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HELMINTHOLOGY - ORIGINAL PAPER

The ABL kinase inhibitor imatinib causes phenotypic changes and lethality in adult *Schistosoma japonicum*

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Abstract

Schistosomiasis caused by different species of schistosome parasites is one of the most debilitating helminthic diseases of humans worldwide. For decades, chemotherapy is the main method of controlling schistosomiasis. However, the fear of drug resistance has motivated the search for alternatives. It has been demonstrated that the ABL kinase inhibitor imatinib affected the development and survival of *Schistosoma mansoni* in vitro; however, there is still lack of information on whether imatinib also affects other schistosome species such as *Schistosoma japonicum*. In the present study, the anti-schistosomal potency of imatinib on adult *S. japonicum* was investigated in vitro, and the results showed that imatinib had a significant impact on various physiological processes of *S. japonicum* adult worms. Besides its negative effects on worm motility, pairing stability, and gonad development, imatinib caused pathological changes in the gastrodermis as well as the death of the parasite. Our findings suggest that imatinib is an intriguing candidate for further development as an option to fight *S. japonicum*.

Keywords Imatinib · ABL kinases · *Schistosoma japonicum* · Development · In vitro culture

Introduction

Schistosomiasis is one of the most important infectious diseases worldwide and mainly caused by three species of schistosome parasites, *Schistosoma mansoni*, *Schistosoma japonicum*, and *Schistosoma haematobium*. The disease occurs in over 78 tropical and subtropical countries, especially in low-income and rural areas. More than 230 million people are infected, and 780 million people are at risk of infection (Lewis and Tucker 2014; WHO 2017), resulting in over 200,000 deaths per year (Thetiot-Laurent et al. 2013; Hess et al. 2015).

As no vaccine is available, chemotherapy is the main strategy for the control of schistosomiasis (Harder 2002; Bergquist et al. 2017) which is effectively treated by a single compound, praziquantel (PZQ). However, PZQ is only effective against adult worms, is incapable of preventing reinfection (Pica-Mattoccia and Cioli 2004), and causes some adverse effects induced by release of contents from treated worms (Grover et al. 2001; Xu et al. 2014). Furthermore, the extensive use of this drug leads to the risk of the occurrence of drug-resistant parasites. Laboratory experiments showed that selection pressure can induce decreased susceptibility of *S. mansoni* and *S. haematobium* to PZQ (Doenhoff and Pica-Mattoccia 2006; Pica-Mattoccia et al. 2009). Although no decrease in susceptibility of *S. japonicum* has been proven, the efficacy of this drug varies in different strains within this species (Wang et al. 2010). Therefore, effective vaccine and alternative drugs are urgently needed for controlling schistosomiasis in endemic regions (Abdulla et al. 2009; Han et al. 2009).

Protein kinases are conserved signal molecules in various organisms that exert regulatory effects in multiple biological processes (Hubbard and Till 2000; Ardito et al. 2017; Wu and Fu 2018). Particularly, protein tyrosine kinases (PTKs) represent a large group of signal transduction molecules involved in pathways linked to cell adhesion, migration, proliferation, and differentiation (Ishizawar and Parsons 2004; Hubbard and Miller 2007). Motivated by their critical roles in cellular signaling pathways, PTKs became attractive drug targets for

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treating human diseases and developing antihelminthic strategies (Dissous et al. 2007; Knobloch et al. 2007; Beckmann 2012; O'Connell et al. 2015). Among PTKs, Abelson (ABL) kinases are involved in various physiological processes such as cell propagation, stress reactions, and survival processes (Pendergast 2002; Beckmann and Grevelding 2010; Beckmann et al. 2011). In humans, upon chromosomal translocation, ABL kinases are causative for developing chronic myelogenous leukemia (CML) (Deininger et al. 2000). CML can be successfully treated by the ABL kinase inhibitor imatinib (Buchdunger et al. 2002; O'Connell et al. 2017; Rossari et al. 2018). Imatinib deactivates the ABL kinases by competing for its ATP binding site (Manley et al. 2002; Larson et al. 2008) and blocking other targets such as the transmembrane receptor cKIT, which is a proto-oncogene receptor tyrosine kinase, and platelet-derived growth factor receptors (PDGF-R) (Goswami et al. 2016). Interestingly, ABL kinases have been identified in schistosomes (Berriman et al. 2009). Two *S. mansoni* orthologs of the human ABL kinases, SmABL1 and SmABL2, are expressed mainly in the ovary, vitellarium, and testes, as well as in the parenchyma and gastrodermis of *S. mansoni* adults (Beckmann and Grevelding 2010). Imatinib exhibited strong effects on the development and survival of *S. mansoni* in vitro and significantly influenced the transcriptional profiles of genes involved in male-female interaction, gut physiology, muscle activities, and egg production (Beckmann and Grevelding 2010; Buro et al. 2014). In addition, imatinib has detrimental effects on *Echinococcus* larval stages in vitro (Hemer and Brehm 2012), on microfilaria of *Brugia malayi* (O'Connell et al. 2015), and even on the maturation of *Plasmodium* (Pathak et al. 2015). Furthermore, the drug can suppress or reverse host hepatic fibrosis induced by *S. mansoni* in vivo in mice (El-Agamy et al. 2011). However, it is unknown to date whether imatinib also affects other schistosome species. Because any novel anti-schistosomal compound should ideally be effective against several schistosome species, we investigated the anti-schistosomal activity of imatinib on *S. japonicum* adult worms in vitro. Our study found effects caused by imatinib on the survival, morphology, and physiology of the worms.

