels in platyhelminth reproductive processes could provide insights into strategies for interfering with this essential parasite function.

TRP channels also appear to play key roles in embryonic development. Notably, TRPM7, a ubiquitously expressed TRP channel that also includes a kinase domain, is required for embryonic development in mice (Jin et al., 2012), zebrafish (Elizondo et al., 2005), and the African clawed frog *Xenopus laevis* (Liu et al., 2011), with apparent roles in development of multiple organ systems (Jin et al., 2012). Other TRP channels function in early vertebrate development (Komiya and Runnels, 2015; Dong et al., 2018), and a TRPA1 channel is involved in regulation of *C. elegans* aging (Xiao et al., 2013). TRP channels are also implicated in stem cell biology, including differentiation of neuronal cells (Weick et al., 2009) and mechanical regulation of stem cell activity (He et al., 2019). These results could have special relevance to schistosomes, given the extensive developmental changes they undergo in vastly disparate environmental milieus, the ability of the parasites to survive in their human hosts for decades (Chabasse et al., 1985), and the importance of parasite stem cells in schistosome and platyhelminth biology and pathogenesis (Wendt and Collins, 2016; Wang et al., 2018).

A critical interaction in schistosomes is that between male and female worms in the intramammalian host. Unlike the great majority of trematodes, schistosomes are sexually dioecious. Female physical and reproductive maturation depends on pairing with a male worm. A mature, egg-laying female separated from her male partner will cease laying eggs and regress to an immature state. Thus, physical interaction with a male worm is essential to development and maintenance of female reproductive and physical maturity. When paired, females reside within a ventral groove, the gynecophoric canal, of the male worm. A *S. mansoni* gynecophoral canal protein (SmGCP) localizes to the surface of the male gynecophoric canal and to the entire surface of interacting females, but not to non-mated males or immature females (reviewed by LoVerde et al., 2004).

SmGCP appears to be regulated by transforming growth factor β (TGF-β); human TGF-β ligands upregulate expression of SmGCP, an effect that can be suppressed by RNAi knockdown of a *S. mansoni* TGF-β receptor (Osman et al., 2006). The TGF-β signaling pathway plays key roles in a variety of cellular processes that include cell proliferation, lineage determination, differentiation, and adhesion, and several components of the TGF-β signaling system, including receptors and TGF-β-like ligands, have been identified in schistosomes (reviewed by LoVerde et al., 2009; Doenhoff et al., 2019). Human TGF-β alters gene expression in adult worms (Oliveira et al., 2012) and TGF-β signaling appears to play a key role in *S. mansoni* embryonic development (Freitas et al., 2007).

In vertebrates, several reports indicate that various types of TRP channels, including TRPA1, are required for, contribute to, and are regulated by TGF-β signaling (Davis et al., 2012; Okada et al., 2015; Sharma et al., 2017; Falcon et al., 2019). For example, TRPA1 is required for TGF-β signaling in mouse corneal stroma and loss or blockade of TRPA1 reduces inflammatory fibrosis in corneal wound healing (Okada et al., 2014). It is tempting to speculate that TRP channels also play key roles host- and parasite-induced TGF-β-like signaling pathways in schistosomes.

Insights into the authentic physiological functions of TRP channels in schistosomes and other platyhelminths will accrue through a variety of approaches used in both free-living and parasitic worms. These will include survival and behavioral studies on whole worms, both *ex vivo* and *in vivo*, within the host, characterization of the channels themselves using imaging and electrophysiological assays, biochemical analyses, and molecular genetic dissection (*eg*, RNAi). One approach that can provide important clues to function is to determine where and when particular TRP channels are expressed within the worm. For example, according to the *S. mansoni* genome database, SmTRPA RNA, though expressed in all tested life cycle stages, is found most abundantly in larval and juvenile stages, perhaps indicating a role in host finding and migration within the definitive host. Localization of SmTRPA expression could provide key insights into host-parasite interactions and sensory biology.

6. Conclusions

It was only a few years ago that parasite TRP channels were first proposed as potential targets for anthelmintic and antischistosomal therapeutics (Prole and Taylor, 2011; Wolstenholme et al., 2011; Bais and Greenberg, 2016, 2018). In that short period, however, progress has been extensive. Schistosome TRP channels characterized to date have clearly been shown to exhibit pharmacology that differs from that of host TRP channels, and a schistosome TRP channel is now implicated in the mode of action of PZQ. The fact that these findings have appeared so shortly following the onset of investigation of these channels suggests that TRP channels in schistosomes and other parasites may serve as fertile ground for future novel drug targets. Additionally, these channels may provide important insights into parasite physiology and the types of host-parasite interactions that have been discussed in detail elsewhere (Bais and Greenberg, 2018). The results so far suggest a long, productive road ahead.

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