Human schistosomiasis is a chronic inflammatory disease caused by blood fluke worms belonging to the genus Schistosoma. Health metrics indicate that the disease is related to an elevated number of years lost-to-disability and years lost-to-life. Schistosomiasis is an intravascular disease that is related to a Th1 and Th2 immune response polarization, and the degree of polarization affects the outcome of the disease. The purinergic system is composed of adenosine and nucleotides acting as key messenger molecules. Moreover, nucleotide-transforming enzymes and cell-surface purinergic receptors are obligatory partners of this purinergic signaling. In mammalian cells, purinergic signaling modulates innate immune responses and inflammation among other functions; conversely purinergic signaling may also be modulated by inflammatory mediators. Moreover, schistosomes also express some enzymes of the purinergic system, and it is possible that worms modulate host purinergic signaling. Current data obtained in murine models of schistosomiasis support the notion that the host purinergic system is altered by the disease. The dysfunction of adenosine receptors, metabotropic P2Y and ionotropic P2X7 receptors, and NTPDases likely contributes to disease morbidity.
and the years lost-to-life of a specific disease. According to recent data, schistosomiasis is related to a DALY of 3.3 million and is associated with a substantial socioeconomic burden in low- and middle-income countries[1,2].

**Schistosoma lifecycle**

The majority of cases of human schistosomiasis are caused by three main species of the genus Schistosoma: *Schistosoma mansoni*, *Schistosoma japonicum* and *Schistosoma hematobium*. Each species has a geographical and pathological importance: *S. mansoni* (in Africa, the Middle East and the Americas) and *S. japonicum* (in South and Middle Asia) cause intestinal and hepatosplenic schistosomiasis; *S. hematobium* (in Africa and the Middle East) causes urinary schistosomiasis[3].

The parasite lifecycle includes an intermediate (snail) and a definitive (mammalian) host[3] and shows remarkable features of adaptive biology. Infected aquatic snails release cercariae that are highly infective for the definitive host. The human infection starts when an individual comes into contact with a body of water infested with cercariae. These larval forms explore host thermostatic gradient or chemical signals, attach to the epidermis and penetrate human skin. Both the head and acetabular cercarial glands secrete enzymes such as elastases that are serine proteases and immunomodulators involved in epidermis and dermis penetration[4]. After entering the dermis, cercariae must reach a venule or a lymphatic vessel while transforming into schistosomula[5,6]. Perivascular CD4+ T cells are found in human skin accompanied by interleukin (IL)-7 production that seems to favor skin invasion and worm survival[7]. Next, during schistosomula migration via the heart and lungs to their specific vascular site, they undergo a series of structural and physiologic transformations before becoming adults. Adult worms mate in the vessels of the intestine (*S. mansoni* and *S. japonicum*) or the vesical plexus around the bladder (*S. hematobium*) and then become permanent pairs and start oviposition. Each egg contains a miracidium larva and secretes proteolytic enzymes that favor egg migration into the lumen of the intestine or bladder; these eggs are then consequently excreted in feces or urine, respectively. In due course, eggs that are not eliminated are trapped in the organs and result in immune responses. Voided eggs, once in contact with freshwater, release the free-swimming miracidium that infects snails and a new lifecycle is started[Fig. 1]. The asexual reproduction of a miracidium generates several cercariae that are released via the snail. Adult male worms are about 1 cm long. They have smooth muscle layers beneath the external tegument and two suckers by which they attach to the blood vessel wall.

**Host immunologic responses during schistosomal infection**

Human and schistosomes co-evolved, which favored worm survival in the host[10]. Some abilities of schistosomes have been noted to favor parasite survival (e.g., the capacity to regenerate the outer tegument, molecular mimicry, acquisition of host antigens and immunomodulation)[8]. Murine infection with *S. mansoni* resembles human infection, and therefore, several lines of data have derived from this experimental model[8]. Worm- and egg-derived antigens recognized by T and B lymphocytes modulate host immune system by down- or up-regulating cellular and humoral immune responses[8,10–17]. Briefly, the host immune response polarizes to a Th1-cell response in the first five weeks after infection. At this stage, Th1 cells and peripheral mononuclear blood cells produce large amounts of tumor necrosis factor (TNF)-α, interferon (IFN)-γ, IL-1 and IL-6. In the very beginning of the infection, lung immune responses are able to kill schistosomula[11]. However, Trottein and colleagues[18] showed that schistosomula reduces lung vascular cell adhesion molecule (VCAM)-1 expression and leukocyte recruitment,
suggesting that at this stage of the disease endothelial cells are driven to an anti-inflammatory phenotype. As the worms mature, mate and start egg deposition, a largely Th2 response emerges with the production of cytokines such as IL-4, IL-5 and IL-13, as well as eosinophilia and intestinal and mesenteric mastocytosis, and high circulating levels of IgE [8]. IL-17 production is also tightly regulated by IFN-γ and IL-4. The capacity of limiting the pro-inflammatory Th1 response is essential for host survival. In murine model, the infection of IL-4 knockout mice (a model of polarized Th1 response) resulted in tissue damage and mortality [8,19–22]. Natural regulatory T cell (Treg) also modulates Th cell responses during schistosomiasis [23].