Materials and methods

Parasite material

Oncomelania hupensis infected with *S. japonicum* were purchased from Nanjing Municipal Center for Disease Control and Prevention, China. Six-week-old Kunming female mice purchased from the Hubei Provincial Center for Disease Control, China, were infected percutaneously with 70 cercariae per mouse. *S. japonicum* adults were collected by hepato-portal perfusion from mice at 35 days post-infection (Wang et al. 1987).

Inhibitor treatment of *S. japonicum* adult worms

After being collected from mice, adult worms were washed three times with supplemented 841 medium consisting of RPMI-1640 (Gibco), 10% new born calf serum (Sigma-Aldrich), 1 mg/ml lactalbumin hydrolysate, 10^{-6} mol/l hydrocortisone, 5×10^{-7} mol/l hypoxanthine, 10^{-6} mol/l serotonin, 100 U/ml penicillin, 100 μg/ml streptomycin, and 0.8% saturated $NaHCO_3$ in 60-mm-diameter culture dishes (Fisher Scientific) (Ye et al. 2013). After washing, worms were cultured in 6-well cell-culture plates with 5 couples per well, containing 5 ml supplemented 841 medium and 10, 25, 50, and 100 μM imatinib (imatinib mesylate, $C_{29}H_{31}N_7O \cdot CH_3SO_3H$, dissolved in DMSO; Enzo Life Sciences) at 37 °C in 5% CO_2 atmosphere for 120 h. Worms incubated with an equivalent concentration of DMSO were used as control, and cultured under the same conditions for 120 h. The medium including compound was changed every 24 h during the 120-h in vitro culture periods. The experiments were performed in duplicate and repeated three times.

Assessment of phenotypic changes in imatinib-treated adult *S. japonicum*

To analyze the morphological effects of imatinib treatment on worms, microscopic evaluation was carried out under an inverted microscope after in vitro culture for 0, 24, 48, 72, 96, and 120 h. Worm behavior, pairing stability, and worm viability (including worm motility, worm morphology, gut peristalsis, mortality), as well as egg production were determined.

Worm viability of *S. japonicum* was scored using a scale from 0 to 4, adapted from the WHO-TDR recommendations (Townson et al. 2007), 4: hyperactivity, increased motility, or frequent spastic movements; 3: normal activity, no morphological alterations; 2: reduced movement, slight morphological alterations, and weak, slow, and rare movements; 1: minimal movement, severe morphological alterations, and granularity, 0: no activity, no gut peristalsis in 30 s observation time. The number of eggs laid ex vivo was counted every 24 h using a McMaster's egg count plate.

Confocal laser scanning microscopy

To analyze morphological effects of imatinib treatment on worm organs and tissues, confocal laser scanning microscopy (CLSM) analyses were conducted as previously

described (Neves et al. 2005; Beckmann et al. 2010; Xiao et al. 2012). All worms were fixed in AFA containing 95% ethanol, 3% formalin, and 2% glacial acetic acid not less than 24 h, stained for 30 min with 0.25% hydrochloric carmine (Solarbio, China), then destained in acidic 70% ethanol and followed by dehydration for 3 min with 70, 90, and 100% ethanol, respectively. After that, worms were immersed in methyl salicylates, and preserved as whole-mounts with neutral resins on glass slides. Specimens were visualized under an Olympus FV1000 confocal laser scanning microscope using a 559 nm He/Ne laser. The experiments were performed in duplicate and repeated three times.

Sequence analyses

Based on the amino acid sequences of SmABL1 (4992 bp; GenBank Accession No. FN582310) and SmABL (3927 bp; GenBank Accession No. FN582311) (Buro et al. 2014), two ABL-like *S. japonicum* amino acid sequences (Sjp_0007210 and Sjp_0040100) were obtained from the Wormbase ParaSite database by using the Blast algorithm (http://parasite.wormbase.org /Multi/Tools/Blast). Amino acid sequences of human ABL kinases were retrieved from GenBank database for multiple-alignment. Sequence alignment was performed using MAFFT version 7 (https://mafft.cbrc.jp/alignment/server/).

