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Receptors for growth and development of *Schistosoma mansoni*

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Review Article

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Abstract

The growth and development of schistosomes are tightly regulated by various receptors throughout their life cycle. Each stage of the parasite inhabits a distinct habitat and responds to different factors that drive its growth and development. With two hosts involved in its life cycle (mammalian and snail), the parasite must go through additional free-living stages to transition between them. Moreover, communication between male and female worms is essential for the maturation of females. The ability of adult schistosomes to survive in human hosts for up to thirty years demonstrates their capacity to efficiently utilize host nutrients for metabolic processes and growth. In *Schistosoma mansoni*, receptors mediate the utilization of growth factors derived from both the parasite itself and the host. Nuclear receptors, in particular, collaborate with other proteins to regulate the expression of genes essential for various developmental functions. Receptors also play a pivotal role in RNA export, which is crucial for the parasite development. Additionally, neurotransmitter receptors are essential for the growth and development of larval stages. This review aims to elucidate the mechanisms by which these receptors regulate cell proliferation, differentiation, and maturation throughout the parasite life cycle. Understanding these processes could provide insights into the role of receptors in *Schistosoma mansoni* development and potentially lead to innovative therapeutic strategies to combat human schistosomiasis.

Introduction

Schistosomiasis is a major neglected tropical disease affecting approximately 240 million people (World Health Organization 2024). *Schistosoma mansoni* (*S. mansoni*), *S. japonicum*, and *S. haematobium* are the three main schistosome species that cause schistosomiasis in humans. *S. mansoni* is the causative agent of intestinal schistosomiasis in humans. The disease is usually linked with impoverished socioeconomic conditions (Abou-El-Naga 2015) and is characterized by hepatosplenomegaly, portal hypertension, anemia, and eosinophilia (el Zawawy *et al.* 1995; Shaker et al. 2014). There is currently no effective vaccine against the parasite. Various molluscicides have been evaluated to control the intermediate snail host of the disease (Younis et al. 2023; Zheng et al. 2021). The primary strategy for controlling schistosomiasis is the mass drug administration of praziquantel (PZQ) (Abou-El-Naga 2018). However, PZQ is ineffective against immature worms and offers no protection against re-infection (Mogahed *et al.* 2023). Reports of isolates with reduced susceptibility to PZQ and the possibility of experimentally producing praziquantel resistance (Amer *et al.* 2022) highlight the risks of relying on a single therapeutic agent for a disease of this magnitude.

Adult schistosomes parasitize humans and lay eggs, many of which are eventually expelled from their definitive hosts with feces. However, some eggs fail to undergo the extravasation process needed for expulsion; instead, they are carried by the bloodstream and become trapped in the liver (Walker 2011). In fresh waters, each egg hatches into a ciliated miracidium that infects a snail intermediate host of genus *Biomphalaria.*

Snails show varying degrees of susceptibility and maintain a complex relationship with the parasite (Abou-El-Naga and Radwan 2012; Abou-El-Naga et al. 2015; El Naga et al. 2010). Inside the snail, the miracidium undergoes a dramatic transformation into an obligate asexually reproducing mother sporocyst. The proliferation of stem cells in a mother sporocyst gives rise to a new asexual stage, the daughter sporocyst. Germinal cells proliferate in a mother sporocyst to produce a daughter sporocyst. The cercariae that emerge from the daughter sporocyst are released into the water (Walker 2011). They penetrate human skin with the aid of the fatty acids present in the skin (Hammouda *et al.* 1994; Salter *et al.* 2000). The cercariae transform into schistosomula that migrate into the branches of the hepatic portal vein. They ingest blood cells and grow into juvenile schistosomes in the liver. The juveniles then couple and mature into adult male and female worms, which migrate to the mesenteric veins to mate and lay eggs (Walker 2011).

Throughout its life cycle, *Schistosoma* inhabits distinct habitats and alternates between mammalian and snail hosts. This dual-host life cycle requires additional free-living stages that

facilitate these transitions. Each stage of the parasite inhabits a distinct habitat and responds to different factors that promote its growth and development. Furthermore, the male *Schistosoma* worm controls the development of the female. The sexual development of the female is determined by mating with a male schistosome worm (Severinghaus 1928). Maintaining the female mature reproductive state requires perpetual mating with a male worm, not sperm transfer (Popiel *et al.* 1984). Chen *et al.* (2022) identified a non-ribosomal peptide synthetase that is activated in male worms when they mate with a female and determined that it is crucial for male worms to promote female development. Adult schistosomes can survive in human hosts for up to thirty years (von Lichtenberg 1987), demonstrating their ability to effectively utilize the host's nutrients for metabolic processes and growth (You *et al.* 2011). Among trematodes, schistosomes are unique in that they have separate sexes. Adult male and female schistosomes live constantly paired, which is essential for the development of the female gonads. Females without pairing experience are sexually immature. When pairing occurs, differentiation processes are triggered that lead to maturation of the ovary and vitellarium, resulting in a sexually mature female. Unlike females, pairing-inexperienced males already have testes with differentiated spermatocytes and show no morphological differences compared to pairing-experienced males. However, pairing also induces changes in male gene expression (Lu *et al.* 2016).

S. mansoni utilizes a variety of receptors to regulate its growth and development. This review seeks to clarify how these receptors regulate cell proliferation, differentiation, and maturation throughout the parasite life cycle. The findings presented here will provide a comprehensive understanding of the crucial role of these receptors in the development of *S. mansoni*.

With the increasing availability of genomic data from *S. mansoni*, an increase in studies focusing on elucidating the role of receptors in host-parasite interactions is expected. Understanding the molecular basis of receptor functions and the development of more specific receptor agonists and antagonists represents a substantial challenge for future research.

Growth factor receptors (Table 1)

Growth factors are a group of polypeptides that play a crucial role in regulating a variety of cellular processes, including cell growth, proliferation, and differentiation. They are essential for the normal development and function of tissues and organs. Growth factors are considered a subset of cytokines. While all cytokines influence signal transduction pathways, only those cytokines affecting cell growth/differentiation signalling pathways are considered growth factors. Thus, growth factors have a positive effect on cell division, while cytokine is a neutral term in relation to whether a molecule affects proliferation. They are produced by various cell types and typically act locally in an autocrine or paracrine manner. They can circulate in the plasma and bind to specific proteins. In this bound form, they remain inactive but can be activated locally. The most important growth factors are epidermal growth factor, insulin-like growth factor, fibroblast growth factor, and transforming growth factor-ß (Stone et al. 2023). Most growth factor receptors have tyrosine kinase activity by phosphorylating downstream protein tyrosine residues. The surface receptors for the TGF-β are an exception. When activated by the binding of TGF-β cytokines, this receptor can phosphorylate downstream proteins on serine and threonine residues (Saito et al. 2018). Molecular data have identified schistosome growth factor receptors (Collins et al. 2013; Du et al. 2023; Wang et al. 2013).

The receptor tyrosine kinases (RTKs) of *S. mansoni* include those receptors responsible for growth, which are four members of the epidermal growth factor receptors (EGFRs) family, two of the insulin receptor family (IRs), and two members of the fibroblast growth factor receptor (FGFRs) (Andrade *et al.* 2011; Avelar *et al.* 2011). In addition, the schistosome genome encodes two Venus kinase receptors (VKRs), which belong to a family of RTKs originally discovered in *S. mansoni* (Vicogne *et al.* 2003).

Epidermal growth factor receptors (Smp_165470; Smp_093930; Smp_152680; Smp_344500)

Epidermal growth factor receptors (EGFRs) are transmembrane glycoprotein and belong to the receptor tyrosine kinases (RTKs) (Grapa *et al.* 2019). The human EGFR is associated with the pathogenesis and progression of various types of carcinomas. In urothelial carcinoma associated with *Schistosoma* infection, a higher level of EGFR is found than in urothelial carcinoma of other causes (AlHariry *et al.* 2024). In *S. mansoni*, EGFR homologs are predominantly expressed in the muscle of adult male and female worms, indicating that this receptor may play a role in muscle development (Ramachandran *et al.* 1996). Moreover, the EGFR substrate is expressed in the vitellarium and the ovary of the adult female and in the testes of the adult male worms, suggesting that this receptor may have additional functions in the gonads (Buro *et al.* 2017). Maharjan *et al.* (2023) demonstrated the anterior localization of EGFR in schistosomula.

EGFR contains a conserved intracellular tyrosine kinase domain, a unique transmembrane hydrophobic domain, and an extracellular domain for binding EGF ligands. Human EGF induces EGFR autophosphorylation in adult worms and larvae of *S. mansoni* and increases protein and DNA synthesis in adult worms, suggesting that host hormones are involved in the regulation of schistosome development. Schistosome EGFR can bind human EGF with the same affinity as human EGFR (Ramachandran *et al.* 1996).

Human growth factors can modulate schistosome-signalling processes such as protein kinase C (PKC) and extracellular signal-regulated kinase (ERK) (Ressurreição *et al.* 2016; Vicogne *et al.* 2004). Human EGF, insulin, and insulin-like growth factor 1 were found to activate PKC and ERK at the schistosomula surface. The stimulation of these signalling by human growth factors is crucial during early host invasion, as the parasite encounters human growth factors for the first time and must rapidly adapt to the host. Host-mediated ERK activation can drive tegument remodeling, ensuring parasite survival while promoting cell growth and differentiation. Depleting of cholesterol from tegument lipid rafts, which are crucial for *S. mansoni* biology, disrupts EGFR/IR binding on the schistosomula surface and alters several protein kinases signalling pathways within the parasite (Ressurreição *et al.* 2016).

Insulin receptors (IRs)

During growth and reproduction, schistosomes consume substantial amounts of energy derived primarily from the host's nutrition. Adult S. mansoni worms absorb large amounts of blood glucose, equivalent to their dry weight every five hours, from the portal and mesenteric veins of the host (Bueding 1950). Glucose uptake occurs primarily through facilitated diffusion across the worm tegument. Human insulin has been shown to enhance glucose uptake in schistosomes (Ahier *et al.* 2008). Two glucose transporters, GTP1

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Table 1. Growth factor receptors

Receptors	Gene ID	Gene expression through the life cycle	Gene expression/protein localization in the parasite	Functional analysis performed	Roles	References
Epidermal growth factor receptors	Smp_165470, Smp_093930, Smp_152680, Smp_344500	Adult worms and schistosomula	Muscles, vitellarium, ovary, and testes	Ligand binding assay, signal transduction assay, in situ hybridization	Muscle development and reproduction	Shoemaker *et al.* 1992; Ramachandran *et al.* 1996; Buro *et al.* 2017; Maharjan *et al.* 2023
Insulin receptors		Adult worms and schistosomula	Tegumental basal membrane, muscle, and intestinal epithelial cells	In vitro interaction with human insulin, in situ immunolocalization, treatment with inhibitor	Nutrition, growth, and reproduction	Vanderstraete *et al.* 2013; Khayath *et al.* 2007; Elhenawy *et al.* 2017
IR1	Smp_341160					
IR2	Smp_009990					
Fibroblast growth factor **receptors**		Eggs, miracidia, cercariae, schistosomula, and adult	Gonads and neoblast-like somatic stem cells	In situ hybridization, signal transduction assay, inhibition treatment	Fertility and maintenance of stem cells	Collins *et al.* 2013; Wang *et al.* 2013; Hahnel *et al.* 2014; Du *et al.* 2022
FGFRA	Smp_175590					
FGFRB	Smp_157300					
Venus kinase receptors		Miracidia, larval stages, and female worms	Germinal cells of miracidia, larval stages, and the oocytes	Inhibition treatment of the kinase domain	Growth, oocytes differentiation, and reproduction	Vicogne *et al.* 2003; Gouignard *et al.* 2012; Vanderstraete *et al.* 2014; Mathavan *et al.* 2022
VKR1	Smp_019790					
VKR2	Smp_153500					
Transforming growth factor receptors		Adult worms	Both receptors are on the surface of the parasite. SmTβRII is in vitelline, gut epithelial, cells and the sub-tegumental cells of male worms	Ligand-binding assay, immuno-histochemistry, knockdown using short interfering RNA	Host-parasite interactions, communication between male and female, development of vitelline cells, and egg embryogenesis	Davies *et al.* 1998; Osman *et al.* 2006; Forrester *et al.* 2004
SmTβRI	Smp_049760					
SmTβRII	Smp_144390					

Gene ID is extracted from the WormBase ParaSite using the reference genome for *S. mansoni*, SM_V10 (WormBase ParaSite 2024).

and GTP4, play a crucial role in this process and are distributed asymmetrically on the tegument. GTP1 is located within the basal membrane and transports glucose into the underlying tissues, whereas GTP4 is located in the apical membrane. GTP4 is expressed on the parasite surface concurrently with the appearance of the apical membrane bilayer during cercaria to schistosomule transformation and remains on the surface throughout all life stages of the parasite in vertebrate hosts (Khayath *et al.* 2007). Glucose uptake in schistosomes is mediated by PI3K/Akt/mTOR signal. The Akt protein, also known as protein kinase B, is associated not only with the expression of GTP4 but also with the shuttling of this transporter within the tegument (Abou-El-Naga 2021; McKenzie *et al.* 2018; Morel *et al.* 2014; Skelly and Shoemaker 1996). Maharjan *et al.* (2023) demonstrated that lipid rafts could be crucial for glucose import into the parasite, potentially in response to host insulin.