Macrophages are important cells for host defense that may be primed by signals from the extracellular milieu. Each subset of macrophage phenotype has distinct patterns of gene expression producing pro- and anti-inflammatory mediators [24]. The different subsets of macrophage phenotypes include the classically [mMΦ (classically activated macrophage); M1 macrophages] or alternatively activated phenotypes [aaMΦ (alternatively activated macrophage); M2 macrophages]. Furthermore, macrophages may express M1 and M2 markers resulting in intermediate polarization subsets [24].

Concerning schistosomiasis, aaMΦ are typically found in the vicinity of granuloma and Th2 cytokines, and express the enzyme arginase 1 (Arg-1) that limits Th2-driven fibrosis [21]. Eggs lodged in tissues may cause necrosis and host defenses form a granuloma around the eggs in order to contain the insult, although the granuloma may also be deleterious to functional assays including ATPases and Ca2+ homeostasis that were initially identified by functional data have been corroborated by the genomic description of both S. mansoni [33] and S. japonicum [34].

Schistosoma biology: evidence of the worm purinergic system

Considering the three main species of schistosomes, molecular biology data referred initially to S. mansoni and S. japonicum; complete genome sequences of these species were published in 2009 [33,34]. Data pertaining to the genome of S. hematobium were published some years later [35]. By relying on proteomic data and bioinformatics, it has been possible to construct schistosome phylogenetic trees of proteins encoded by the genome, the so-called phylome [4]. According to current knowledge, S. mansoni is more closely related to S. hematobium (89.4%) than to S. japonicum (67%) [4]. The genomes were revised and are available in a database (Schistodb; [36]). Additionally, the number of known proteins is higher for S. mansoni than for the other two species [37].

According to the genome of S. mansoni, the worm has at least four genes related to P2X receptors subunits [33]. Previously, the gene of a P2X-like receptor (schP2X) was cloned and heterologously expressed in Xenopus oocytes. Electrophysiological studies have revealed that both ATP and the ATP analog benzoyl-ATP (BzATP) evoked inward currents at these recombinant schP2X receptors that were blocked completely by suramin and partially by pyridoxalphosphate-6-azophenyl-2,4-disulfonic acid (PPADS) (100 μM) [38]. Furthermore, high agonist concentrations desensitized the receptor [39]. A comparison of the amino acid sequence between schP2X and human P2X1,7 receptors revealed an identity of 25.8% for P2X7 and 36.6% for P2X4 receptors [38] and 36% for P2X2 [39]; the latter authors referred to the receptor as SmP2X. This level of identity is remarkable since an acoelomate primitive platyhelminth has been considered to be the organism from which many other phyla have evolved [40], and some Schistosoma genes may be ancestors of mammalian genes [41]. Moreover, S. mansoni expresses other enzymes and channels involved in intracellular Ca2+ homeostasis that were initially identified by functional data have been corroborated by the genomic description of both S. mansoni [33] and S. japonicum [34].

Purines are considered to be one of the most primitive chemical messengers in the animal kingdom [50]. Schistosomes take advantage of host signaling pathways. Unlike mammalian cells, schistosomes are unable to synthesize purine nucleotides de novo. Therefore, they depend on host-preformed purines and salvage pathways for the conversion of bases and nucleosides back into nucleotides [51]. It has been suggested that nucleotide hydrolysis occurs in the tegument (external face) of the worms near the site of the uptake of the products of such hydrolysis [52,53].

The tegumental nucleotide-metabolizing ecto-enzymes are alkaline phosphatase (smAP), ecto-phosphodiesterase (smPDE) and ecto-ATP diphosphohydrolase (also known as apryrase or E-NTPDase) (smATPDase) [54,55]. smATPDase1 is expressed in schistosomula, female and male worms and seems to hydrolyze ATP and ADP equally (i.e., the enzyme has the same affinity for both substrates) [55,56]. On the other hand, the homolog smATPDase2 is not present in the tegument but is highly expressed in eggs (compared with worms), and the evidence obtained so far has not shown that this enzyme is responsible for the hydrolysis of exogenous (host-derived) ATP or ADP [55]. Nevertheless, a synthetic peptide belonging to smATPase2 was shown to be immunogenic when injected into mice [57]. Moreover, an IgG antibody from schistosomiasis patients showed cross-immunoreactivity with a domain from smATPDase2 [58], which could be useful for diagnostic purposes or vaccine development. Furthermore, adenosine monophosphate (AMP) seems to be hydrolyzed by smAP [55].
On the other hand, intact schistosomes are able to deaminate adenosine to inosine and convert adenosine to adenine, which suggests that the worms also possess adenosine deaminase (ADA) and adenosine phosphorylase [51,59]. However, the conversion of adenosine to AMP by adenosine kinase seems to be minor [50]. Moreover, schistosomes are also able to convert the adenine analog 2-fluoroadenine into 2-fluoro ATP [60]. Therefore, schistosomes also have adenine phosphorylase and nucleoside kinases [51,61], and they incorporate adenine into ATP in a higher rate than that of mammalian cells [62,63]. Overall, schistosomes are able to convert adenosine, adenine and inosine to AMP and ultimately to ATP. In addition, inosine may also be converted to inosine monophosphate (IMP) and ultimately to GTP [51].