Statistical analysis

Statistically significant differences were analyzed by using one-way ANOVA (GraphPad Prism 7). *P* values $\leq$ 0.0003 and *P* values $\leq$ 0.002 were considered as highly statistically significant and statistically significant, respectively.

Results and discussion

Imatinib treatment significantly decreased pairing stability, worm motility, and vitality of adult *S. japonicum*

To investigate whether imatinib influences adult *S. japonicum*, freshly harvested worms were treated with different concentrations of this drug over a 120-h period in vitro. In contrast to DMSO-treated control worms, which showed normal behavior (sucked to the bottom of the culture well), perfect pairing stability, and strong movement during the entire in vitro cultivation period (120 h), effects on treated worms were observed within 24 h. Worms failed to attach to the bottom of the culture well following treatment with 100 μM imatinib, and all worm pairs had completely separated. Furthermore, treated worms showed significant reduction of motility ($P \leq 0.0001$) (Fig. 1a-b) including less frequent wavy and peristaltic movements. After 48 h, worm motility further decreased (Fig. 1a) with minimal movement only in head and tail regions. By 72 h, all worms were dead ($P \leq 0.0001$) (Fig. 1a). With 50 μM imatinib, over 60% of worms failed to attach to the bottom of the culture well, and worm motility dramatically decreased after 24 h ($P \leq 0.0001$) showing slow and rare movements. Nearly 60% of the couples had separated after 72 h ($P < 0.0001$), and all worms showed minimal movement. After 120 h, all worms were dead (Fig. 1a-b). After exposure to 25 μM imatinib for 120 h, about 75% of the couples separated ($P \leq 0.0001$) (Fig. 1b), all worms

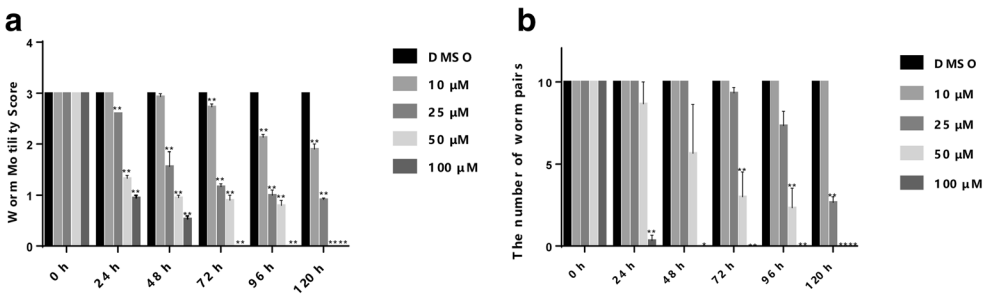

Fig. 1 Effects of imatinib on pairing stability and motility of adult *Schistosoma japonicum*. *S. japonicum* couples were treated with different concentrations of imatinib (10, 25, 50, or 100 μM) for 0, 24, 48, 72, 96, and 120 h in vitro. The status of worm motility (**a**) and the number of worm pairs (**b**) were detected after imatinib treatment. Data are representative of the mean + SEM of three separate experiments. All imatinib-treated groups were compared with DMSO-treated group, and statistically significant differences between imatinib-treated and DMSO-treated groups are indicated with $^{*}P \leq 0.002$ and $^{**}P \leq 0.0003$

Fig. 2 Morphological changes of imatinib-treated adult *Schistosoma japonicum* in bright-field microscopy. DMSO-treated *S. japonicum* couples as control (**a**), showing normal morphological feature; *S. japonicum* couples were treated for 48 and 72 h in vitro with 100 μM (**b**–**d**) and 50 μM (**e**–**g**) imatinib, respectively, showing severe morphological changes such as tegument bubbles (**b**, **e**, indicated by an asterisk), detachment of tegument (**c**, **f**, indicated by an arrow), and accompanied bulges (**d**, **g**, encircled area) along their bodies. *S. japonicum* adults were treated with 25 μM (**h**), 10 μM (**i**) imatinib in vitro for 120 h, showing slightly swellings along their bodies; scale bars, **a**–**e** 100 μm and **f**–**i** 200 μm

failed to attach to the bottom of the well and showed weak, slow, and rare movements. Worms exposed to 10 μM imatinib stayed paired for the whole in vitro cultivation period, and their motility was modestly but significantly decreased from 72 h in vitro cultivation onwards ($P \leq 0.0001$) (Fig. 1a-b).