Adult *S. mansoni* possesses two insulin receptors (IR1 and IR2) (Smp_341160; Smp_009990) (Khayath *et al.* 2007). Both receptors are also present in schistosomula (Maharjan *et al.* 2023). A potential insulin-like peptide has been identified in *S. mansoni*, although it is still unclear whether this peptide interacts with the IRs of *S. mansoni* (Wang *et al.* 2014). Each IR has a unique extracellular N-terminal domain that stabilizes the conformation around the bound ligand (Vicogne *et al.* 2003). These receptors differ in essential signalling motifs and expression locations. IR1 is expressed at the tegumental basal membrane, in muscle tissues, and in the epithelial cells of the intestine, whereas IR2 is predominantly found in the parenchymal cells of adult worms (Khayath *et al.* 2007). Invertebrates typically have a single IR that regulates both metabolism and growth, whereas vertebrates have two receptors: the IR and the insulin-like growth factor 1 receptor, which control glucose uptake and growth, respectively (Kim and Accili 2002). Similarly, in *Schistosoma*, IR1 is likely specialized for glucose uptake, given its colocalization with glucose transporters GTP1 and GTP4 in the tegument. In contrast, the widespread expression of IR2 in the worm parenchyma suggests a role in growth control, similar to the insulin-like growth factor 1 receptor in mammals. Stimulation of IRs by human insulin activates the phosphatidylinositol 3 kinase/Akt/ mechanistic target of rapamycin (PI3K/Akt/mTOR) leading to increase the glucose uptake in *S. mansoni* (Abou-

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El-Naga 2021; McKenzie *et al.* 2018). Several studies have highlighted the significance of schistosome insulin receptors for nutrition, growth, and reproduction (Abou-El-Naga 2021; Elhenawy *et al.* 2017; Vanderstraete *et al.* 2013). RNA interference (RNAi) of the IRs decreases uptake and affects schistosome development (You *et al.* 2015).

Fibroblast growth factor receptors (FGFRs)

Secreted human fibroblast growth factor (FGF) interacts with surface RTKs of the FGF receptors (FGFRs) family, which includes four isoforms (FGFR1–FGFR4). FGF binds FGF ligand to FGFR, thereby phosphorylating mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K)/AKT pathways. Human FGF1 (acidic FGF) and FGF2 (basic FGF) are the most active members of the FGF family and are universally expressed in human tissues. They are released in a signal peptide-independent manner (Ornitz and Itoh 2015).

In the genome of *S. mansoni*, two genes encoding FGFRs were identified. The *fgfrA* gene (Smp_175590) encodes a predicted protein with two extracellular immunoglobulin domains and a split tyrosine kinase domain, while the *fgfrB* gene (Smp_157300) product contains only one extracellular immunoglobulin domain. FGFRA and FGFRB are enzymatically active, expressed in the gonads of schistosomes, and upregulated following pairing, suggesting a role in parasite fertility (Hahnel *et al.* 2014). The expression of *fgfrA* and *fgfrB* has been demonstrated in neoblast-like somatic stem cells, with evidence indicating that both receptors play a crucial role in maintaining schistosome stem cells (Wang *et al.* 2013). FGFRA is abundantly expressed in germinal/stem cells across various *S. mansoni* developmental stages including eggs, miracidia, cercariae, schistosomula, and adult worms. The distribution of FGFRA in embryonic cells of immature eggs and in the neural mass of mature eggs and miracidia, and its co-localization with stem cells in adult *S. mansoni*, strongly suggest its crucial roles in the maintenance of schistosome stem cells, in the development of the nervous and reproductive systems, and in the host-parasite interaction (Wang *et al.* 2013; Wendt and Collins 2016). In vitro, FGFRA of adult worms binds to human FGFs and activates the mitogen activated protein kinase (MAPK) pathway (Du *et al.* 2022). Inhibition of FGF signalling by the TK inhibitor significantly reduced egg hatching ability and altered the behavior of hatched miracidia from treated eggs, highlighting the critical role of FGF signalling in the life cycle of *S. mansoni* (Du *et al.* 2022). Inhibition of *fgfrA* in *S. mansoni* reduces stem cell signalling and increases cell apoptosis. Intravenous injection of mice with *fgfrA*-repressed eggs resulted in significantly smaller granulomas and a reduction in serum IgE levels, underscoring the crucial role of FGFRA in regulating the host immune response during schistosome infection (Du *et al.* 2023).

Venus kinase receptors (VKRs)

S. mansoni expresses an unconventional family of receptor tyrosine kinases (RTKs) known as the Venus kinase receptor (VKR) family, which is unique to invertebrates and was first identified in *S. mansoni.* Typically, invertebrate genomes contain a single VKR gene, but platyhelminths possess two distinct copies of VKR (Vanderstraete *et al.* 2013). VKRs have an extracellular Venus flytrap module, similar to the ligand-binding domain of class C G-protein coupled receptors, connected via a transmembrane segment to an intracellular tyrosine kinase (TK) domain. This Venus flytrap module has two lobes that close upon ligand binding (Vicogne *et al.* 2003). In *S. mansoni*, the two receptors, VKR1 (Smp_019790) and VKR2 (Smp_153500), are activated by L-arginine and calcium ions, respectively (Gouignard *et al.* 2012).

S. mansoni beta-integrin receptor Smβ-Int1 interacts with the SmVKRI. The three putative bridging molecule – SmILK, SmPINCH, and SmNck2 – mediate the Smβ-Int1/SmVKR1 cooperation. This process indicates that SmVKR1 can be activated in a ligand independent manner mediated by receptor/complex interaction (Gelmedin *et al.* 2017).

VKRs are abundantly present in the germinal cells of miracidia, in the larval stage of the parasite, and in the oocytes within the ovary and oviduct of adult female worms. They play crucial roles in growth, differentiation, and reproduction through the PI3K/Akt/mTOR and mitogen-activated protein kinase (MAPK) pathways. VKR1 can also activate the c-Jun N-terminal kinase signal transduction pathway (Gouignard *et al.* 2012; Vanderstraete *et al.* 2014; Vicogne *et al.* 2003). The Smβ-Int1/SmVKR1 signalling complex plays a crucial role in oocytes differentiation and survival of paired schistosomes (Gelmedin *et al.* 2017).

Both *S. mansoni* VKR1 (Smp_019790) and VKR2 (Smp_153500) genes are highly transcribed in the ovaries of females compared to the testes of male worms, and each gene exhibits a distinct expression profile. The distribution of each VKR in *S. mansoni* correlates with its role in oocyte maturation. VKR1 is expressed in mature oocytes located in the posterior part of the ovary and is involved in oocyte migration. VKR2, on the other hand, is expressed in immature oocytes in the anterior part of the ovary and is responsible for their proliferation and growth (Gouignard *et al.* 2012; Vanderstraete *et al.* 2014). Mathavan *et al.* (2022) identified GSK1520489, GSK986310, GW696155, and SB- 710363 as kinase inhibitors of *S. mansoni* VKR2. They inhibit the enzymatic activity and induce phenotypic changes in the worm.

Transforming growth factor receptors

The TGF-β superfamily consists of a wide variety of structurally related polypeptide growth factors that are known to mediate numerous physiological processes, including growth and differentiation, cell death, and tissue repair (Chen *et al.* 2023). Members of the TGF-β superfamily are divided into two major subfamilies based on sequence homology and the distinct downstream pathways they activate. The two subfamilies are the TGF-β/activin/nodal subfamily and the bone morphogenetic protein/growth and differentiation factor/Muellerian inhibiting substance (BMP/GDF/MIS) subfamily (Baba *et al.* 2022).

When activated by a ligand, TGF-β family members bind to a group of transmembrane receptor serine/threonine kinases and transmit signals through them. The receptors are divided into two subtypes: transforming growth factor–β type I receptor (TβRI) (Smp_049760) and type II (TβRII) (Smp_144390). Type II receptor is crucial for ligand binding, and upon ligand binding, it activates type I receptor through phosphorylation (Osman *et al.* 2006). Activated TβRI subsequently transmits the signal to a member of the cytoplasmic Smad family, which can transport the signal to the nucleus and regulate the transcription of specific genes in response to the ligand (Freitas *et al.* 2009). Smads are a group of proteins that act as intracellular signalling transducers for the TGF-β family. In mammals, the two subfamilies of the TGF-β superfamily activate different classes of Smad proteins. Members of the TGF-β subfamily activate Smad2 and Smad3 homologues, while members of the

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BMP subfamily activate Smad1, Smad5, and Smad8 homologues (Hata and Chen 2016).

Several components of TGF-β signalling have been identified in *S. mansoni*, including the TGF-β transmembrane receptor serine/threonine kinases, also known as SmTβRI (Davies *et al.* 1998) and SmTβRII (Osman *et al.* 2006), and two ligands of the schistosome TGF-β family: inhibin/Activin (SmInAct) (Freitas *et al.* 2007) and SmBMP. SmBMP is expressed in the egg, cercariae, and the protonephridia of adult *S. mansoni* worm (Freitas *et al.* 2009). The TGF-β signal also includes four Smad proteins (SmSmad1, SmSmad2, SmSmad4, SmSmad1B) (Carlo *et al.* 2007; Osman *et al.* 2004), in addition to six scaffolding/regulatory proteins that play an important role in signal regulation in the TGF-β pathway. They comprise SmSARA (Verjovski-Almeida *et al.* 2003), SmGCN5, SmCBP (Carlo *et al.* 2007), SmFKBP12 (Knobloch *et al.* 2004), SmeIF2α (McGonigle *et al.* 2002), and Sm14-3-3ε (McGonigle *et al.* 2001).

SmTβRII and SmTβRI are expressed on the surface of the parasite, and in the case of SmTβRI, its expression is upregulated following infection of the mammalian host (Davies *et al.* 1998). TβRII is also localized in the vitelline and gut epithelial cells of female worms and the sub-tegumental cells of male worms (Osman *et al.* 2006). Due to this localization, the schistosome TGF-β signalling pathway may play a crucial role in the development of vitelline cells in female worms and egg embryogenesis (LoVerde *et al.* 2007). SmInAct expression is closely associated with the reproductive potential of the parasite. RNAi-mediated knockdown of SmInAct in eggs halted their development, indicating that SmInAct plays a crucial role in embryogenesis (Freitas *et al.* 2007; Osman *et al.* 2006). SmSmad4 is localized within the epithelia surrounding the gut and vitellarium, as well as in the sub-tegument and muscles of males (Osman *et al.* 2004). SmSmad2 is found within the vitellarium, developing egg and ovary of the female worm, as well as in the testes and tubercles of the male worm (Osman *et al.* 2001). Therefore, the TGF-β signalling pathway in *S. mansoni* has been implicated in host-parasite interactions, parasite reproductive development, and embryogenesis.