Since schistosomes have a purine salvage network, it has been proposed that purine analogs could be potential antischistosomal drugs. However, so far no such drug has been shown to be both effective and safe for humans. A unique antischistosomal drug in clinical use, praziquantel (at micromolar concentrations), is able to reduce both [3H]-adenosine and [3H]-uridine worm uptake [64], but other mechanisms such as the influx of Ca2+þ, worm muscle paralysis, inhibition of P-glycoprotein-like protein [a member of ATP-binding-cassette (ABC) superfamily of proteins] and tegument rupture have been noted as relevant for the pharmacological effect [65–67]. However, there have been reports of resistance to praziquantel, and the development of new drugs for this neglected tropical disease is most welcome. In this context, the worm purine nucleoside phosphorylase has been considered to be a putative new target for new antischistosomal drugs [37].

**Purinergic signaling**

Cellular ATP was identified at the end of the 1920s [68]. Concomitantly, some initial evidence of a purine acting as a chemical transmitter was also unveiled by the demonstration that an organic compound isolated from animal tissues extracts exerted depressant effects on cardiac rhythm, blood pressure and intestinal movements [69]. A large number of independent studies contributed to the discovery and definition of the purinergic system, and its identification in invertebrates (including S. mansoni) implied an earlier onset of evolution [70–72]. In this context, it is possible that the co-evolution of hosts and parasites has enabled the establishment of a chronic infection.

The purinergic system is an important modulator of innate immune response and inflammation [73]. In addition, this system also regulates neurotransmission and the cardiovascular system. The complexity of the purinergic system encompasses a great variety of agonists, receptors and enzymes [74].

Adenosine and the nucleotides ATP, ADP, uridine 5’-triphosphate (UTP), uridine 5’-diphosphate (UDP) and UDP-glucose are key messenger molecules that mediate a wide diversity of biological actions of purinergic signaling. Moreover, nucleotide-transforming enzymes and cell-surface receptors are obligatory partners in this purinergic signaling. The International Union of Pharmacology (IUPHAR) Committee on Receptor Nomenclature and Drug Classification recognizes distinct receptors pertaining to the purinergic system. Receptors for extracellular adenosine and nucleotides can be divided into three subfamilies: metabotropic purinergic P1 receptor (or A receptor; activated by adenosine), metabotropic P2Y receptor (activated by ATP and other nucleotides) and ionotropic ATP-gated P2X receptor. According to molecular structure and functional data, adenosine P1 receptors can be divided into four subgroups: A1, A2A, A2B and A3. On the other hand, P2Y receptors can be divided into eight subgroups (P2Y1, P2Y2, P2Y4, P2Y6, P2Y11, P2Y12, P2Y13 and P2Y14) and P2X receptors can be divided into seven (P2X1–7) subtypes [75–78] [Fig. 2]. Furthermore, dinucleotide polyphosphates (Np.Np) also modulate the purinergic system and consist of two nucleotides linked by a polyphosphate bridge containing 2–7 phosphate groups. One of most studied classes of these

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**Fig. 2** – Purinergic receptors. Extracellular nucleotides mediate intracellular signaling through cell surface ionotropic ATP-gated receptors (P2X) and metabotropic P2Y receptors. On the other hand, adenosine receptors (A) are activated by adenosine (Ado). The conversion of ATP to other nucleotides and adenosine is mediated by ecto-enzymes [76]. Reproduced from Ref. [122] with permission.
Host purinergic signaling during schistosomal infection

Besides the salvage nucleotide metabolism, it is possible that schistosomes may modulate host immune responses and platelet aggregation mediated by purinergic signaling [55]. The presence of intravascular parasites may damage endothelial cells and induce nucleotide release (DAMPs). The worm capacity to reduce ATP and ADP concentrations around themselves may limit host inflammation and platelet aggregation; adenosine formation may favor vasodilation and worm migration [54], and eventually worm's metabolism [52,53]. Human and mice schistosomiasis is related to thrombocytopenia. Additionally the tegumental smATPase1 possibly contribute to inhibit ADP-mediated platelet aggregation [55,87].

A large amount of data about schistosomiasis has been obtained using S. mansoni-infected mice. Important evidence for the alteration of purinergic signaling during schistosomal infection came from work by De Man and colleagues [88]. In control mice, both adenosine and ATP attenuated the ileum contraction induced by neural-released acetylcholine, but not in response to carbachol (exogenous agonist). The adenosine effect was blocked by the antagonist 8-phenyltheophylline and mimicked by the agonist N(6)-cyclohexyladenosine, implying the participation of the presynaptic A1 receptor. Since the ATP effect was also blocked by the A1 receptor antagonist, the authors suggested that ATP was converted to adenosine to exert the inhibitory effect. According to the data, the purinergic control of cholinergic neurotransmission by A1 receptor was compromised during infection with S. mansoni, and increased ileum contraction was observed. During intestinal inflammation, there is an increased number of mast cells close to the myenteric neurons, and the continuous exposure of A1 receptors to adenosine may lead to receptor desensitization. Chronic intestinal inflammation is related to alterations of intestinal motility, and it is accordingly possible that the enteric dysfunctional purinergic signaling contributes to schistosomal morbidity [3].