Our results showed a concentration- and time-dependent effect of imatinib treatment involving a series of physiological changes such as abnormal behavior, reduced pairing stability, and decreased motility in vitro. Moreover, imatinib killed *S. japonicum* adults within 3–5 days in culture (100% lethality after 3 days at 100 μM, after 5 days at 50 μM). These results were similar to the observations of imatinib-treated *S. mansoni* adult worms. Exposure to 100 and 50 μM for 96 h led to 100 and 75% mortality, respectively. However, while 10 μM imatinib was lethal to over 60% of *S. mansoni* worms within 96 h (Beckmann and Grevelding 2010), this was not observed in *S. japonicum*, suggesting a longer treatment time might be needed for *S. japonicum* to get the same efficacy as for *S. mansoni*.

Imatinib caused tegumental damage in treated adult *S. japonicum*

CLSM analysis was performed to study the morphological effects caused by imatinib treatment. While DMSO-treated worms showed normal morphological features during in vitro cultivation (Fig. 2a), 100 μM imatinib caused severe morphological changes. Already within 48 h, tegument bubbles (Fig. 2b), tegument detachment (Fig. 2c), and accompanied bulges along the bodies

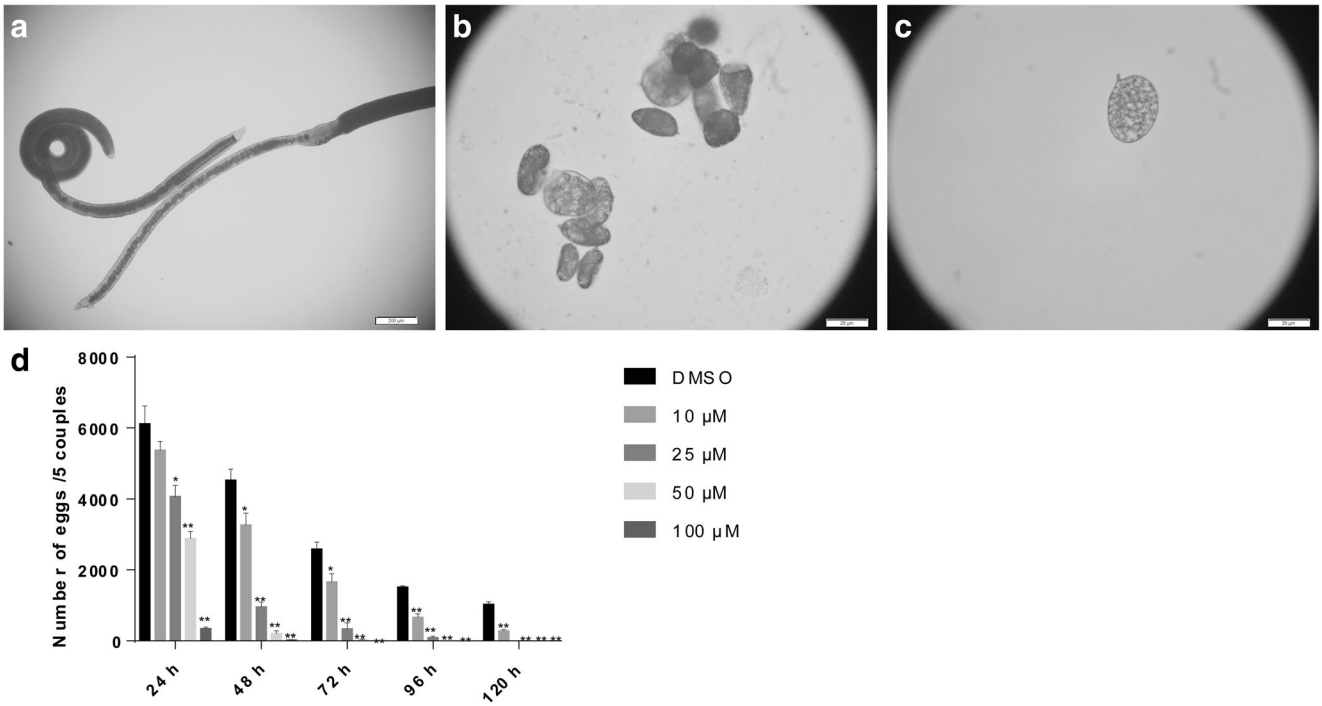

Fig. 3 Effect of imatinib on egg production of *Schistosoma japonicum* couples. **a** Accumulation of eggs within the uterus in the worms treated with 100 μM after 24 h; scale bar, 200 μm. Morphology of eggs produced by imatinib-treated worms (**b**) and DMSO-treated worms (**c**) is shown. Compared with the DMSO-treated group, some abnormal eggs with smaller size and absence of spine were observed in imatinib-treated worms; scale bar, 20 μm. **d** The number of eggs produced by worms treated with different concentrations of imatinib (10, 25, 50, or 100 μM) or DMSO as control after different time points in vitro. Data are representative of the mean ± SEM of three separate experiments. Statistically significant differences between imatinib-treated and control groups of each time-point are indicated by $*P \leq 0.002$ and $**P \leq 0.0003$