SmTβRII is able to activate SmTβRI in the presence of human TGF-β1, which subsequently activates SmSmad2 and promotes its interaction with SmSmad4, thereby facilitating the transfer of the signal from the receptor complex to the Smad proteins. The newly formed Smad complex translocates into the nucleus, where it associates with nuclear proteins that guide the complex to specific promoter sequences, regulating the transcription of target genes (Freitas *et al.* 2009). Oliveira *et al.* (2012) demonstrated that in vitro treatment with human TGF-β1 led to changes in expression levels of 381 *S. mansoni* genes, including 316 downregulated genes and 65 upregulated genes. Among these genes, there are genes related to morphology, development, and cell cycle that could influence effects of cytokine on the worm. Osman *et al.* (2006) demonstrated that TGF-β signalling regulates the expression of the gynecophoral canal protein (SmGCP). This protein is located on the surface of the gynecophoric canal of the male where the female resides for sexual maturation. It is also found on the entire surface of females in copula, but not on unmated males or immature females (Bostic and Strand 1996). Therefore, it could be suggested that SmGCP might be a gene product induced by the TGF-β pathway and could serve as a crucial signalling molecule for worm pairing (Osman *et al.* 2006).

A distinctive biological trait of schistosomes is that sexual maturation of the female depends on continuous pairing contact with the male. After pairing, mitosis and differentiation are triggered in the female, leading to the development of reproductive organs, including the ovary and vitellarium, followed by the production of eggs (Kunz 2001). Eggs are important for propagation of the parasite life cycle and provoking pathogenesis. In *S. mansoni*, the TGF-β pathway is involved in female reproductive development and egg embryogenesis (Freitas *el al.* 2007; Knobloch *et al.* 2007; Osman *et al.* 2006). As TβRs are exposed on the surface, this creates the potential for communication between the male and female parasites. In addition to utilizing host growth factors, it is suggested that schistosomes might also encode endogenous growth factor peptides that have a high degree of sequence similarity with their mammalian orthologues as developmental signals (LoVerde *et al.* 2007).

Nuclear hormone receptors (Table 2)

Nuclear receptors (NRs) are crucial transcriptional regulators that control the expression of specific genes involved in animal development, differentiation, and reproduction. Regulation is achieved by controlling the transcription of target genes through binding to specific DNA response elements (Kunz 2001). NRs are part of a large protein superfamily that includes intracellular receptors for hydrophobic signalling molecules such as steroid hormones, thyroid hormones, and proteins activated by intracellular metabolites (Wu and LoVerde 2019). During the development of schistosomes in their hosts, several hormonal signals may be derived from the schistosome itself or from the host and exert this control through nuclear receptors. As mentioned previously, sexual maturation of female schistosomes depends on continuous pairing contact with the male leading to the development of the reproductive organs and production of eggs (Kunz 2001). Male worms also react to the excretory-secretory products of female worms (Childs *et al.* 1986). Although mammalian sex hormones have no direct effect on the fertility of paired adult schistosome worm maintained in culture (Morrison *et al.* 1986), however, estrogens and androgens influence worm survival in the host (Escobedo *et al.* 2005).

Typically, NRs share a common structure consisting of A/B, C, D, E, F domains and N and C terminals. The N-terminal A/B domain is highly variable and is regulated by interaction with coregulatory proteins and also contains a ligand independent activation function (AF-1), while the C domain, known as the DNA-binding domain (DBD), is the most conserved region, featuring two zinc finger motifs, and is responsible for NR binding to specific DNA sequences. They provide sequence-specific DNA recognition to the regulatory region of the target gene called the hormone response element (HRE). The conserved sequence of the first zinc finger contains a motif called P-box, which is responsible for binding to the target gene, while the conserved sequence of the second zinc finger with a motif called D-box is involved in dimerization. The D domain is poorly conserved and acts as a flexible hinge between DBD and ligand-binding (LBD) domains, giving them some independent mobility. The E domain contains the LBD that controls receptor activity by binding to other LBDs and interacting directly with co-regulatory proteins. It also contains the dimerization surface and a ligand-dependent transcription activation domain (AF-2) (Simons *et al.* 2014). The F domain is sometimes included as part of domain E (E/F domain) (Patel and Skafar 2015; Schote 2007) (Figure 1a).

Atypical NRs are found in certain animals. In arthropods and nematodes, some NRs have a DBD but lack an LBD. In contrast, vertebrates have NRs that lack a DBD but contain an LBD. In addition, the most notable outcome of identifying NRs in *S. mansoni* leads to the discovery of three new members, each of

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Table 2. Nuclear hormone receptors and nuclear transport receptors

Receptors	Gene ID	Gene expression through the life cycle	Gene expression/protein localization in the parasite	Functional analysis performed	Roles	References
Nuclear hormone receptors						
Nuclear receptors subfamily 1						
Thyroid receptors		All stages	In the nucleus	GST pull-down experiments to detect protein-protein interaction	Regulate gene expression for development, growth, and metabolism	Wu *et al.* 2006; Wu *et al.* 2007a
SmTRα	Smp_134490					
SmTRβ	Smp_174260					
Ecdysone-induced protein 78	Smp_000340	All stages, with the highest expression in the miracidia and eggs	In the nucleus	Quantitative real-time RT-PCR	Stimulates host location activities in miracidia	Shiff and Dossaji, 1991; Wu *et al.* 2006; Wu *et al.* 2008
Nuclear receptors in subfamily 2						
Retinoic acid receptors		All stages	RNA in parenchymal cells, epithelial cells surrounding the intestine in both male and female, and vitelline cells	Yeast one-o Assay, protein-protein interaction, in situ hybridization, RNA interference, EdU cell-proliferation assay, in vivo studies	Control the activity of other NRs, oocyte differentiation	Freebern *et al.* 1999a; Freebern *et al.* 1999b; de Mendonça *et al.* 2000; Bertin *et al.* 2005; Fantappié *et al.* 2001 Fantappié *et al.* 2008b; Moescheid *et al.* 2024
RXR 1	Smp_097700					
RXR 2	Smp_073470					
Hepatocyte nuclear factor 4	Smp_174700	All stages with a higher level in cercaria	Stem cells of the gut	RNA interference	Maintenance of gut and nutrient digestion	Wu et al. 2006; Wendt *et al.* 2020
Nuclear receptors in subfamily 5						
Fushi tarazu-factor 1 (SmFTZ-F1)	Smp_328000	All stages	Esophageal gland	RNA interference, chromatin immune precipitation, ChIP-qPCR, fluorescence in situ hybridization	Maintains the esophageal gland	de Mendonça *et al.* 2002; Lu *et al.* 2006; Wu *et al.* 2006; Romero *et al.* 2021
Nuclear transport receptors						
XPO–1	Smp_124820	All stages with a higher level in the schistosomula	In the nucleus	Quantitative RT-PCR	Gene expression and regulation of cellular processes	Abreu *et al.* 2013
XPO–5	Smp_152800					
XPOT	Smp_137650					

Gene ID is extracted from the WormBase ParaSite using the reference genome for *S. mansoni*, SM_V10 (WormBase ParaSite 2024).

which contains a distinctive combination of two DBDs arranged in tandem with a single LBD (Wu *et al.* 2006; Wu *et al.* 2007a). This is followed by further identification of this member in other invertebrates (Wu *et al.* 2007b; Wu and LoVerde 2023).

Based on phylogenetic reconstructions of the DBD and LBD, NRs are divided into six classical subfamilies (NR1-NR6). In addition, an extra subfamily, NR0, has been identified. Members of this subfamily either contain only a DBD (NR0A) or only an LBD (NR0B) (Nuclear Receptors Nomenclature Committee 1999). *S. mansoni* contains 21 NRs that can be categorized into many subfamilies, including NR1, NR2, NR4, and NR5 (Wu and LoVerde 2019). NRs in *S. mansoni* consist of six members in subfamily 1 (NR1), nine members in subfamily 2 (NR2), one member in subfamily 4 (NR4), and two members in subfamily 5 (NR5). *S. mansoni* contains also three novel members, each characterized by a distinctive combination of two DBDs in tandem with LBD – Sm2DBD-NRα, Sm2DBD-NRβ, and Sm2DBD-NRγ with a novel modular structure: A/B-DBD-DBD-hinge-LBD organization (Wu *et al.* 2006; Wu *et al.* 2007a). The worm does not contain NRs in subfamily 3 (NR3) or subfamily 6 (NR6). Among these 21 receptors, the full-length cDNA of 14 members has been isolated and studied (Wu *et al.* 2006).

The control function of the NRs on gene expression often requires interaction with endogenous or exogenous ligands. Unlike other transcription factors, NRs can modulate their activity by binding to specific ligands, which are primarily small lipophilic molecules that readily penetrate biological membranes (Novac and Heinzel 2004). This binding creates a direct link between cellular signals and the transcriptional responses of the cell. These lipophilic ligands include fatty acids, steroids, retinoids, phospholipids,

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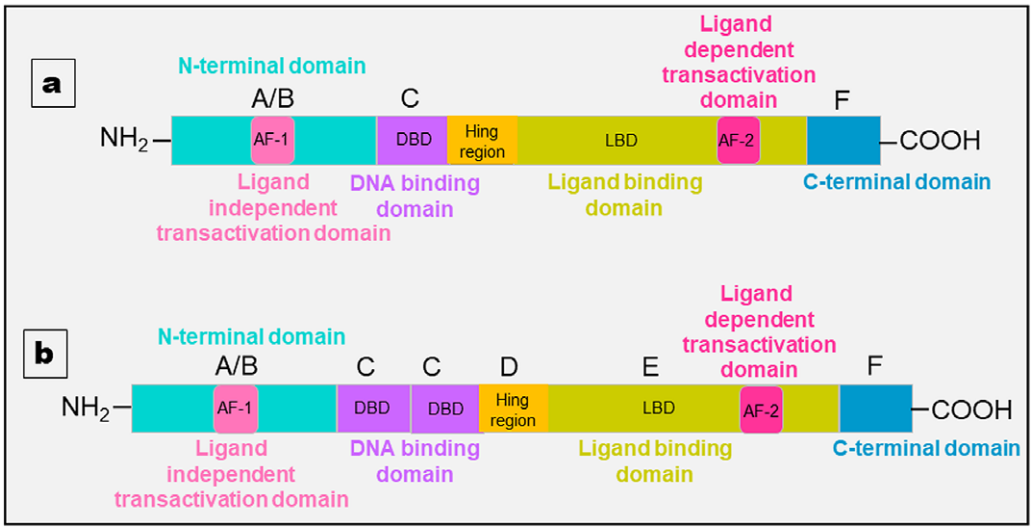

Figure 1. (a) Schematic diagram of a typical nuclear receptor (NR) consisting of A/B, C, D, E, F domains and N and C terminals. The A/B domain includes the activation function 1 (AF-1), C domain is a DNA binding domain (DBD), D domain is a hinge region, E domain contains a ligand binding domain (LBD), and AF-2. **(b)** Schematic diagram for atypical NRs of *S. mansoni* containing two DBDs and a single LBD.

vitamin D, and thyroid hormone. However, NRs without known ligands have yet been identified and referred to as orphan receptors (Li *et al.* 2024). NRs execute their gene regulatory role by binding to the regulatory regions of target genes (often called hormone response elements (HREs) to activate or repress mRNA synthesis. Binding occurs following ligand-induced activation and subsequent recruitment of co-factors. NRs can bind to HREs as homodimers, heterodimers, or monomers (Weikum *et al.* 2018). Response elements are composed of distinct arrangements of the core motif that can be recognized by NRs derivatives of this same DNA core motif (Pawlak *et al.* 2012). HRE-like elements have been identified in several schistosome genes, and gel-shift assays have shown that nuclear proteins can bind to these sequences. Notably, the F10 gene, encoding the F10 egg shell protein, contains a monomeric HRE-like element, and the protein binding pattern to the F10 promoter is modified by the estrogen antagonist tamoxifen (Giannini *et al.* 1995).