Tissue insult recruits eosinophils as inflammatory effector cells. The intracellular eosinophil granules contain preformed cytokines, eosinophil peroxidase and cationic proteins that may be released by degranulation and exocytosis. Alternatively, the presence of intact eosinophil cell-free granules in tissues is evidence of eosinophil necrosis [89]. However, such extracellular granules are secretion-competent organelles responsive to external stimuli [90]. Eosinophilia is a key feature of human schistosomiasis [10], and some lines of evidence point to a capacity of eliminating helminths. For instance, it has been shown that eosinophils are able to induce dying schistosomes, and eosinophil granule proteins may contribute to killing [91]. Using a reporter animal model characterized by an eosinophil peroxidase-luciferase (EPX-luc) transgenic mice, Davies and colleagues [91] showed that there is increased eosinophilopoese in the bone marrow and eosinophilia in the liver and intestine in response to both worms and eggs during schistosomiasis.

Human and murine eosinophils (and other immune cells) express mRNA encoding several P2X and P2Y receptors [92]. In addition, immunoreactivity against the P2Y12 receptor protein...
has also been identified in cells from both species. Functional data additionally suggest the expression of human P2Y₁₂ receptors since stimulation with the agonist ADP induced the secretion of eosinophil peroxidase, which was selectively reduced by the P2Y₁₂ receptor antagonist MRS2395 [93]. In the murine model, treatment of S. mansoni-infected mice with the P2Y₁₂ receptor antagonist clopidogrel reduced the size of liver granuloma, collagen deposition, the number of infiltrated eosinophils, IL-4 and IL-13 levels in liver homogenates compared with infected, untreated animals. However, clopidogrel did not interfere with Th2 polarization during schistosomiasis since the plasma levels of IL-13 were only slightly reduced, and the IL-4 levels were not changed [93]. These data suggest that pro-inflammatory P2Y₁₂ receptor signaling takes part in eosinophil migration to liver granulomas and may contribute to fibrosis.

Co-infections with Schistosoma and bacteria, virus, protozoa or other helminths are known [94,95]. The association among Salmonella infections and eventually bacteremia and schistosomiasis has also been reported [95]. It is possible that Th2 polarization plays a role in such co-infections [96].

Macrophages are resident phagocytic cells of the innate immune system. They act as the first line of the host defense against pathogens in non-adaptive responses and may also contribute to adaptive immune responses, ultimately leading to pathogen killing [97,98]. Moreover, during schistosomiasis the degree of differentiation between cM and Th2 defense.

The lumen of blood vessels and lymphatics is covered by endothelial cells that are considered important regulators of leukocyte adhesion, vascular permeability and mechanisms of vascular contraction and dilation [106–108]. The intravascular location of Schistosoma makes endothelial cells as first target of the disease. Endothelial cells show remarkable phenotypic heterogeneity and undergo epigenetic regulation [106]. According to previous data with infected mice, endothelial cells primed by schistosomiasis keep in culture the acquired phenotype [109].

In view of the reduced P2X₇ receptor function it could be expected a failure of host IL-1β expression in response to pathogen. However, Ritter et al. [105] showed that egg-derived soluble antigens (SEA) (i.e., “pathogen-associated molecular patterns” (PAMPs)) stimulate IL-1β expression by dendritic cells through a dectin-2 pathway. Moreover, the stimulation of dendritic cells from P2X₇ receptor knockout mice with SEA also induced IL-1β expression suggesting that this signaling does not depend largely on P2X₇ receptor function. Thereby this finding implicates that the infection influences directly inflammasome activation [105].

Purinergic P2X₇ receptors are expressed on monocytes and macrophages, regulate cytokine production, apoptosis, and take part in inflammamaome. These receptors are localized in lipid rafts and therefore they interact with caveolin and also modulate the activity of phospholipases A₂, C and D [99]. P2X₇ receptors activation by agonists such as ATP (mM) and the analog BzATP induces a cation-specific channel opening along with Ca²⁺ influx and K⁺ efflux; moreover pore dilation allows for the permeation of large molecules such as ethidium bromide [99]. The activation of macrophage P2X₇ receptors stimulates the secretion of cytokines such as TNF-α and IL-1β, but a disproportionate production may be detrimental in chronic inflammation [100]. Moreover, macrophage P2X₇ receptors may function as scavenger receptors for bacteria and apoptotic cells [101]. Previous data with mice infected with S. mansoni pointed to a reduced phagocytic and bactericidal capacity of peritoneal macrophages [102].

Using F4/80⁺ peritoneal macrophages from S. mansoni-infected mice (in the beginning of the chronic phase), we observed that both Ca²⁺ influx and cell permeabilization in response to ATP and BzATP were reduced compared with cells from control mice. Infected animals also exhibited increased levels of transforming growth factor (TGF-β1) [103]. While IFN-γ increases P2X₇ receptor expression [104], treatment of peritoneal macrophages with TGF-β1 reduced cell surface P2X₇ receptor expression [103]. These data point to reduced P2X₇ receptor signaling in macrophages during schistosomiasis. The infection of P2X₇ receptor knockout mice resulted in a reduced survival curve [Fig. 3], a finding that suggests that these receptors are important to host defense.