(Fig. 2d) were observed. After 72 h, these phenotypes were more dramatic (data not shown). Using 50 μM imatinib for 72 h, the worms exhibited similar morphological changes as with 100 μM for 48 h (Fig. 2e–g), and after 96 h, the changes were even more obvious. After being incubated with 25 μM imatinib, worms showed slight swellings within 96 h (Fig. 2h). Worms exposed to 10 μM imatinib for 96 h had reduced vitality but showed no morphological changes (Fig. 2i). As it is likely that worms with tegumental damage will not be able to survive in vivo (Andrews et al. 1983; Weeks et al. 2018), a compound inducing such damage, as imatinib, is highly interesting with respect to application aspects.

Imatinib reduced fecundity of treated adult *S. japonicum*

In addition to the morphological changes in adult *S. japonicum*, egg congestion occurred in imatinib-treated females, leading to the accumulation of eggs within the uterus (Fig. 3a) and diminished numbers of excreted eggs (Table 1). Furthermore, imatinib also caused the formation of abnormal eggs (Fig. 3b). Compared with the DMSO-treated group, worms treated with 100 and 50 μM imatinib for 24 h exhibited a 95% ($P \leq 0.0001$) and 53% ($P \leq 0.0003$) reduction in egg production, respectively (Fig. 3d). The number of eggs persistently decreased after prolonged treatment time until 72 h (100 μM) and 96 h (50 μM), when worms no longer produced eggs. Meanwhile, some abnormal eggs with smaller sizes and missing spines were observed among the produced eggs. However, DMSO-treated couples produced normal eggs during treatment periods (Fig. 3c, d). Significant reduction was also observed in worms treated with lower concentrations in longer treatment periods, showing a 79% ($P \leq 0.0001$) reduction with 25 μM imatinib for 48 h and 74% ($P \leq 0.0001$) reduction with 10 μM imatinib for 120 h.

Although egg production of *S. mansoni* was not quantified in previous studies, imatinib treatment indeed induced transcriptional changes of egg formation-related genes (Buro et al. 2014). Supported by that, it seems that imatinib has the potential to suppress egg production of schistosomes. Considering that the pathogenesis of schistosomiasis is mainly caused by eggs deposited in the host liver inducing severe organ inflammation, blocking egg production of schistosomes is one key factor to fight the disease. Reduced or absent egg production will contribute to lower pathology in patients, and at the same time impede the life cycle of this parasite.

Table 1 In vitro effect of imatinib against adult *Schistosoma japonicum* couples

Group	Number of worms investigated	Incubation period (h)	Separated worms	Motility reduction (%)	Dead worms	
					M	F
DMSO	30	24	0	0	0	0
	30	48	0	0	0	0
	30	72	0	0	0	0
	30	96	0	0	0	0
	30	120	0	0	0	0
10 μM	30	24	0	0	0	0
	30	48	0	0.06%	0	0
	30	72	0	23.33%	0	0
	30	96	0	33.33%	0	0
	30	120	0	40%	0	0
25 μM	30	24	0	23%	0	0
	30	48	0	50%	0	0
	30	72	0	55%	0	0
	30	96	3	65%	0	0
	30	120	7	68%	0	0
50 μM	30	24	0	55%	0	0
	30	48	4	65%	0	0
	30	72	6	70%	0	0
	30	96	10	78%	6	6
	30	120	10	100%	30	30
100 μM	30	24	10	85%	0	0
	30	48	10	94%	9	3
	30	72	10	100%	30	30
	30	96	10	100%	30	30
	30	120	10	100%	30	30

Imatinib treatment caused phenotypic changes in reproductive organs and gastrodermis of adult *S. japonicum*

CLSM was performed to investigate morphological changes of imatinib-treated worms in more details. To this end, dosage- and time-dependent effects were also observed in the ovary, vitellarium, and gastrodermis of females as well as in the testes of males (Fig. 4). In DMSO-treated couples, females showed a normal ovary with small oogonia and immature oocytes located in the anterior part of the ovary, and larger mature oocytes located in the posterior part of the ovary (Fig. 4A, a). After incubation with 10 μM and 25 μM imatinib for 120 h, respectively, *S. japonicum* worms showed a normal ovary shape, but the amount of immature oocytes was decreased, while the number of mature oocytes increased considerably (Fig. 4A, b, c). A similar effect was also observed in the ovary of females treated with 50 μM imatinib (Fig. 4A, d). Moreover, the ovary appeared disorganized and lost its normal oval shape along with a loose arrangement of oocytes. These effects were reinforced after treatment with higher concentration (100 μM) for shorter time (72 h), showing a dramatically dilated, ball-shaped ovary (Fig. 4A, e).

