REVIEW

Gene expression changes in mammalian hosts during schistosomiasis: a review [version 1; peer review: awaiting peer review]

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Abstract

Schistosomiasis affects over 250 million people worldwide with an estimated mortality of more than 200,000 deaths per year in sub-Saharan Africa. Efforts to control schistosomiasis in the affected areas have mainly relied on mass administration of praziquantel, which kills adult but not immature worms of all *Schistosoma* species. Mammalian hosts respond differently to *Schistosoma* infection with some being more susceptible than others, which is associated with risk factors such as sociodemographic, epidemiological, immunological and/or genetic.

Host genetic factors play a major role in influencing molecular processes in response to schistosomiasis as shown in gene expression studies. These studies highlight gene profiles expressed at different time points of infection using model animals. Immune function related genes; cytokines (Th1 and Th17) are upregulated earlier in infection and Th2 upregulated later indicating a mixed Th1/Th2 response. However, Th1 response has been shown to be sustained in *S. japonicum* infection. Immune mediators such as matrix metalloproteinases *(Mmps)* and tissue inhibitors of matrix metalloproteinases (*Timps*) are expressed later in the infection and these are linked to wound healing and fibrosis. Downregulation of metabolic associated genes is recorded in later stages of infection. Most mammalian host gene expression studies have been done using rodent models, with fewer in larger hosts such as bovines and

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humans. The majority of these studies have focused on *S. japonicum* infections and less on *S. haematobium* and *S. mansoni* infections (the two species that cause most global infections). The few human schistosomiasis gene expression studies so far have focused on *S. japonicum* and *S. haematobium* infections and none on *S. mansoni*, as far as we are aware. This highlights a paucity of gene expression data in humans, specifically with *S. mansoni* infection. This data is important to understand the disease pathology, identify biomarkers, diagnostics and possible drug targets.

Keywords
Transcriptome, immune pathways, metabolic pathways, Schistosoma

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Schistosomiasis

Schistosomiasis is a debilitating disease caused by trematodes of the genus *Schistosoma* that belong to the Schistosomatidae family. By World Health Organization (WHO) estimates, approximately 236.6 million people required treatment in 2019 (WHO, 2020). *Schistosoma haematobium*, *S. mansoni* and *S. japonicum*, are the most prevalent human disease-causing species globally while *S. guineensis, S. intercalatum* and *S. mekongi* cause smaller localized numbers of infections (McManus *et al.*, 2018)(LoVerde, 2019). The distribution of each species is defined by their intermediate hosts' (snails) habitat range. Aquatic *Biomphalaria* and *Bulinus* snails are the intermediate hosts for *S. mansoni* and *S. haematobium,* respectively, while the amphibious *Oncomelania* spp snails are the hosts for *S. japonicum*. *S. mansoni* and *S. japonicum* cause intestinal schistosomiasis whereas *S. haematobium* causes urogenital schistosomiasis (WHO *Schistosomiasis*, 2021).

The schistosome life cycle consists of an asexual phase in the intermediate freshwater snail and a sexual phase in the definitive mammalian host (Figure 1). Infection occurs when the definitive host comes into contact with schistosome larvae, cercariae, in fresh water. The cercariae transform into schistosomula on entry into the host skin, mature and develop into adults which pair up and mate. Females lay eggs, some of which are excreted through feces or urine depending on the *Schistosoma* species, hatch in fresh water and penetrate the intermediate host and develop into cercariae and the cycle continues. Other eggs are lodged into host tissues such as the bladder, liver, spleen and lungs causing morbidity (Tukahebwa *et al.*, 2013), which when untreated leads to chronic schistosomiasis (Nelwan, 2019).

According to the WHO, intensity of infection of an individual is expressed as eggs per gram (epg) of stool and categorised as low (1–99 epg), moderate (100–399 epg) and high (≥400 epg) (Montresor *et al.*, 1998). Differences in infection intensity are associated with sociodemographic, epidemiological, immunological (Tukahebwa *et al.*, 2013) and genetic factors of the host (Mbanefo *et al.*, 2014). The genetic factors that may be associated with infection intensity have been shown through a range of studies on the differential gene expression in different mammalian hosts. In this paper, we review studies on the gene expression profiles of mammalian hosts in response to schistosomiasis and highlight the different experimental transcriptomic approaches and methods used.

Transcriptomics studies show dynamics of gene expression during schistosomiasis

Evolution of mammalian host schistosomiasis transcriptomics studies

Host transcriptomics has been used to give insights to genes that are expressed during disease. The major role of this is to identify genes that can be used for diagnosis of disease and pathways that are affected to direct development of therapeutics. The earliest transcriptomic studies of mammalian host schistosomiasis focused on understanding the gene expression in a particular cell type; the T cells in the spleen (Ji *et al.*, 2003), in liver and lungs (Jiang *et al.*, 2010). In early 2010, the first whole genome liver transcriptome microarray analysis of mice infected with *S. japonicum* showed that immune pathways were mainly affected, and a number of genes differentially expressed (Burke *et al.*, 2010a). Subsequently, studies have been conducted to understand the dynamics of gene expression in whole organs affected during