![Fig. 3 – Survival curves of S. mansoni-infected mice (black line: C57BL/6 wild type; Red line: P2X₇ receptor knockout mice (P2X₇-RKO)). Newborn mice were infected and observed for 9 weeks. Reproduced from Ref. [103] with permission.](image-url)
nucleotidases [73,75,84]. Endothelial cells from different vascular beds express several subtypes of purinergic P2Y receptors, including P2Y1, P2Y12, P2Y4, P2Y6 and P2Y11 receptors [73,111,112]. Moreover, P2X4 and P2X7 receptors [73,113,114] and NTPDases 1, 2 and 3 are also expressed [85,115].

Vascular P2X7 receptors activation induces endothelium-dependent vasodilation [116] and constitutive NO production in cultured endothelial cells [113]. However, excessive P2X7 receptor activation may lead to apoptosis [99]. Mesenteric endothelial cells from S. mansoni-infected mice exhibited a reduced Ca2+ influx and ethidium bromide uptake in response to the agonist BzATP [113]. We found that the downregulation of endothelial P2X7 receptor signaling was related to a reduced protein expression, which also reduced NO production in response to ATP or BzATP. So far there is no evidence of a putative protection against endothelial cell apoptosis. Nevertheless, previously we showed that ATP-induced production of NO was compromised in cells from S. mansoni-infected mice, and this endothelial dysfunction contributed to an increased leukocyte adhesion, vascular inflammation and infiltration of leukocytes in the peritoneal cavity [109] and portal vein [117].

The endothelial expressions of NTPDases 2 and 3 are increased by schistosomal infection along with a higher hydrolysis of ATP, and ADP generation [115]. ADP is the endogenous agonist of P2Y1 receptor, which is widely expressed through the vascular system [73,81,111,112]. P2Y1 receptor induces the expression of adhesion molecules such as intercellular adhesion molecule (ICAM)-1 thereby having a pro-inflammatory effect [118], and ICAM-1 has been noted as the most relevant adhesion molecule for schistosomiasis-related portal inflammation [119]. In the infected group, the increased extracellular concentration of ADP was accompanied by an increased basal leukocyte adhesion to endothelial cells as compared to control group. The P2Y1 receptor agonist 2-methylthioATP (2-MeSATP) also increased leukocyte adhesion. However, the selective P2Y1 receptor antagonist MR52179 blocked 2-MeSATP effect, and also returned basal leukocyte adhesion to control levels suggesting an upregulation of basal P2Y1 receptor signaling during this stage of schistosomiasis [115].

Data from another model of S. mansoni infection (hamster) showed a reduced content of ATP and an increased content of ADP in liver from infected animals compared with controls [120]. The altered ATP/ADP ratio could also reflect alterations of the purine metabolism during the disease.

Chronic mansonic schistosomiasis is related to a repertoire of worm- and host-derived immunomodulators culminating in intestinal and hepatosplenic alterations [3,8,22]. According to murine model, ADP seems to control liver and mesenteric schistosomal inflammation [92,115]. Although the expression of P2X7 receptor and NTPDases 2 and 3 were differently altered by this stage of schistosomiasis, the expressions of P2Y1 receptor, NTPDase 1 and S’ecto-nucleotidase were not altered in the same model [115]. Therefore, these data suggest that the disease affects in different ways the receptors and enzymes of the purinergic system.

If translated to the clinics, the purinergic signaling alterations observed during murine schistosomiasis could contribute to schistosomal morbidity. Moreover, current data suggest that P2Y1 and P2Y12 receptors could be pharmacologic targets to reduce chronic schistosomal inflammation and morbidity. Actually, P2Y receptors have been considered as potential pharmacologic targets in several other chronic inflammatory conditions [121].

Conclusion

Schistosomiasis-related chronic inflammation promotes host intestinal and liver alterations. Current data obtained with experimental models support the notion that host purinergic system is altered by schistosomiasis. The dysfunction of adenosine receptors, metabotropic P2Y receptors, ionotropic P2X7 receptors, and NTPDases likely contributes to some disease morbidity.

Conflict of interests

The author declares that there are no conflicts of interest regarding the publication of this paper.