DMSO-treated males showed normal testicular lobes composed of a large number of spermatogonia and spermatocytes at different stages of maturity (Fig. 4B, a). Mild alterations were observed in males exposed to imatinib at a concentration of 10, 25, or 50 μM after 120 h: the diameters of the testicular lobes were slightly decreased (Fig. 4B, b–d). Similar damaged testes were observed at a higher concentration (100 μM), but after a shorter treatment period (at 72 h) (Fig. 4B, e).

Morphological effects were not only observed in the ovary and testis, but also in the vitellarium and gastrodermis of females. In DMSO-treated worms, the gastrodermis manifests as a continuous and dense layer of coenocyte cells in close contact with the parenchyma (Fig. 4C, a). However, the gastrodermis of female worms treated with 10 and 25 μM imatinib was detached from the parenchyma after 120 h (Fig. 4C, b, c). With 50 μM imatinib treatment after 120 h,

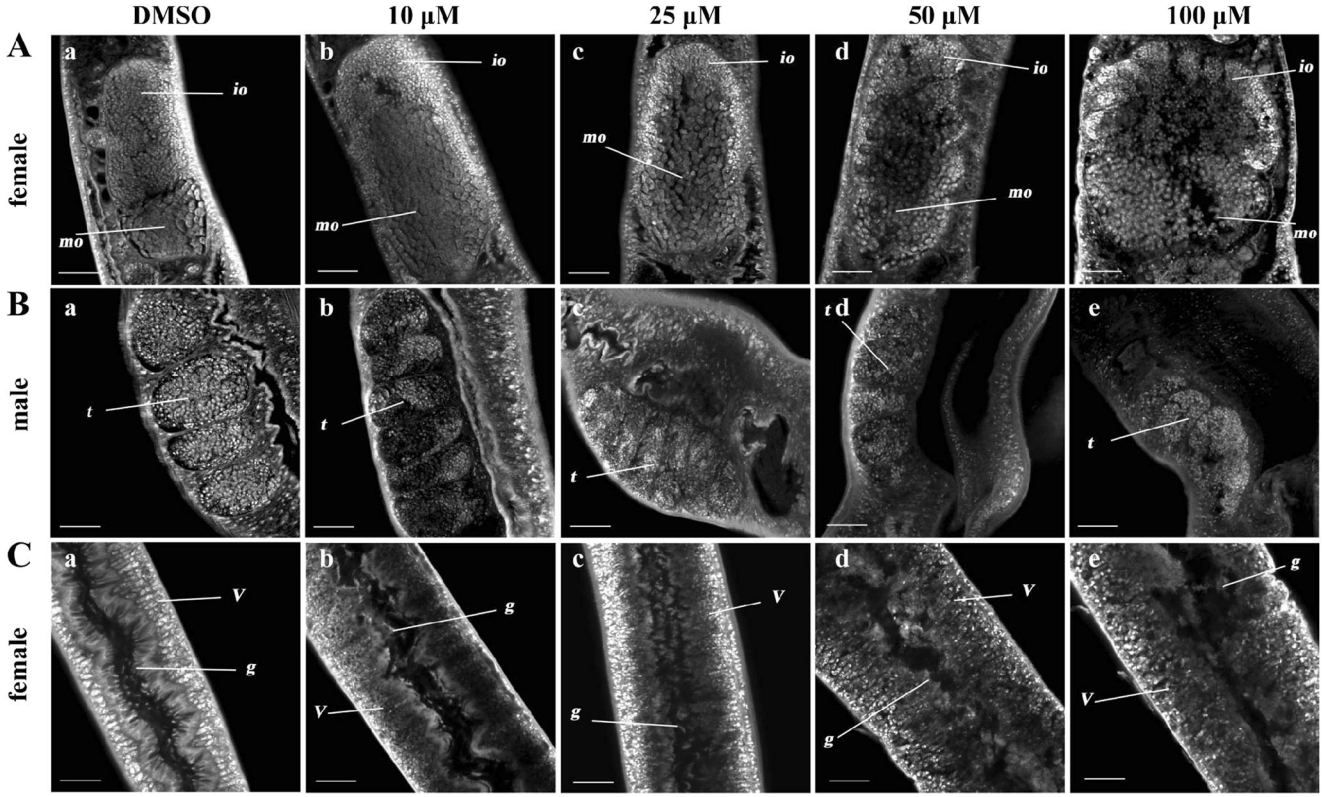

Fig. 4 CLSM morphological analysis of imatinib-treated adult *S. japonicum*. **A** Representative CLSM microscope images of *S. japonicum* females treated with 10, 25, 50, and 100 μM imatinib (*b–e*); (*a*) control worms treated with DMSO only. *mo* mature oocytes, *io* immature oocytes. **B** CLSM microscope images of *S. japonicum* males treated with 10, 25, 50, and 100 μM imatinib (*b–e*); (*a*) control worms treated with DMSO only. *t* testes. **C** CLSM microscope images of a more distal area of *S. japonicum* females treated with 10, 25, 50, and 100 μM imatinib (*b–e*); (*a*) control worms treated with DMSO only. *v* vitellarium, *g* gastrodermis. Scale bar, 50 μm