NRs regulate transcription by binding to the promoter region of their target gene via the DBD and regulating the expression of related target genes through the recruitment of coactivators or corepressors when ligands bind to the receptors (Hong *et al.* 2019). NRs can be classified into two broad subtypes based on their mechanisms of action. Type I NRs are found in the cytoplasm in the absence of ligands, where they form complexes with heat shock proteins (HSPs) that regulate their cellular localization, protein stability, and transcriptional activity (Echeverria and Picard 2010). When a ligand binds, the receptor is released from the HSP, undergoes dimerization, and trans-locates to the nucleus. In the nucleus, the ligand-receptor complex associates with coactivators and RNA polymerase, enabling binding to and activation of target genes (Bulynko and O'Malley 2011). Type II NRs are located in the nucleus, bound to DNA, regardless of their ligand-binding status. These receptors typically form heterodimers with retinoid X receptors (RXRs). In the absence of a ligand, the NR is associated with corepressor proteins. Ligand binding to the NR triggers the dissociation of corepressors and the recruitment of coactivator proteins, which then attract RNA polymerase. This complex facilitates the transcription of downstream DNA into RNA, ultimately leading to protein production and changes in cellular function (Lazar 2017).

S. mansoni *nuclear receptors in subfamily 1*

The well-characterized proteins of *S. mansoni* NR1 are *S. mansoni* thyroid receptors (SmTRs). Two homologs of vertebrate TR have been identified in *S. mansoni* (SmTRα and SmTRβ) (Smp_134490, Smp_174260). Phylogenetic analysis indicates that these two copies resulted from a gene duplication specific to *Schistosoma* (Wu *et al.* 2007a). Both proteins exhibit the consensus structure of TR, featuring a conserved N-terminal signature in the A/B domain typical of TRs, along with the specific CEGCKGFFRR sequence of the NR1 subfamily. Like vertebrate members of this family, SmTRs can form a dimer with retinoid X receptor (SmRXR1). SmTRs could bind to vertebrate TR core DNA elements as a monomer, a homodimer, or a heterodimer by binding with RXR (Wu *et al.* 2006; Wu *et al.* 2007a). Thyroid hormone (TH) binds to the LBD of the TR, inducing a conformational change in C-terminus of the receptor. This change causes the dissociation of corepressors from the TR, allowing coactivators to bind to the C-terminus in a hormone-dependent manner. The TR and coactivator complex then activates target gene expression (Lazar 2017).

An ortholog of the *Drosophila* ecdysone-induced protein 78 has been identified in *S. mansoni* (Wu *et al.* 2006; Wu *et al.* 2008). It is directly involved in ecdysone signaling. *SmE78* (Smp_000340) is expressed throughout schistosome development, with the highest expression levels observed in the miracidia and egg stages (Wu *et al.* 2008). Nirde *et al.* (1983) have shown that *S. mansoni* can synthesize the steroid hormone ecdysone. Ecdysterone effectively stimulates host location activities in miracidia (Shiff and Dossaji 1991). However, it remains to be demonstrated whether ecdysone-induced protein 78 is involved in the transduction of an ecdysone signal in *S. mansoni* (Wu and LoVerde 2011).

Another potential member of the SmNP1 subfamily is Smp_248100, an uncharacterized protein from *S. mansoni.* Primary sequence analysis has confirmed that Smp_248100 contains a DNA-binding domain (DBD) with high sequence similarity to DBDs of other vertebrate and invertebrate NRs, including HR96 from *Drosophila melanogaster* and DAF-12 from *Caenorhabditis elegans.* SmHR96α and SmHR96β are homologues of *Drosophila* hormone receptor 96 (DHR96) (Hu *et al.* 2006a; Wu *et al.* 2006).

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SmHR96α interacts with SmRXR1 (Hu *et al.* 2006b). The mRNA of SmHR96α is expressed throughout every stage of the *S. mansoni* life cycle, with particularly high expression levels in eggs and cercariae. The SmHR96α protein is located in subtegumental and parenchymal cells in both male and female worms, as well as in the ovaries, eggs, and vitelline cells of mature female worms (Hu *et al.* 2006a). SmHR96β is recently named Vitellogenic Factor 1. This factor is important in vitelline cell development, and this NR is important for female sexual development after pairing with a male worm (Wang *et al.* 2019).

The divergent member SmNR1 is a member of NR subfamily I with no known orthologue. The gene of this member is located on chromosome 1 of *S. mansoni* and is highly expressed in eggs, sporocysts, and juvenile worms (Wu *et al.* 2007c). The divergent member SmNR1 is a partner of SmRXR1. It requires RXR to form a heterodimer that confers binding to hormone response element (Kojetin *et al.* 2015). Mutagenesis analysis indicates that SmCBP1, a co-regulatory protein known to interact with SmFTZ-F1 (Bertin *et al.* 2006), can mediate interactions with the LBD of SmRXR1 and SmNR1 (Fantappié *et al.* 2008a). The upstream region of the *p*14 gene has a novel NR response element containing DNA core motif, composed of an atypically spaced direct repeat 17. SmRXR1 and SmNR1 divergent members specifically bound to the p14-direct repeat 17 element as a heterodimer. SmRXR1, but not SmNR1, is bound to the motif as a monomer. The expression of the *S. mansoni p*14 gene, which is an eggshell precursor gene expressed only in the vitelline cells of sexually mature female worms in response to an as yet unidentified male stimulus, is regulated through NR signalling pathway (Fantappié *et al.* 2008b).

S. mansoni *nuclear receptors in subfamily 2*

S. mansoni NRs in subfamily 2 include SmTR2/4, 9-cis-retinoic acid receptors (RXR), and hepatocyte nuclear factor 4 (HNF4). The SmTR2/4 gene is expressed in all developmental stages of *S. mansoni* with a higher level in cercaria and may play a role in regulating female reproductive development (Hu *et al.* 2006c).

SmRXR1 (Smp_097700) and SmRXR2 (Smp_073470) are the vertebrate RXR homologues present in *S. mansoni* (de Mendonça *et al.* 2000; Freebern *et al.* 1999a; Freebern *et al.* 1999b). Both SmRXRs originated from a *Schistosoma*-specific gene duplication, like SmTRs. RXR is involved in multiple signalling pathways within the cell nucleus, and its heterodimers control the activity of other NRs (Bertin *et al.* 2005). SmRXR1 can form heterodimers with SmTRα, SmTRβ (Wu *et al.* 2007b), SmHR96α (Hu *et al.* 2006b), and SmNR1 divergent member (Wu *et al.* 2007c). It can also bind to the cis-elements of the *S. mansoni p*14 gene (Fantappié *et al.* 2008b; Freebern *et al.* 1999b), which is regulated by a stimulus from the male schistosome (LoVerde *et al.* 2004). SmRXR1 mRNA is consistently expressed throughout the developmental stages (Fantappié *et al.* 2008b). The co-regulatory protein SmCBP1 can mediate interactions with both SmRXR1 and SmNR1 (Fantappié *et al.* 2008a). In contrast, SmRXR2 fails to form a heterodimer with SmTRα or SmTRβ (Wu *et al.* 2007b), SmHR96α (Hu *et al.* 2006b) or SmNR1 divergent member (Wu *et al.* 2007c). SmRXR2 mRNA is expressed at all life cycle stages, with higher levels in cercariae and miracidia – the free-living larval stages (de Mendonça *et al.* 2000; Freebern *et al.* 1999a). However, the protein expression differs significantly from mRNA, showing high levels in schistosomula but much lower levels in cercariae and miracidia (de Mendonça et al. 2000).

HNF4 is a class of NRs responsible for regulation of gluconeogenesis, bile acid synthesis, cholesterol, and lipid metabolism in the liver of mammals (Chen *et al.* 2020). Stem cells from the blood-digesting gut of *S. mansoni* express the hnf4 gene (Smp_174700), identified by single-cell sequencing. RNAi assay revealed the importance of the hnf4 gene for gut maintenance, nutrient digestion, and pathology induction, and indirectly showed its importance for parasite growth (Wendt *et al.* 2020). In *S. japonicum*, HNF4 expression is higher in female than in male worms, both at transcriptional and protein levels. HNF4 is expressed in the reproductive system and intestinal tissues of worms, as well as in cercariae and eggs (Wu *et al.* 2024). Furthermore, HNF4 plays an important role in blood feeding and interaction with vital pathways such as glucose, lipid, and nucleotide metabolism. Schistosomes obtain hemoglobin, plasma proteins, and immunoglobulins from the blood to meet their energy needs. The processing of these proteins is carried out by a complex system comprising various proteases, many of which are associated with HNF4 in *S. japonicum*. Furthermore, HNF4 is connected to several proteins involved in carbohydrate metabolism (Wu *et al.* 2024). Glucose, an essential nutrient, serves as the main energy source for schistosomes, providing them with the energy necessary for their growth and reproduction (You *et al.* 2014). Adult worms possess a higher lipid content and rely on their host for lipid acquisition (Skelly *et al.* 2014). A strong correlation between SjHNF4 and the phospholipid metabolism pathway suggests that SjHNF4 also contributes to lipid metabolism in *S. japonicum* (Wu *et al.* 2024).

S. mansoni *nuclear receptors in subfamily 4*

NR4A is the only member of subfamily 4 identified in *Schistosoma* worms. SmNR4A, like the human and *Drosophila* members of NR subfamily 4, has an atypical LBD suggesting that SmNR4A is an orthologue of *Drosophila* and human NR4A (Wu and LoVerde 2021). SmNR4A is highly expressed in daughter sporocysts and adult worms, but scarcely in cercariae and early schistosomules (Wu and LoVerde 2008).

S. mansoni *nuclear receptors in subfamily 5*

Fushi tarazu-factor 1 (FTZ-F1) (Smp_328000) NRs are the only receptors of subfamily 5 that have been characterized in *S. mansoni*. SmFTZ-F1 NRs contain two NRs: the SmFTZ-F1α belonging to NR5A group and the SmFTZ-F1 belonging to NR5B group (Lu *et al.* 2006; Wu *et al.* 2006). Smftz-f1α is continuously expressed throughout the schistosome life cycle, with the highest expression level observed at the egg stage (Lu *et al.* 2006). RT-PCR reveals that Smftz-f1 is expressed at all developmental stages, with higher mRNA levels in miracidia, sporocysts, and cercariae. However, protein expression levels differ, being highest in cercariae, schistosomula, and male worms (de Mendonça et al. 2002). Romero *et al.* (2021) identified the micro-exon gene meg-8.3 as a target gene of SmFtz-F1, and this gene is expressed exclusively in the esophageal gland of the worm. They also found that Smftz-f1 and meg-8.3 are essential for maintaining the esophageal gland and preserving the integrity of the worm's head. The esophageal gland plays a crucial role in protecting the worm from host attacks (Lee *et al.* 2020).

S. mansoni *nuclear receptors subfamily with two DBDs and a single LBD (2DBD-NRs) (Figure 1b)*

One of the most interesting findings is the isolation of a new group of NRs from *S. mansoni*, in which each receptor contains two DBDs and a single LBD (2DBD-NRs) (Wu *et al.* 2006). *S. mansoni*

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Genome Project verified its presence (Berriman *et al.* 2009). These NRs have a novel modular structure: A/B-DBD-DBD-hinge-LBD organization in the NR. Sm2DBD-NRα is able to form a homodimer but cannot form a heterodimer with RXRs. *S. mansoni* expresses three 2DBD-NRs (Sm2DBD-NRα, Sm2DBD-NRβ, and Sm2DBD-NRγ) located on different chromosomes (Wu *et al.* 2007a). 2DBD-NRs have been identified and/or isolated only in Platyhelminths (Wu *et al.* 2006; Wu *et al.* 2007a; Wu and LoVerde 2021) and Mollusca (Kaur *et al.* 2015; Vogeler *et al.* 2014), suggesting they may be species-specific. Recently, 2DBD-NRs were identified in different animals (Wu and LoVerde 2023). As shown by qRT-PCR, the three Sm2DBD NRs are developmentally regulated. Sm2DBD-NRα was found in sporocysts, cercariae, schistosomules, and male and female worms; Sm2DBDNRβ was expressed at high levels in eggs, sporocysts, cercariae, and male worms; and Sm2DBD-NRγ was only found in cercariae and juvenile worms (Wu *et al.* 2007a).