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REFERENCES

[1] King CH. Health metrics for helminth infections. Acta Trop 2015;141:150–60.
[2] Nascimento GL, de Oliveira MR. Severe forms of schistosomiasis mansoni: epidemiologic and economic impact in Brazil, 2010. Trans R Soc Trop Med Hyg 2014;108:29–36.
[3] Gryseels B, Polman K, Clerinx J, Kestens L. Human schistosomiasis. Lancet 2006;368:1106–18.
[4] Silva LL, Marbet-Houben M, Nahum LA, Zerlotini A, Gabaldón T, Oliveira G. The Schistosoma mansoni phylome: using evolutionary genomics to gain insight into a parasite’s biology. BMC Genomics 2012;13:617.
[5] He YX, Salafsky B, Ramaswamy K. Comparison of skin invasion among three major species of Schistosoma. Trends Parasitol 2005;21:201–3.
[6] Grabe K, Haas W. Navigation within host tissues: Schistosoma mansoni and Trichobilharzia ocellata schistosomula respond to chemical gradients. Int J Parasitol 2004;34:927–34.
[7] Wolowczuk I, Roye O, Nutten S, Delacre M, Trottein F, Auriault C. Role of interleukin-7 in the relation between Schistosoma mansoni and its definitive vertebrate host. Microbes Infect 1999;1:545–51.
[8] Colley DG, Secor WE. Immunology of human schistosomiasis. Parasite Immunol 2014;36:347–57.
[9] Barsoum RS, Esmat G, El-Baz T. Human schistosomiasis: clinical perspective. J Adv Res 2013;4:433–44.
[10] Lenzi HL, Pacheco RG, Pelajo-Machado M, Panasco MS, Romanha WS, Lenzi JA. Immunological system and Schistosoma mansoni: co-evolutionary immunobiology. What is the ecosinophil role in parasite-host relationship? Mem Inst Oswaldo Cruz 1997;92:19–32.
Silva CLM. Endothelial cells as targets of the intravascular parasitic disease schistosomiasis. In: Gavins FNE, Stokes KY, editors. Vascular responses to pathogens. London: Academic Press; 2015. p. 195–208.

Wilson RA. Virulence factors of schistosomes. Microbes Infect 2012;14:1442–50.

Schramm G, Haas H. Th2 immune response against Schistosoma mansoni infection. Microbes Infect 2010;12:881–8.

Wilson RA, Coulson PS. Immune effector mechanisms against schistosomiasis: looking for a chink in the parasite’s armour. Trends Parasitol 2009;25:423–31.

Jacobs W, van Dam G, Bogers J, van Marck E, Arends K, van Wijk P. Association of type 2 cytokines with hepatic fibrosis in human Schistosoma mansoni infection. Infect Immun 2004;72:3391–7.

Deaton AM, Cook PC, De Sousa D, Phythian-Adams AT, Bird A, MacDonald AS. A unique DNA methylation signature defines a population of IFN-γ/IL-4 double-positive T cells during helminth infection. Eur J Immunol 2014;44:1835–41.

Berriman M, Haas BJ, LoVerde PT, Wilson RA, Dillon GP, Cerqueira GC, et al. The genome of the blood fluke Schistosoma mansoni. Nature 2009;460:352–8.

Zhou Y, Zheng H, Chen Y, Zhang L, Wang K, Guo J, et al. The Schistosoma japonicum Genome Sequencing and Functional Analysis Consortium. The Schistosoma japonicum genome reveals features of host-parasite interplay. Nature 2009;460:345–51.

Young ND, Jex AR, Li B, Liu S, Yang L, Xiong Z, et al. Whole-genome sequence of Schistosoma haematobium. Nat Genet 2012;44:221–5.

Zerlotini A, Aguilar ER, Yu F, Xu H, Li Y, Young ND, et al. SchistoDB: an updated genome resource for the three key schistosomes of humans. Nucleic Acids Res 2013;41(Database issue):D728–31.

Feirera LG, Oliva G, Andricopulo AD. Target-based molecular modeling strategies for schistosomiasis drug discovery. Future Med Chem 2015;7:753–64.

Agboh KC, Webb TE, Evans RJ, Ennion SJ. Functional characterization of a P2X receptor from Schistosoma mansoni. J Biol Chem 2004;279:41650–7.

Raouf R, Blais D, Séguela P. High zinc sensitivity and pore formation in an invertebrate P2X receptor. Biochim Biophys Acta 2005;176:135–41.

Feirera ZS, Silva CL. Comparative aspects of purinergic receptors in the phylogenetic scale. In: Lazari MFM, Yamanouye N, editors. G protein-coupled receptors in the phylogenetic scale. In: Lazari MFM, editors. G protein-coupled receptors in the phylogenetic scale. Kerala: Research Signpost; 2009. p. 73–91.

Verjovski-Almeida S, Leite LC, Dias-Neto E, Menck CF, Wilson RA. Schistosome transcriptome: insights and perspectives for functional genomics. Trends Parasitol 2004;20:304–8.

Pax R, Bennett JL, Fetterer R. A benzodiazepine derivative and praziquantel effects on musculature of Schistosoma mansoni and Schistosoma japonicum. Naunyn Schmiedeber Arch Pharmacol 1978;304:309–15.

Noel F, Pardon RS. Vanadate sensitivity of Na+,K+-ATPase from Schistosoma mansoni and its modulation by Na+, K+ and Mg2+. Life Sci 1989;44:1677–83.

Cunha VM, Meyer-Fernandes JR, Noel F. A (Ca2+/Mg2+) ATPase from Schistosoma mansoni is coupled to an active transport of calcium. Mol Biochem Parasitol 1992;52:167–73.

Silva CL, Cunha VM, Mendoça-Silva DL, Noel F. Evidence for ryanoide receptors in Schistosoma mansoni. Biochem Pharmacol 1998;56:997–1003.

Mendoça-Silva DL, Novozhilova E, Cobbett PJ, Silva CL, Noel F, Totten MI, et al. Role of calcium influx through voltage-operated calcium channels and of calcium mobilization in the physiology of Schistosoma mansoni muscle contractions. Parasitolology 2006;133:67–74.
Mendonça-Silva DL, Pessoa RF, Noel F. Evidence for the presence of glutamatergic receptors in adult Schistosoma mansoni. Biochem Pharmacol 2002;64:1377–44.