the number of vitelline cells was considerably decreased, resulting in holes in the texture of the vitellarium (Fig. 4C, d), compared to the DMSO-treated females (Fig. 4C, a). And at the same time, the gastrodermis was largely disconnected from the parenchyma (Fig. 4C, d). Treatment with 100 μM imatinib for 72 h caused similar alterations of vitellarium as with 50 μM imatinib for 120 h, and the gastrodermis was completely disconnected from the parenchyma (Fig. 4C, e).

Therefore, in the CLSM analysis of adult *S. japonicum* treated with the ABL kinase inhibitor imatinib, the ovary appeared disorganized and lost its normal oval shape along with increased numbers of mature oocytes and decreased numbers of immature oocytes, reduced sizes of testicular lobes, and dramatically decreased vitelline cell number within the vitellarium. Besides the reproductive organs, CLSM analyses also revealed severe destruction and detachment of the gastrodermis in imatinib-treated adult *S. japonicum*. These results were similar with the observed effects of imatinib on adult *S. mansoni* (Beckmann and Grevelding 2010; Buro et al. 2014).

Based on the amino acid sequences of SmABL1 and SmABL2, two ABL orthologs of *S. japonicum* (Sjp_0007210 and Sjp_0040100) were found in the Wormbase ParaSite database (http://parasite. wormbase.org/Multi/Tools /Blast). Multi-alignment analysis (Fig. 5) showed that Sjp_0007210 and Sjp_0040100 have 96.8 and 98.2% identity to SmABL1 and SmABL2, respectively, therefore being named as SjABL1 and SjABL2. Moreover, SjABL1 and SjABL2 shared the same predicted imatinib binding sites in the TK domains of SmABL1 (E473, T502, M505) and SmABL2 (L289, M331, M359, D422) (Buro et al. 2014). Supported by the high sequence identity and the same key binding sites of ABL kinase inhibitors in these two schistosome species, we speculated that the concentration- and time-dependent effects of imatinib on *S. japonicum* couples in vitro (Table 1) resulted from the inhibition of ABL (SjABL1 and SjABL2) kinases. In addition, previous in situ hybridization analyses showed that SmABL1 and SmABL2 were mainly localized in the ovary, vitellarium, and testes, and also detected in the parenchyma and gastrodermis of *S. mansoni* adults (Beckmann and Grevelding 2010), which matches with the observed imatinib-induced tissue alterations in *S. mansoni* (Beckmann and Grevelding 2010) and *S. japonicum*. Based on this, one can speculate that ABL kinases could be involved in reproduction and development of *S. japonicum* and *S. mansoni*, making them a potential target for developing anti-