Nuclear transport receptors (Table 2)

Nuclear transport is the mechanism by which molecules move across the nuclear membrane of a cell. Transport of proteins and RNA across the nucleus occurs through the nuclear pore complex and is facilitated by a superfamily of transport receptors collectively known as karyopherins. The entry and exit of the molecules from the nucleus is tightly controlled by the nuclear pore complexes (NPCs). Although small molecules can enter the nucleus without regulation, macromolecules such as RNA and proteins require association with nuclear transport receptors (Mackmull *et al.* 2017).

Transport receptors that import cargo are called importins, and transport receptors that export cargo are called exportins. Exportins (XPOs) are nuclear export receptors concerned with export of various RNA species generated in the nucleus to the cytoplasm via the NPCs. This transport is vital for gene expression in eukaryotic cells. The nucleocytoplasmic transport occurs through different mechanisms: small RNAs (such as tRNAs and microRNAs) bind directly to export receptors, while larger RNAs (including ribosomal RNAs and mRNAs) use a more complex process. XPOs bind nuclear cargo only by identifying short signal peptides on cargo proteins or specific motifs on RNA cargoes (Köhler and Hurt 2007). Furthermore, XPOs export only functional mRNAs into the cytoplasm. This quality control step is an important step, as faulty or unprocessed mRNAs can be harmful if translated in the cytoplasm (Lackner and Bähler 2008).

Eight XPOs have been characterized (XPOs1-7), in addition to XPOT (Mingot *et al.* 2004). Homologs of XPO1 (Smp_124820), XPO5 (Smp_152800), and XPOT (Smp_137650) are present in animals, fungi, and plants, while nematodes and arthropods lose XPO5 or XPO1 during evolution (Murphy *et al.* 2008). Schistosoma has a complex life cycle, and several life cycle stages are present in different hosts and environments, thus indicating differential gene regulation. Abreu *et al.* (2013) identified the presence of XPO5, XPOT, and XPO1 at various stages of the *S. mansoni* life cycle, suggesting that exportins play a key role in the transport of different RNAs. Moreover, the authors demonstrated that XPOs are upregulated in schistosomula more than cercariae. As the level of protein synthesis is increased in schistosomula during the first 24 h after transformation (Blanton and Licate 1992), this may involve an alteration in protein synthesis (Abreu *et al.* 2013). XPO1 was found to be the most expressed receptor in all stages of life cycle of schistosomes compared to XPO5 and XPOT (Abreu *et al.* 2013). XPO5 is involved in the export of microRNAs, while XPOT is involved in the export of tRNAs. XPO1 plays a crucial role in the transport of several proteins with leucine-rich nuclear export signals: snRNAs involved in splicing, rRNA subunits, and certain mRNAs (Yang *et al.* 2023). Thus, it is suggested that RNA transport by exportins may regulate cellular processes during the development of cercariae, schistosomula, and adult worms (Abreu *et al.* 2013).

Nuclear transport receptors are regulated by the small GTPase, Ran. Importins bind to the cargo protein that carries components of nuclear export signal (NES) into the cytoplasm through NPCs, and the cargo is released into the nucleus after transport, a process that is triggered by the binding of RanGTP (Tran *et al.* 2014).

XPOs form a complex with RanGTP to be translocated to the cytoplasm. In the cytoplasm, RanGDP dissociates the complex upon hydrolysis of RanGTP, resulting in the release of the cargo (Köhler and Hurt 2007). XPO5 is responsible for exporting precursor miRNAs across the nuclear membrane into the cytoplasm and is therefore a critical step in miRNA biogenesis. The pre-miRNAs are transported from the nucleus to the cytoplasm, where they are enzymatically processed to become mature miRNAs. However, miRNAs can also use XPO1 for nuclear-cytoplasmic shuttling (Castanotto *et al.* 2009). Both XPO5 and XPOT bind directly to pre-miRNA and tRNA, respectively, in a RanGTP dependent manner and diffuse into the cytoplasm through the NPC, where the complex dissociates (Köhler and Hurt 2007; Okada *et al.* 2009). Ran-GTP is hydrolyzed, forming a Ran-GDP complex, which is then transported back to the nucleus. Thus, while importins rely on RanGTP to release their cargo, exportins need RanGTP to bind theirs. XPO1 does not directly interact with the snRNA, rRNA, and mRNA cargo proteins, but requires the cap-binding complex (CBC) protein and a NES containing adaptor protein and RanGTP to be released into the cytoplasm (Köhler and Hurt 2007). Transport of different *S. mansoni* RNAs by XPO5, XPOT, and XPO1 is illustrated in Figure 2.

Neurotransmitter receptors (Table 3)

The schistosome nervous system is fundamental to the successful migration of the parasite through the host, as well as its feeding and egg-laying activities. The central nervous system of trematodes includes two pairs of cerebral ganglia, each of which is a bi-lobed structure. From each lobe of the cerebral ganglia extend pairs of dorsal, ventral, and lateral nerve cords. These longitudinal nerve cords are interconnected by transverse commissures along the length of the worm. Trematodes also possess a peripheral nervous system consisting of finer nerve fibers and plexuses. These connect to all major body structures, including the somatic musculature, the tegument, the oral and ventral suckers, the reproductive organs, and the alimentary tract. In addition, the surface of the worm is abundant in sensory nerve endings that act as an interface between the parasite and the host environment (Halton and Maule 2004).

The schistosome nervous system is involved in signal transduction through synaptic and paracrine mechanisms, since schistosomes lack a circulatory system and therefore cannot carry out classical endocrine signalling (El-Shabasy *et al.* 2024; Halton and Maule 2004). Neurotransmitters bind to their cognate receptors and elicit effects directly or through second messenger cascades (Ribeiro and Geary 2010; Ribeiro *et al.* 2012). Neurotransmitter receptors can be categorized into two main classes: Cys-loop ligand-

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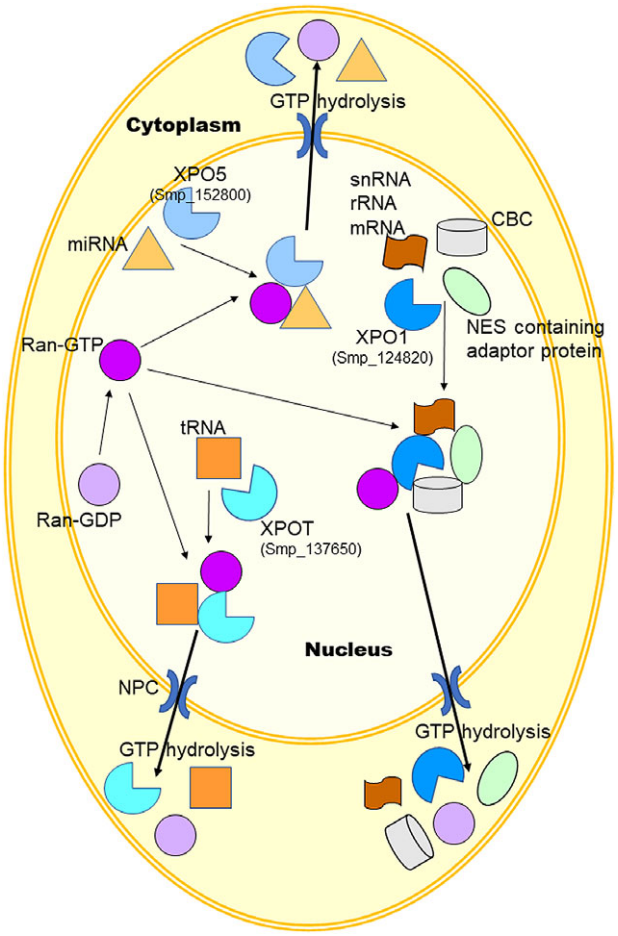

Figure 2. Schematic diagram of *S. mansoni* RNAs transport by XPO5, XPOT, and XPO1. XPO5 (Smp_152800) binds to pre-miRNA, and XPOT (Smp_137650) binds to tRNA directly in a RanGTP dependent manner. Once RNA proteins are exported to the cytoplasm, the RanGTP is converted to GDP resulting in the release of pre-miRNA from the XPO5 and tRNA from the XPOT. Nuclear export of snRNA, rRNA, and mRNA by XPO1 (Smp_124820) requires the cap-binding complex (CBC) protein, a nuclear export signal (NES) containing adaptor protein and RanGTP. The complex transits to the cytoplasm through the nuclear pore complex (NPC) and releases the cargo protein upon the hydrolysis of RanGTP.

gated ion channels and metabotropic, seven-transmembrane G protein-coupled receptors (GPCRs). Neurotransmitters include acetylcholine (ACh), glutamate, and the biogenic amines. Biogenic amines are a group of structurally related amino acid derivatives that serve as neurotransmitters across various organisms. This group includes catecholamines synthesized from tyrosine (dopamine, noradrenaline, adrenaline), serotonin from tryptophan (5-hydroxytryptamine (5-HT)), and histamine form histidine. In addition, biogenic amines include octopamine and its precursor tyramine. Octopamine is a tyrosine-derived and invertebrate-specific neurotransmitter (El-Sakkary *et al.* 2018). In flatworms, including *S. mansoni*, biogenic amines play a crucial role in regulating muscle contraction and movement, activities essential for survival of the parasite within the host (Cheng *et al.* 2019; El-Sakkary *et al.* 2018; Ribeiro and Geary, 2010). The most studied of these amines is serotonin, which causes muscle excitation in all flatworm species examined so far. Serotonin is widely distributed in *S. mansoni* nervous system, with evidence of a serotonin transport system in the worm (Patocka and Ribeiro 2007). In addition to serotonin, flatworms possess both dopamine and histamine in their nervous systems. Dopamine, in particular, plays significant neuromuscular roles, which can be either excitatory or inhibitory depending on the flatworm species. In *S. mansoni*, dopamine induces relaxation of the body wall muscles, possibly by activating a receptor associated with neuromuscular structures (Taman and Ribeiro 2009). In addition to their motor effects, biogenic amines have been implicated in the regulation of metabolic activity in several flatworms (Caveney *et al.* 2006). Moreover, serotonin and dopamine are involved in the transformation of *S. mansoni* miracidia to the sporocyst stage (Ribeiro and Patocka 2013; Taft *et al.* 2010;), suggesting a probable role in parasite development.

G protein-coupled receptors (GPCRs)

GPCRs represent the largest family of trans-membrane receptors involved in cellular communication in living organisms. These receptors can detect extracellular signalling molecules such as ions, light, hormones, neurotransmitters, amino acids, and neuropeptides, subsequently initiating a series of intracellular signal transduction pathways to produce the corresponding physiological effects (Weis and Kobilka 2018). Biogenic amines exert their effects by interacting with cell-surface receptors, most of which belong to the superfamily of GPCRs. These receptors play roles in various biological processes, including growth, differentiation, neuronal signaling, olfaction, metabolism, and reproduction. The significance of GPCRs is underscored by their medical importance, as 30% to 50% of all pharmaceutical compounds target GPCRs and the signalling pathways they mediate (Miao and McCammon 2016).

GPCRs are composed of an extracellular N-terminus, a bundle of seven transmembrane α-helices (7TM), connected by extracellular and intracellular loops, and an intracellular C-terminus. The extracellular region, which includes the N-terminus, is responsible for ligand binding and varies in size from relatively short and often unstructured sequences in rhodopsin-like receptors to larger globular domains in other GPCR classes (Lagerström and Schiöth 2008). The intracellular region interacts with G proteins, arrestins, and other downstream effectors (Tobin *et al.* 2008).