Mendonça-Silva DL, Gardino PF, Kubrusly RC, De Mello FG, Noel F. Characterization of a GABAergic neurotransmission in adult Schistosoma mansoni. Parasitology 2004;129:137–46.

Pessoa RF, Castro NG, Noel F. Binding of [3H]MK-801 in subcellular fractions of Schistosoma mansoni: evidence for interaction with nicotinic receptors. Biochem Pharmacol 2005;69:1509–16.

Burnstock G, Verkhratsky A. Evolutionary origins of the purinergic signalling system. Acta Physiol (Oxf) 2009;195:415–47.

Senft AW, Crabtree GW. Purine metabolism in the schistosomes: potential targets for chemotherapy. Pharmacol Ther 1983;20:341–56.

Levy MG, Read CP. Relation of tegumentary phosphohydrolase to purine and pyrimidine transport in Schistosoma mansoni. J Parasitol 1975;61:648–56.

Levy MG, Read CP. Purine and pyrimidine transport in Schistosoma mansoni. J Parasitol 1975;61:627–32.

Bhardwaj R, Skelly PJ. Purinergic signaling and immune modulation at the schistosome surface? Trends Parasitol 2009;25:256–60.

Da’da’ra AA, Bhardwaj R, Skelly PJ. Schistosome apyrase SmATPase1, but not SmATPase2, hydrolyses exogenous ATP and ADP. Purinergic Signal 2014;10:573–80.

Vasconcelos EG, Nascimento PS, Meirelles MN, Verjovski-Almeida S, Ferreira ST. Characterization and localization of an ATP-diphosphohydrolase on the external surface of the tegument of Schistosoma mansoni. Mol Biochem Parasitol 1993;58:205–14.

Mendes RG, Gusmão MA, Maia AC, Detoni Mle D, Porcino GN, Soares TV, et al. Immunostimulatory property of a synthetic peptide belonging to the soluble ATP diphosphohydrolase isoform (SmATPase 2) and immunolocalisation of this protein in the Schistosoma mansoni egg. Mem Inst Oswaldo Cruz 2011;106:808–13.

Maia AC, Detoni ML, Porcino GN, Soares TV, do Nascimento Gusmão MA, Fessel MR, et al. Occurrence of a conserved domain in ATP diphosphohydrolases from pathogenic organisms associated to antigenicity in human parasitic diseases. Dev Comp Immunol 2011;35:1059–67.

Crabtree GW, Senft AW. Pathways of nucleotide metabolism in Schistosoma mansoni. V. Adenosine cleavage enzyme and effects of purine analogues on adenosine metabolism in vitro. Biochem Pharmacol 1974;23:649–60.

Stegman RJ, Senft AW, Brown PR, Parks JR RE. Pathways of nucleotide metabolism in Schistosoma mansoni. IV. Incorporation of adenosine analogs in vitro. Biochem Pharmacol 1973;22:459–68.

Romanello L, Bachega JF, Cassago A, Brandão-Neto J, DeMarco R, Garett RC, et al. Adenosine kinase from Schistosoma mansoni: structural basis for the differential incorporation of nucleoside analogues. Acta Crystallogr D Biol Crystallogr 2013;69:126–36.

Dovey HF, McKerrow JH, Wang CC. Purine salvage in Schistosoma mansoni schistosomules. Mol Biochem Parasitol 1984;11:157–67.

Senft AW, Miech RP, Brown PR, Senft DG. Purine metabolism in Schistosoma mansoni. Int J Parasitol 1972;2:249–60.

Angelucci F, Passo A, Bellelli A, Brunori M, Pica Mattoccia L, Valle C. The anti-schistosomal drug praziquantel is an adenosine antagonist. Parasitology 2007;134:1215–21.

da Silva SP, Noel F. Time course of the effect of praziquantel on Schistosoma mansoni attachment in vitro: comparison with its effects on worm length and motility. Parasitol Res 1995;81:543–8.

Kohn AB, Anderson PA, Roberts-Misterly JM, Greenberg RM. Schistosome calcium channel beta subunits. Unusual modulatory effects and potential role in the action of the antischistosomal drug praziquantel. J Biol Chem 2001;276:36873–6.

Messerli SM, Kasinathan RS, Morgan W, Spranger S, Greenberg RM. Schistosoma mansoni P-glycoprotein levels increase in response to praziquantel exposure and correlate with reduced praziquantel susceptibility. Mol Biochem Parasitol 2009;167:54–9.

Fiske CH, Subbarow Y. Phosphorous compounds of muscle and liver. Science 1929;70:381–2.

Drury AN, Szent-Györgyi A. The physiological activity of adenine compounds with especial reference to their action upon the mammalian heart. J Physiol 1929;68:213–37.

Verkhratsky A, Burnstock G. Biology of purinergic signalling: its ancient evolutionary roots, its omnipresence and its multiple functional significance. Bioessays 2014;36:697–705.

Burnstock G. Purinergic signalling: from discovery to current developments. Exp Physiol 2014;99:16–34.