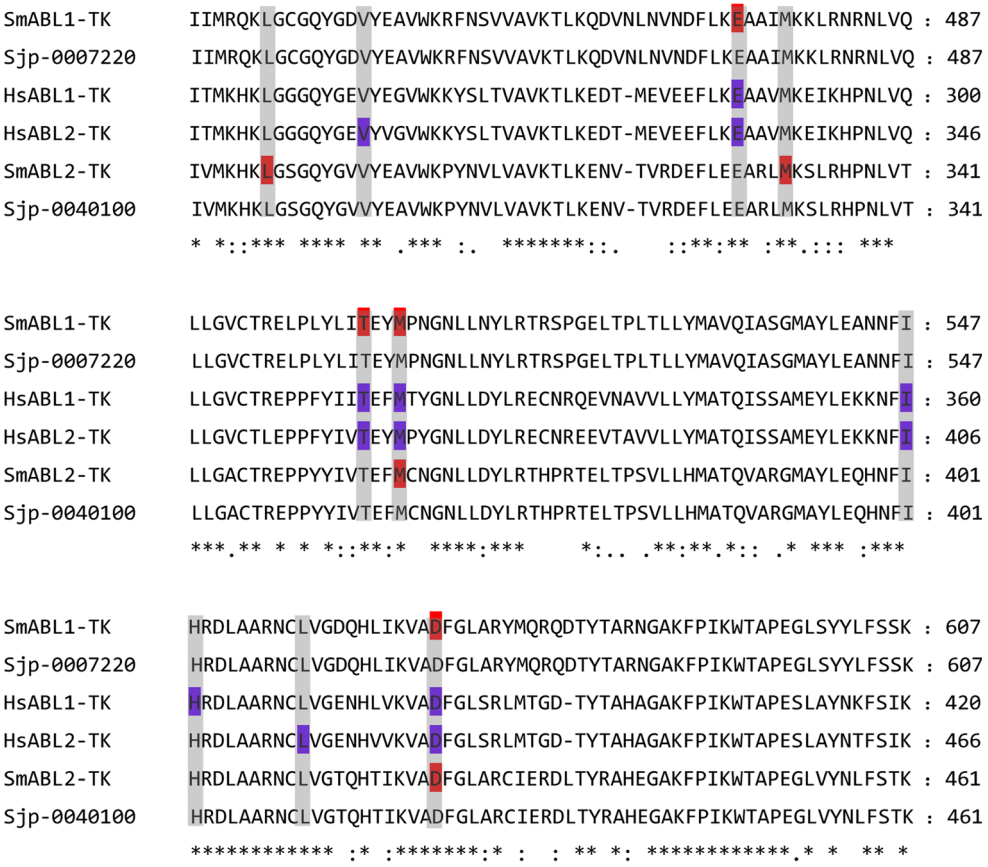

Fig. 5 Alignment of human and *Schistosoma* ABL kinase TK domains. *S. mansoni* ABL (SmABL1, SmABL2) kinase TK domains were aligned with those from human (ABL1, ABL2), and *S. japonicum* (Sjp_0007210, Sjp_0040100). Red and blue boxes indicate imatinib binding sites of SmABL1/2 and HsABL1/2, respectively

reproductive drugs against schistosomes. Despite the clear in vitro effect, the ABL kinase inhibitor imatinib seems not suitable for in vivo application against schistosomes, as therapeutic treatment in rodent experiments failed, which may be due to its high affinity to serum proteins (Beckmann et al. 2014); however, this requires further studies to confirm. Nevertheless, because of the now well-understood detrimental effects of imatinib in different schistosome species, it could be a promising basis for further development of anti-schistosomal compounds.

Although imatinib caused similar types of effects in both *S. mansoni* and *S. japonicum* adults, the impact of imatinib on adult *S. japonicum* was weaker than that on *S. mansoni.* These differences might be based on the distinct body sizes and fecundities of these two species, which could contribute to their different susceptibilities to imatinib. Firstly, *S. japonicum* adults are twofold larger than *S. mansoni* adults. Secondly, *S. japonicum* adults produce a considerably higher amount of eggs, with more than 2000 eggs per day compared to about 300 eggs per day for *S. mansoni* (Cheever et al. 1994; Cheever and Powers 1969). These differences in physiology might associate with different kinetics of drug activity in both species and make a strong (higher concentration) and lasting (longer time) compound exposure necessary in *S. japonicum*. This is underlined by a previous study in which three major species infecting humans, including *S. haematobium*, *S. mansoni*, and *S. japonicum*, had different sensitivities to several anti-schistosomal drugs. Of note, the predicted successful rate of mass chemotherapy using available compounds appeared to be highest for *S. haematobium* and lowest for *S. japonicum* (Webbe and James 1977; Kovac et al. 2017). Future studies should focus more on such drug-sensitivity differences and explore how to overcome these.

Conclusions

This study showed a wide range of anti-schistosomal effects of the ABL kinase inhibitor imatinib against *S. japonicum* in vitro, including reduced motility, reduced viability, and defective reproduction as well as gonadal and gastrodermal tissue alterations. The remarkable effects of imatinib on different schistosome species and even other parasites demonstrates the potential of imatinib, or maybe ABL kinase inhibitors in general, to serve as basis for further development and rational drug design.

Authors' contributions Conceived and designed the experiments: SH, CGG, and MH. Performed the experiments: XS, LZ, MM, TZ, and LL. Analyzed the data: XS, SH, LZ, CGG, and MH. Contributed reagents/materials/analysis tools: RF, YQZ, and JLZ. Wrote the paper: XS, SH, LZ, CGG, and MH. All authors read and approved the final manuscript.

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Compliance with ethical standards

Ethical approval and consent to participate The conduct and procedures involving animal experimentation in this study were approved by the Scientific Ethics Committee of Huazhong Agricultural University (HZAUMO-2017-024) according to the regulations for the Administration of Affairs Concerning Experimental Animals of Hubei Province.

Conflict of interests The authors declare that they have no competing interests.

Abbreviations PZQ, Praziquantel; *S. japonicum*, *Schistosoma japonicum*; *S. mansoni*, *Schistosoma mansoni*; PTKs, Protein tyrosine kinases; ABL, Abelson; CML, Chronic myelogenous leukemia; cKIT, Proto-oncogene receptor tyrosine kinase; PDGF-R, Platelet-derived growth factor receptors; Imatinib, Imatinib mesylate; CLSM, Confocal laser scanning microscopy

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