GPCRs can activate guanine nucleotide-binding proteins (G proteins), which are responsible for signal transduction within the cell. G proteins transmit signals within the cell by interacting with various effector molecules, typically leading to changes in second messenger concentrations and subsequent cellular responses (Luttrell 2008). In addition, GPCRs can activate G protein-independent signalling pathways via adaptor proteins such as arrestins (Bologna *et al.* 2017). Moreover, GPCRs can collaborate with other membrane proteins such as integrins and receptor tyrosine kinases (RTKs) (Cattaneo *et al.* 2014; Pyne and Pyne 2011). When a ligand binds to a GPCR, it undergoes conformational changes and releases membrane-associated G-protein subunits (α, β, and γ). In this activated state, the GPCR functions as a guanine nucleotide exchange factor, promoting the exchange of GDP for GTP in the α subunit, leading to its dissociation from the βγ dimer. Both the dissociated α subunit and the βγ dimer can then trigger downstream signalling pathways (Frooninckx *et al.* 2012).

According to the GRAFS classification, the mammalian GPCR are classified into five main families; Rhodopsin (Class A), Glutamate (Class C), Adhesion (Class B2), Frizzled/taste2 (Class F), and Secretin (Class B) (Bjarnadóttir *et al.* 2006). In addition to these major families, some organisms have lineage-specific receptors that

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Table 3. Neurotransmitter receptors

Receptors	Gene ID	Gene expression through the life cycle	Gene expression/ protein localization in the parasite	Functional analysis performed	Roles	References
G protein-coupled receptors						
Rhodopsin receptors α						
Histamine receptors						
SmGPR–1	Smp_043260	Adult and cercaria	Tegument and muscles	Confocal immunofluorescence studies	Muscle excitation	El-Shehabi *et al.* 2009
SmGPR–2	Smp_043340	Schistosomula	Sub-tegumental neuronal plexus	Confocal immunofluorescence studies, Ligand-binding assay	Muscle excitation	El-Shehabi and Ribeiro 2010
Dopamine receptors						
SmD2	Smp_127310	Adult, cercaria, and schistosomula	Sub-tegumental somatic musculature and acetabulum	Confocal immunofluorescence studies	Inhibits adenylyl cyclase, muscle control	Taman and Ribeiro 2009
SmGPR–3	Smp_043290	Adult and schistosomula	Nervous system particularly in the main nerve cords and in the peripheral innervation of body wall muscles	Confocal immunofluorescence studies	Indirect muscle control	El-Shehabi *et al.* 2012
Serotonin receptors	Smp_126730	Adult and schistosomula	Cerebral ganglia, main nerve cords and peripheral nerves of the body wall, muscles, and tegument	Confocal immunofluorescence studies and motility assays	Motor control	Patocka *et al.* 2014
Octopamine	Smp_150180	Adult and schistosomula	Central and peripheral nerves	Confocal immunofluorescence studies	Motor control	Protasio *et al.* 2012
Tyramine	Smp_043290	Adult and schistosomula	Central and peripheral nerves	Confocal immunofluorescence studies	Motor control	Protasio *et al.* 2012
Rhodopsin β receptors						
Rhodopsin orphan GPCR20	Smp_084270	Paired male, unpaired male, and unpaired females	Neural cells	Double fluorescence, in situ hybridization, RNA interference	Egg production, oogenesis, and growth of females	Hahnel *et al.* 2018; Lu *et al.* 2016; Li *et al.* 2024
Adhesion and Secretin receptors						
Integrins						
Smα-Int1	Smp_126140	Adult worms	Gonads	Interaction studies by yeast two-hybrid analyses and coimmunoprecipitation, signal transduction assay, RNA interference	Adhesion, regulation of growth and reproductive organs differentiation, and modulating the immune response	Knobloch *et al.* 2007; Beckmann *et al.* 2012; Gelmedin *et al.* 2017; Samoil *et al.* 2018
Smα-Int2	Smp_170280	Adult worms	Surrounding the ootype			
Smβ-Int1	Smp_089700	Adult worms	Gonads, surrounding the ootype			
Glutamate receptors						
SmGluR	Smp 128940	All life cycle stages	Cerebral ganglia, longitudinal nerve cords, and female reproductive tract	Indirect immunofluorescence, confocal immunofluorescence analysis, RT-PCR	Modulating excitatory neurotransmission and influencing behavioral responses	Mendonça-Silva *et al.* 2002; Taman and Ribeiro, 2011a

(*Continued*)

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Table 3. (*Continued*)

Receptors	Gene ID	Gene expression through the life cycle	Gene expression/ protein localization in the parasite	Functional analysis performed	Roles	References
SmGBP	Smp_052660	Male worms	Surface membranes of adult male, especially the dorsal tubercles	Surface biotinylation combined with western blot analyses and confocal immunolocalization, quantitative PCR	Host-parasite interaction	Taman and Ribeiro, 2011b
Frizzled receptors						
SmFz1 gene	Smp_11897, Smp_173940	Female adult worms	Gonads	In situ hybridization, signal transduction assay, inhibition treatment	Fertility	Hahnel *et al*. 2014
Acetyl choline receptors						
- SmACCs						
SmACC–1	Smp_176310	Adults and schistosomula	Peripheral nervous system	Pharmacological and RNA interference, immunolocalization using confocal microscopy	Inhibition of neuromuscular function	MacDonald *et al.* 2014
SmACC–2	Smp_142690	Adults and schistosomula	Peripheral nervous system	Pharmacological and RNA interference, immunolocalization using confocal microscopy	Inhibition of neuromuscular function	MacDonald *et al.* 2014
- SmGAR	Smp_145540	Cercaria and schistosomula	Peripheral nervous system	RNA interference	Excitatory motor activity	MacDonald *et al.* 2015

Gene ID is extracted from the WormBase ParaSite using the reference genome for *S. mansoni*, SM_V10 (WormBase ParaSite 2024).

establish distinct GPCR families (Hofmann and Palczewski 2015). Rhodopsin-like receptors (Class A) are the most common of all known GPCRs. They are distinguished by short N-termini and their ability to interact with a wide range of ligands. The Glutamate receptor family is characterized by long N-termini that function as the binding site for ligands. Similarly, Adhesion receptors possess long N-termini containing a variety of domains, whereas Frizzled receptors feature long, cysteine-rich N-termini (Lagerström and Schiöth 2008).

All major GPCR subfamilies were represented in schistosomes, and most of them respond to classical biogenic amines and neurotransmitters like dopamine, histamine, and serotonin (El-Shehabi *et al.* 2012; Hahnel *et al.* 2014; MacDonald *et al.* 2015; Patocka *et al.* 2014; Ribeiro *et al.* 2012). *Schistosoma* GPCRs (SmGPCRs) are detected at the cell membrane and have a typical GPCR structure, an extracellular N-terminus, and an intracellular C-terminus. Most of homologues of SmGPR are characterized by the replacement of the highly conserved aspartate $D^{3.32}$ of TM domain 3 with asparagine (Hamdan *et al.* 2002). Zamanian *et al.* (2011) identified 117 *S. mansoni* G PCRs genes that include all major families; 105 Rhodopsin, 2 Glutamate, 3 Adhesion, 2 Secretin, and 5 Frizzled. Among these gene receptors, novel receptor groups have been detected, including a highly diverged Platyhelminth-specific Rhodopsin and atypical Glutamate-like receptors. Genome sequencing of *S. mansoni* has identified 126 GPCRs (Hahnel *et al.* 2018; Kamara *et al.* 2023). However, only a few of these GPCRs have been characterized in terms of its molecular and functional properties (Hoffmann *et al.* 2001; MacDonald *et al.* 2015; Patocka *et al.* 2014; Taman and Ribeiro 2009). The diversity of GPCR genes in *S. mansoni* indicates a wide array of functions, potentially including reproductive development (Hahnel *et al.* 2018).

Rhodopsin receptors

Rhodopsin receptors are prototypical GPCRs (Class A). They are further characterized by a relatively short extracellular N-terminus, which is typically glycosylated, and an intracellular C-terminal tail of variable length (Kristiansen 2004). Analysis of mammalian genomes revealed that the Rhodopsin family is divided into four main groups (α, β, γ, and δ) (Fredriksson *et al.* 2003). The α and β subfamilies are the only subfamilies present in *S. mansoni.* Alpha receptors contain amines (the largest group), opsin-like receptors, and melatonin receptors. *S. mansoni* possesses at least 24 putative aminergic receptors and four melanopsin-like receptors, but no melatonin-like receptors. The β subfamily contains the neuropeptide and peptide hormone GPCRs. *S. mansoni* contains 36 putative peptide receptors. In addition, unclassified Rhodopsin receptors have been found. A new receptor, Platyhelminth Rhodopsin Orphan Family 1, has been identified. These receptors, although displaying remnants of classical Rhodopsin, do not show homology to any previously identified GPCRs (Zamanian *et al.* 2011).

Ortholog of Rhodopsin GPCRs identified in *S. mansoni* miracidia share similarity with Rhodopsin GPCRs of the intermediate host *B. glabrata.* These GPCRs may detect similar ligands, including snail-derived odorants that could facilitate miracidial host finding (Phan *et al.* 2022).

Rhodopsin Alpha (α) subfamily receptors

S. mansoni has histamine receptors belonging to Class A (rhodopsin-like) GPCRs. Histamine is strongly myo-excitatory in *S. mansoni* and is endogenously biosynthesized (Hamdan and Ribeiro 1999). A histamine receptor called SmGPR-1 (Smp_043260) (formerly SmGPCR)

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was cloned in *S. mansoni*. SmGPR-1 has a structure characteristic of the amine GPCR family but does not obviously resemble any of the histamine receptors in mammals. Histamine activation of SmGPCR triggered mobilization of intracellular calcium, but not cAMP. Furthermore, SmGPCR-1 showed a glycine (Gly^{196}) substitution instead of (Asn/Thr) or charged residue (Glu) in TM domain 5 and an asparagine (Asn^{111}) instead of aspartate of TM domain 3 (Hamdan *et al.* 2002). El-Shehabi *et al.* (2009) revealed that this receptor is expressed in the tegument and musculature of both cercariae and adult parasites.

SmGPR-2 (Smp_043340) is a second histamine receptor of *S. mansoni*. It is an orphan receptor expressed in the vicinity of histamine-containing neurons in the sub-tegumental neuronal plexus. It is developmentally regulated showing up-regulation in the parasitic stages compared to cercaria, with the highest level of expression in young schistosomula. The highly conserved aspartate $D^{3.32}$ of TM domain 3 is also absent in SmGPR-2. This receptor has a novel pharmacological profile. It is inhibited by drugs not known to interact with histamine receptors, while classical anti-histamines had no effect on the receptor activity (El-Shehabi and Ribeiro 2010).

Dopamine receptors are GPCRs of the Class A Rhodopsin family. Mammals and invertebrates possess five dopamine receptors (D1-D5), which are categorized into two classes, D1-type and D2-type, based on their amino acid sequence homology and pharmacological profiles. D1-type dopamine receptors (D1 and D5) are associated with G-stimulatory proteins. Its activation leads to stimulation of adenylyl cyclase, resulting in an increase in cyclic adenosine monophosphate production from adenosine triphosphate (Gurevich *et al.* 2016). In contrast, D2-type dopamine receptors (D2, D3, and D4) are linked to G-inhibitory proteins, which inhibit adenylyl cyclase and decrease cyclic adenosine monophosphate levels. *S. mansoni* D2 (SmD2) (Smp_127310) dopamine receptor exhibits an unusual pharmacological profile. Apomorphine, a potent antagonist of mammalian D2-type receptors, acts as an agonist for the SmD2 receptor, while other classic mammalian antagonists have no effect. This receptor is found in the membrane protein fractions of *S. mansoni* cercaria, schistosomula, and adult worms. SmD2 is also present in the sub-tegumental somatic musculature and acetabulum of cercaria and schistosomula. In adult parasites, SmD2 is enriched in the somatic muscles and, to a lesser extent, in the muscular lining of the caecum (Taman and Ribeiro 2009). In miracidium, antagonists of D2-type receptors have been found to delay miracidial transformation (Taft *et al.* 2010).