Burnstock G. Purinoceptors: ontogeny and phylogeny. Drug Dev Res 1996;39:204–42.

la Sala A, Ferrari D, Di Virgilio F, Idzko M, Norgauer J, Girolomoni G. Alerting and tuning the immune response by extracellular nucleotides. J Leukoc Biol 2003;73:339–43.

Burnstock G, Ralevic V. Purinergic signalling and blood vessels in health and disease. Pharmacol Rev 2013;66:102–92.

Ijzerman AP, Fredholm B, Jacobson KA, Linden J, Müeller C, Frenguelli B, et al. Adenosine receptors. IUPHAR/BPS Guide to PHARMACOLOGY. http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyID=3 [accessed on June 2016].

Zimmermann H, Zebisch M, Sträter N. Cellular function and molecular structure of ecto-nucleotidases. Purinergic Signal 2012;8:437–502.

Burnstock G, Abbracchio M-P, Boeynaems J-M, Boyer JL, Cerutti S, Fumagalli M, et al. IUPHAR/BPS Guide to PHARMACOLOGY. http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyID=52 [accessed on June 2016].

Volonte C, Amadio S, D’Ambrosi N, Colpi M, Burnstock G. P2 receptor web: complexity and fine-tuning. Pharmacol Ther 2006;112:264–80.

Jankowski V, van der Giet M, Mischak H, Morgan M, Lohman AW, Billaud M, Isakson BE. Mechanisms of ATP release and signalling in the blood vessel wall. Cardiovasc Res 2012;95:269–80.

Fraga H, Fontes R. Enzymatic synthesis of mono and dinucleoside polyphosphates. Biochim Biophys Acta 1996;208:204–10.

Thimm D, Nkonde P, Abdelrahman A, Moutinho M, Alsdorf BB, von Kügelgen I, et al. Characterization of new G protein-coupled adenine receptors in mouse and hamster. Purinergic Signal 2013;9:415–26.

Lohman AW, Billaud M, Isakson BE. Mechanisms of C5a release. Purinergic Signal 2012;8:359–73.

Lazarowski ER. Vesicular and conductive mechanisms of nucleotide release. Purinergic Signal 2003;4:695–704.
Eltzschig HK, Sitkovsky MV, Robson SC. Purinergic signaling during inflammation. N Engl J Med 2012;367:2322–33.

Robson SC, Sévigny J, Zimmermann H. The E-NTPDase family of ectonucleotidases: structure function relationships and pathophysiological significance. Purinergic Signal 2006;2:409–30.

Mebius MM, van Genderen PJ, Urbanus RT, Tielens AG, de Groot FG, van Hellemont JJ. Interference with the host haemostatic system by schistosomes. PLoS Pathog 2013;9:e1003781.

De Man JG, Seerden TC, De Winter BY, Van Marck EA, De Man JG, Seerden TC, De Winter BY, Van Marck EA, De Winter BY, Van Marck EA. Interferon-γ triggers Dectin-2, which activates the Nlrp3 inflammasome and alters adaptive immune responses. Proc Natl Acad Sci U S A 2010;107:20459–64.

Aird WC. Endothelium in health and disease. Pharmacol Rep 2008;60:139–43.

Rothermel AL, Wang Y, Schechner J, Mook-Kanamori B, Aird WC, Pober JS, et al. Endothelial cells present antigens in vivo. BMC Immunol 2004;5:5.

Pober JS, Sessa WC. Evolving functions of endothelial cells in inflammation. Nat Rev Immunol 2007;7:803–15.

Oliveira SD, Quintas LE, Amaral LS, Noel F, Farsky SH, Silva CL. Increased endothelial cell-leukocyte interaction in murine schistosomiasis: possible priming of endothelial cells by the disease. PLoS One 2011;6:e23547.

Vila E, Salaices M. Cytokines and vascular reactivity in resistance arteries. Am J Physiol Heart Circ Physiol 2005;288:H1016–21.

Wang L, Karlsson L, Moses S, Hultgårdh-Nilsson A, Anderson M, Borna C, et al. P2 receptor expression profiles in human vascular smooth muscle and endothelial cells. J Cardiovasc Pharmacol 2002;40:841–53.

Lyubchenko T, Woodward H, Vee KD, Burns N, Nijmeh H, Liubchenko GA, et al. P2Y1 and P2Y13 purinergic receptors mediate Ca2+ signaling and proliferative responses in pulmonary artery vasa vasorum endothelial cells. Am J Physiol Cell Physiol 2011;300:C2266–75.

Oliveira SD, Coutinho-Silva R, Silva CL. Endothelial P2X7 receptors’ expression is reduced by schistosomiasis. Purinergic Signal 2013;9:81–9.

Yamamoto K, Korenaga R, Kamiya A, Qi Z, Sokabe M, Ando J. P2X(4) receptors mediate ATP-induced calcium influx in human vascular endothelial cells. Am J Physiol Heart Circ Physiol 2000;279:H1016–21.

Silva CL, Morel N, Lenzi HL, Oliveira SD, Coutinho-Silva R, Silva CL. Endothelial P2X7 receptors’ expression is reduced by schistosomiasis. Mediat Inflamm 2014;2014:134974.