Another neurotransmitter dopaminergic receptor belonging to GPCRs has been identified in *S. mansoni* and is named SmGPR-3 (Smp_043290) (El-Shehabi *et al.* 2012). This receptor is an orphan amine-like receptor found in schistosomes but not in mammals and has an atypical antagonist profile compared to mammalian receptors. Some mammalian D2 antagonists enhanced the activity of SmGPR-3 (El-Shehabi *et al.* 2012). SmGPR-3 is abundantly expressed in the nervous system of schistosomes, particularly in the main nerve cords and in the peripheral innervation of body wall muscles. Therefore, there are at least two routes of dopaminergic motor control in *S. mansoni*, involving both direct and indirect mechanisms. One pathway is mediated by SmD2, which is predicted to act directly on the musculature, while the other is a more indirect neuronal pathway mediated by SmGPR-3 (El-Shehabi *et al.* 2012).

In addition to histamine and dopamine, serotonin is one of the best characterized amines in flatworms and causes muscle excitation in *S. mansoni*. The worm contains a serotonergic receptor (Sm5HTR) that belongs to the Class A Rhodopsin family and is distantly related to serotonergic type 7 (5HT7) receptors found in other species. Sm5HTR signals through an increase in intracellular cAMP. The receptor is distributed in the cerebral ganglia and main nerve cords and in peripheral nerves of the body wall muscles and tegument. The serotonin receptor (Smp_126730) is a crucial component of the motor control system in *S. mansoni* (Patocka *et al.* 2014). It is worth mentioning that PZQ, the sole treatment of schistosomiasis, has been identified as a GPCR ligand that acts by modulating serotoninergic signalling. PZQ modulates serotonergic signalling within a concentration range adequate to regulate the vascular tone of mesenteric blood vessels, where adult parasites reside in their host. The activity of PZQ on both parasite and host GPCRs likely contributes to its clinical efficacy by combining a harmful paralytic effect on the parasite with favorable effects on the host that aid in worm clearance (Chan *et al.* 2017).

Octopamine and its precursor tyramine (phenolamines) are invertebrate specific biogenic proteins and neurotransmitter derived from tyrosine. They are considered the invertebrate counterpart of the adrenergic system. The schistosome genome annotated two putative GPCRs; octopamine (Smp_150180) and tyramine (Smp_043290) GPCRs (Protasio *et al.* 2012). Octopamine receptor is a G protein-coupled receptor (GPCR) belonging to class A Rhodopsin-like subfamily (Hill *et al.* 2018). Octopamine labeling leads to the discovery of two pairs of ganglia in the adult schistosome brain. This neurotransmitter is localized in both ganglia and is also distributed throughout central and peripheral nerves and modulates schistosomula motility and length (El-Sakkary *et al.* 2018).

Rhodopsin Beta (β) subfamily receptors

The β subfamily contains the great majority of neuropeptide and neuropeptide hormone GPCRs. Their neuropeptide signalling is known to play an essential role in flatworm locomotion, feeding, reproduction, host-finding, and regeneration (Kreshchenko 2008). The genome of *S. mansoni* identifies at least 14 potential neuropeptide receptors, including several FLP-like and NPY/F-like receptors (Berriman *et al.* 2009). The invertebrate neuropeptide F family is related to the neuropeptide Y family of vertebrate peptides (with a *C*-terminal F instead of a Y) (McVeigh *et al.* 2009). Zamanian *et al.* (2011) identified several peptide receptors in *S. mansoni*, denoting that the peptidergic signalling is important for neurotransmission in the worm. They found that the number of potential flatworm peptide receptors significantly exceeds the peptide ligands identified so far. Most of the identified receptors cannot be associated with specific ligands with certainty. Peptides include FMRF amide-like peptides (FLPs), neuropeptide Fs (NPFs), and various other specific amides, some of which have similarities to peptides found in other phyla, such as neuropeptide FF (NPFF)-like and gonadotropin- or thyrotropin-releasing hormone-like peptides.

S. mansoni neuropeptide Y/F and its receptors have been identified in intramolluscan stages of *S. mansoni* and have been found to be associated with maintenance of schistosome germinal cell during intramolluscan development (Buddenborg *et al.* 2019). This neuropeptide has been also linked to a reduction in egg production of the infected snails (de Jong-Brink *et al.* 2001).

Rhodopsin orphan receptor

A transcriptomics study revealed a rhodopsin orphan GPCR20 of *S. mansoni* (*Sm*GPCR20) (Li *et al.* 2024). This receptor belongs to the paired males-unpaired males-unpaired females subgroup of

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*Sm*GPCRs, which is differentially transcribed between males and females expressing high transcript levels in paired male worms (bM), unpaired male worms (sM), and unpaired females (sF), whereas low or no transcripts of this subgroup were present in paired female worms (bF) (Hahnel *et al.* 2018; Lu *et al.* 2016). This SmGPCR20 orphan receptor (Smp_084270) interacts with two neuropeptides – SmNPP26 and SmNPP40 – as potential interaction legends. qRT-PCR revealed that Smgpcr20, Smnpp26, and Smnpp40 genes showed sex- and/or pairing-dependent expression. The combination of SmGPCR20 with these neuropeptides affects egg production, oogenesis, and growth of the *S. mansoni* females (Li *et al.* 2024).

Adhesion and Secretin receptors

Adhesion and Secretin receptors belong to Class B2 and Class B, respectively. In vertebrates, this family represents the second largest group of GPCRs, following the Rhodopsin family. Adhesion and Secretin receptors were identified in *S. mansoni* (Zamanian *et al.* 2011). They share sequence similarity in their 7-TM domains, but they showed structural differences in their N-terminal domains. Adhesion GPCRs possess a long N-terminal domain that features a varied arrangement of functional domains. Secretin GPCRs have N-terminal hormone-binding domains (HBD) that enable them to respond to peptide hormones (Nordström *et al.* 2009).

Cellular adhesion molecules are involved in the pathogenesis of *S. mansoni*. Integrins are one of the cellular adhesion molecules that also include cadherins, selectins, and the immunoglobulin (Ig) (Figliuolo et al. 2019). Integrins are a family of heterodimeric transmembrane receptors comprising at least 18 α and 8 β subunits in mammals (Hynes 2002). They mediate cell adhesion, functioning as connectors between the extracellular matrix and the cytoskeleton, while transmitting biochemical and mechanical signals between cells and their surroundings. They function bidirectionally across the plasma membrane, facilitating both inside-out and outside-in signalling (Fu *et al.* 2012). Integrins are also involved in various immune-related signalling pathways in mammals (Zhang *et al.* 2023).

Integrins work synergistically with other molecules, such as VKR1 and RTKs, within complex signalling pathways that regulate growth and differentiation processes (Gelmedin *et al.* 2017). A significant portion of integrin signalling functions is dependent on a cytoplasmic TK (Harburger and Calderwood 2009). In *S. mansoni*, the genes coding for these signalling transduction protein kinases have been shown to have roles in reproductive organs differentiation process (Knobloch *et al.* 2007). These kinases are cellular tyrosine kinases members that act in a multi-kinase complex (Beckmann *et al.* 2011) such as Src (SmTK3) (Kapp *et al.* 2004), Syk (SmTK4) (Beckmann *et al.* 2010), and Src/Abl (SmTK6) families (Beckmann *et al.* 2011).

Beckmann *et al.* (2012) characterized four alpha-integrins (Smα-Int1–Smα-Int4) and one beta-integrin (Smβ-Int1) subunit from *S. mansoni*. The α (Smα-Int1, Smp_126140 and Smα-Int2, Smp_170280) and β (Smβ-Int1, Smp_089700) subunits are also present in *S. mansoni* exosomes (Samoil *et al.* 2018). The α-integrins of the free-living planarian *Schmidtea mediterranea* differ from those of *S. mansoni* in having only three α-integrin subunits. The β-integrins of *S. mansoni* did not bind fibronectin (Beckmann *et al.* 2012). These β-integrins are closely related to the human β4 subunit that binds laminin (Hynes 2002). The Smβ-Int1/Smα-Int1 heterodimer are found in the gonads, whereas the Smβ-Int1/Smα-Int2 heterodimer might fulfill more specialized functions in the area surrounding the ootype. Smβ-Int1 interacts and co-localizes with cellular tyrosine kinases in the reproductive organs of schistosomes with SmTK4, a Syk kinase, being its most significant interaction partner (Beckmann *et al.* 2012). The Smβ-Int1/SmVKR1 signalling complex plays a crucial role in the oocyte differentiation and survival in paired schistosomes (Gelmedin *et al.* 2017). If *Schistosoma* integrins function in the same way as the mammalian homologues, these proteins could also help the parasite modulate the immune response of host cells (Samoil *et al.* 2018).

Glutamate receptors (GluRs)

L-glutamate is an important amino acid neurotransmitter in vertebrates and many invertebrates. It exerts its effects through interactions with ionotropic glutamate receptors (iGluRs) and metabotropic glutamate receptors (mGluRs). The iGluRs function as voltage-gated ion channels, while the metabotropic glutamate receptors (mGluRs) belong to the Class C GPCR superfamily, characterized by the typical seven transmembrane domain structure (Reiner and Levitz 2018). Glutamate-gated chloride channels (GluCls) (Smp_128940) are pentameric ligand-gated inhibitory ion channels found exclusively in invertebrates. Their absence in vertebrates makes them an ideal target for antiparasitic drugs. However, GluCls of *S. mansoni* worms differ significantly from the GluCls of nematodes. This is exemplified by ivermectin, which leads to flaccid paralysis or kills roundworms by activating GluCls, while schistosomes are not susceptible to the drug (Dufour *et al.* 2013). Callau-Vázquez *et al.* (2018) demonstrated that the GluCl-2 from *S. mansoni* is activated by glutamate with a potency similar to that of nematode GluCls, despite substantial divergence in the ligand-binding C loop that differs in length compared to other pentameric ligand-gated ion channels, as well as the difference in hydrophobic channel gate.

Upon binding glutamate, mGluRs trigger signalling cascades or facilitate cation influx. mGluRs are structurally related to metabotropic gamma-aminobutyric acid (GABA) receptors and calcium-sensing, taste, and pheromone receptors (Niswender and Conn 2010). mGluRs are divided into three main groups. Group I (mGluR1 and mGluR5) signals through changes in intracellular calcium and the inositol phospholipid pathway, whereas Group II (mGluR2 and mGluR3) and Group III (mGluR4, mGluR6, mGluR7 and mGluR8) signal primarily through inhibition of adenylate cyclase, which in turn decreases intracellular cAMP signalling (Kryszkowski and Boczek 2021). mGluRs consist of a large N-terminal extracellular ligand binding domain (LBD), the characteristic 7-transmembrane (7-TM) segment, and a variable-length intracellular C-terminal domain (ICD). The LBD of mGluRs contains the glutamate-binding site within a Venus Flytrap module, which is connected to the 7-TM region by a short cysteine-rich domain (CRD) (Niswender and Conn 2010) (Figure 3a).

Glutamate immunoreactivity in *S. mansoni* was detected in the nervous system, including the cerebral ganglia, longitudinal nerve cords, and commissures (Mendonça-Silva *et al.* 2002). The genome of *S. mansoni* encodes at least three sequences that are homologous to mGluRs from other species (Berriman *et al.* 2009). Taman and Ribeiro (2011a) described a mGluR in *S. mansoni* (SmGluR) in the nervous system of adult worms and cercariae, as well as in the female reproductive tract. SmGluR belongs to the GPCR superfamily and shares a distant relationship with mGluRs found in other species (Figure 3a). However, SmGluR differs from mammalian mGluRs with respect to signalling mechanism and pharmacological

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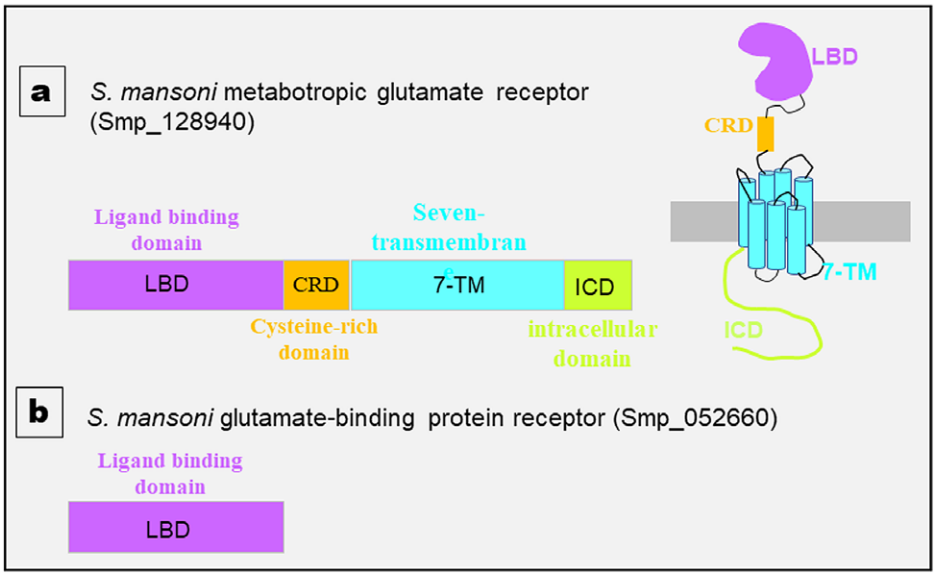

Figure 3. (a) Schematic diagram of the expected *S. mansoni* metabotropic glutamate receptor (SmGluR) (Smp_128940) comprising a large N-terminal extracellular ligand binding domain (LBD), a seven-transmembrane (7-TM) anchoring segment, and a C-terminal intracellular domain (ICD) of varying lengths. The LBD is connected to the 7-TM region by a short cysteine-rich domain (CRD). **(b)** *S. mansoni* glutamate-binding protein (SmGBP) (Smp_052660) receptor has a conserved ligand binding domain (LBD) but is missing the cysteine-rich domain, the characteristic 7-TM region, and intracellular domain.

profile. SmGluR is activated by glutamate, whereas GABA has no significant effect. Phylogenetic analyses indicated that SmGluR shares a similar degree of sequence homology with mGluRs as it does with other family C GPCRs, such as GABA receptors.

The second metabotropic glutamate receptor identified in *S. mansoni* is glutamate-binding protein (SmGBP) (Smp_052660) (Taman and Ribeiro 2011b). SmGBP represents a new type of glutamate receptor that may be unique to flatworms. Genes encoding similarly truncated receptors have been found in the *S. japonicum* genome (The Schistosoma japonicum Genome Sequencing and Functional Analysis Consortium 2009) and the partially annotated genome of the planarian *Schmidtea mediterranea* (Robb *et al.* 2008), but they are not known to occur in other metazoans. SmGBP receptor is an atypical receptor; it is a C-terminally truncated mGluR with a conserved ligand (glutamate)-binding domain (LBD) located within a Venus Flytrap module but lacking the cysteine-rich domain (CRD), the characteristic 7-TM region, and the intracellular domain (ICD) (Figure 3b). SmGBP is suggested to be either an integral membrane protein or a peripheral protein closely associated with the membrane. This receptor is gender- and stage-specific. SmGBP is localized on the surface of male worms, especially on the dorsal tubercles but not in females or larval stages (Taman and Ribeiro 2011b). In *S. japonicum*, the related schistosome species, two putative mGluRs, are identified: SjGRM7 and SjGRM. SjGRM7 has been found to be crucial for normal physiological functions, growth, development, and egg production (Wang *et al.* 2022).

Frizzled receptors

Frizzled protein receptors belong to GPCRs Class F. They consist of seven trans-membrane proteins with a cysteine-rich domain in the N-terminal extracellular region required for Wnt ligand binding. Most Frizzled receptors share a common C-terminal motif that is a binding site for the cytoplasmic protein domain (Hering and Sheng 2002). Wnt signalling plays a key role in embryonic development, energy metabolism, and balance (Nusse 2015). Zamanian *et al.* (2011) identified four Frizzled sequences *S. mansoni*. SmFz1 genes (Smp_118970, Smp_173940) are regulated by pairing in gonads. In vitro inhibition of the gene affects the survival of adult worms, decreases the egg production, and affects the gonad differentiation, morphology, and embryogenesis (Hahnel *et al.* 2014). Secreted frizzled-related protein can inhibit Wnt signalling by competitive binding to the frizzled protein-specific receptor (García-Tobilla *et al.* 2016). Knockdown of *S. japonicum* secreted frizzled-related protein gene impairs worm growth and development, survival and morphological structure, reproductive ability, and viability of the eggs produced (Cheng *et al.* 2019).

Acetylcholine receptors

Acetylcholine (ACh) is a crucial neurotransmitter in both vertebrate and invertebrate species. In vertebrates, ACh functions primarily as an excitatory neurotransmitter, regulating processes such as muscle contraction, glandular secretion, and memory formation. ACh similarly plays an excitatory role in invertebrates, and its involvement in nematode motor function is well documented. However, there is a significant exception in schistosomes, where ACh acts as a major inhibitory neurotransmitter or modulator. Activation of ACh receptors (AChR) in *S. mansoni* leads to muscle relaxation, resulting in flaccid paralysis (Day *et al.* 1996). Metrifonate, an Acetylcholinesterase (AChE) inhibitor, elevates synaptic levels of ACh, resulting in prolonged paralysis of the axial muscles of schistosomes and halting its movement. This action is suggested to be due to the secondary effects of muscle paralysis. The drug demonstrates equal potency and efficacy in vitro against both *S. mansoni* and *S. haematobium* but is only effective in vivo against the latter species (Bueding et al. 1972).

Most of AChRs in schistosomes are nicotinic AChRs (nAChRs), so named because of their high affinity for nicotine. However, muscarinic cholinergic receptors are also expected to be present. One of these receptors possesses all the structural characteristics of GPCR (MacDonald *et al.* 2015). In vertebrates, nAChRs are invariably cation-selective (Na^+, $Ca2^+$, K^+) and mediate excitatory

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responses. In contrast, invertebrates have cation and anion-selective (Cl) ACh-gated channels. These acetylcholine-gated chloride channels (ACC) mediate Cl^--driven membrane hyperpolarization and are believed to play a role in inhibitory responses to ACh. These ACC are structurally related to nAChRs but are selective for chloride ions (Beech *et al.* 2013). Structurally, nAChRs belong to the superfamily of Cys-loop ligand-gated ion channel. They form homo- and hetero-pentameric structures organized in a barrel shape around a central ion-selective pore (Albuquerque *et al.* 2009). A key characteristic of ACCs is the presence of a Pro-Ala motif in the pore-lining M2 domains of their subunits. This motif has been shown to convey anion selectivity to other ligand-gated ion channels (LGICs), replacing a Glu residue typically found in cation-selective channels (Keramidas *et al.* 2002). These ACCs that appear to be specific to invertebrates are found in S. mansoni (SmACCs) and have an inhibitory modulatory effect on the neuromuscular system of schistosome potentially through a chloride influx produced by the activation of SmACCs and their receptors (SmACC-1 and SmACC-2) (Smp_176310 and Smp_142690) (MacDonald *et al.* 2014). Treatment with ACh antagonists and RNA interference (RNAi) leads to suppression of SmACCs and induces a hypermotile effect. Two of the SmACCs were localized to regions of the peripheral nervous system that innervate the body wall muscles; however, none appear to be directly expressed in the muscle tissue (MacDonald *et al.* 2014).

Muscarinic acetylcholine receptors (mAChRs) belong to GPCR superfamily and are related to Rhodopsin (Family A GPCRs) in their structure. The term 'muscarinic' originates from the preference of receptors to bind to and be activated by the fungal toxin muscarine (Dale 1914). Schistosome muscarinic acetylcholine receptor is also referred to as G protein-coupled acetylcholine receptors (SmGAR) (Smp_145540). Expression of this receptor is predicted to be high during the early larval stages of schistosomes (Protasio *et al.* 2012). SmGAR is constitutively active but can be further stimulated by ACh and, to a lesser extent, by the cholinergic agonist carbachol. Anti-cholinergic drugs exhibit an inverse agonist activity towards SmGAR, significantly reducing its basal activity. A phenotypic RNAi assay demonstrated that suppression of SmGAR activity in early-stage larval schistosomula results in a marked decrease in larval motility (MacDonald *et al.* 2015).

In addition to its neuromuscular effects, ACh has been linked to glucose transport across the tegument and increased glucose uptake in schistosomes. AChE has been shown to play a role in modulating glucose uptake by schistosomes from the blood of mammalian hosts. Two main molecular forms of AChE are found in *S. mansoni.* One form is located within the muscle and plays a role in cholinergic processes, while the other form is found on the surface, anchored to the membrane by a covalently bound glycophosphatidylinositol anchor. This surface-localized AChE may participate in non-cholinergic processes and signal transduction (Espinoza *et al.* 1991). Glycophosphatidylinositol-anchored AChE can be released from the schistosome surface membrane by a PI-specific phospholipase C, which can remove significant amounts of AChE from the tegument of schistosomula in vitro without affecting the parasite viability (Espinoza *et al.* 1988). It has been suggested that release of AChE triggers immediate replenishment of the surface enzyme. However, this process occurs with another glycophosphatidylinositol-anchored protein, alkaline phosphatase, which is also present on the surface of schistosome (Arnon *et al.* 1999).

Glucose uptake is regulated through the interaction of ACh with tegumental nAChRs and AChE. The effect of ACh on glucose uptake can be inhibited by blocking any of the ACh cholinergic systems. AChE is thought to regulate interaction of ACh with its receptor since inhibition of AChE produces an effect similar to excessive presence of ligand (Jones *et al.* 2002). Exposure to the same concentration of ACh present in host blood was found to enhance glucose uptake in *S. haematobium* and *S. bovis*, but not in *S. mansoni.* However, at higher concentrations, ACh inhibited glucose uptake from the host blood into the parasites. The glucose uptake rate in adult *S. haematobium* and *S. bovis* is roughly double that of *S. mansoni* (Camacho and Agnew 1995), and the first two species have relatively higher AChE activity on their teguments compared to *S. mansoni* (Camacho *et al.* 1994). These elevated levels of AChE activity contribute to its increased susceptibility to metrifonate (Harder 2002), which may explain why metrifonate is effective against *S. haematobium* and *S. bovis* but not *S. mansoni.*

Adult stages of schistosomes possess AChE and nAChR on their teguments, and both components are concentrated on the surface of the adult male, a key site for nutrient uptake for the worm pair (Camacho and Agnew 1995). AChR expression increases during parasites pairing and sexual maturation as the pairing state increases the uptake of several host compounds (Camacho *et al.* 1994). AChE inhibitors impair the parasite glucose uptake ability, which affects the parasite growth and development (Sundaraneedi *et al.* 2017; You *et al.* 2018).

Conclusion and perspectives

The success of *Schistosoma mansoni* infections is partly attributed to its ability to utilize host-derived molecules through several receptors, which are essential for its growth and development. These receptors play a coordinated role in regulating the parasite's life processes, using growth factors from both the parasite itself and host-derived molecules. The key receptors involved include growth factor receptors, nuclear hormone receptors, nuclear transport receptors, and neurotransmitter receptors. A deeper understanding of how schistosomes exploit host nutrients, neuro-endocrine hormones, and signalling pathways for their growth, development, and maturation is expected to lead to improved interventions to control schistosomiasis.

More and more new receptors, along with related proteins, ligands, and genes, are being identified and characterized in schistosomes, especially with the availability of extensive genomic data for *S. mansoni.* Understanding the molecular roles that these receptors play in *S. mansoni* growth, as well as developing more specific receptor agonists and antagonists, presents a major challenge for future research. Notably, many of these receptors share minimal sequence homology with those of the human host, making them particularly suitable for selective drug targeting.

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Competing interest. The author declares none.

Ethical standard. The protocol of the present study was approved by the ethics Committee of the Faculty of Medicine, Alexandria University according to the institutional ethical guidelines.

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