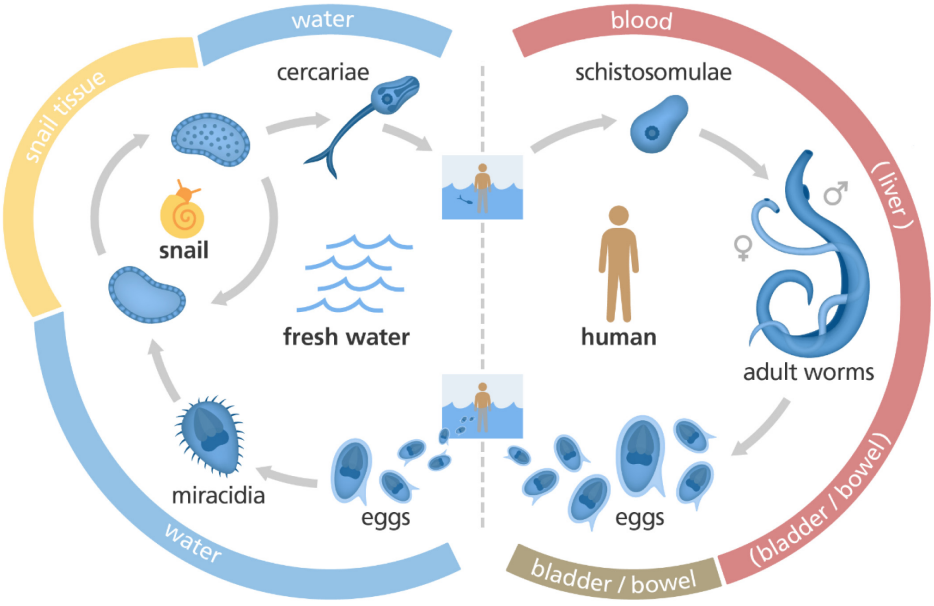

Figure 1. Schistosomiasis life cycle. Image is reproduced under the under a Creative Commons Attribution 4.0 CC-BY License (https://creativecommons.org/licenses/by/4.0/), from Yourgenome (2021) Genome Research Limited. Available at: https://www.yourgenome.org/facts/what-is-schistosomiasis/copyright

schistosomiasis. These studies have been done in a range of animal models and have shown that immune and metabolic processes are the major responders to infection.

Schistosomiasis transcriptomics studies

Experimental animal models have been used to study human schistosomiasis and include rodent, bovine and non-human primates. Since 2003, transcriptomics studies have used animal models to study gene expression changes occurring during schistosomiasis in mammalian hosts (Table 1). These range from voles (reed vole; *Microtus fortis)* (Hu *et al.*, 2014) (Hu *et al.*, 2017) (Xiong *et al.*, 2021), BALB/c, CBA and C57BL/6 mice (Ji *et al.*, 2003) (Burke *et al.*, 2010a) (Burke *et al.*, 2010b) (Perry *et al.*, 2011) (Ray *et al.*, 2012) (Chuah *et al.*, 2013) (Wijayawardena *et al.*, 2016) (Hu *et al.*, 2017) and bovines (cattle and buffalo) (Yang *et al.*, 2015). Recently transcriptomics studies have also been conducted in humans (Gobert *et al.*, 2015) (Dupnik *et al.*, 2019). Some studies have been targeted to identify immune genes expressed during infection (Ji *et al.*, 2003) while others have identified all genes affected through the course of the infection. Importantly, these studies have looked at gene expression changes in different tissues; spleen (Ji *et al.*, 2003) (Burke *et al.*, 2010a), peripheral blood (Yang *et al.*, 2015) and liver/liver biopsies (Burke *et al.*, 2010b) (Perry *et al.*, 2011) (Ray *et al.*, 2012) (Chuah *et al.*, 2013) (Gobert *et al.*, 2015) (Hu *et al.*, 2017)(Wijayawardena *et al.*, 2016) (Xiong *et al.*, 2021), bladder (Ray *et al.*, 2012) and peripheral blood (Dupnik *et al.*, 2019) depending on the *Schistosoma* species studied.

Most of these studies have been conducted in Asia using *S. japonicum* species (Ji *et al.*, 2003) (Burke *et al.*, 2010a) (Burke *et al.*, 2010b) (Perry *et al.*, 2011)(Chuah *et al.*, 2013) (Yang *et al.*, 2015) (Gobert *et al.*, 2015) (Hu *et al.*, 2017) (Xiong *et al.*, 2021). The research on *S. japonicum* may be linked to the importance attached to eliminating schistosomiasis in Asia (Gordon *et al.*, 2019), whereas fewer studies have been conducted using *S. haematobium* (Ray *et al.*, 2012) (Dupnik *et al.*, 2019) and *S. mansoni* species (Wijayawardena *et al.*, 2016).

Sequencing approaches

Since the first works to study the human transcriptome decades ago, technology has advanced from serial analysis of gene expression (SAGE) identifying expressed sequence tags, to microarray technology and recently RNA-seq technology allowing for assessment of even larger groups of expressed genes at one time. The earliest transcriptome studies in schistosomiasis employed microarray technology (Table 2). These technology advances have made it possible to understand the causes of differences in *Schistosoma* infection intensity through studies of gene expression in a number of mammalian hosts using different parasite species and at different time points. Also to note is that the gene expression studies have been conducted

Table 1. Studies of mammalian host gene expression during schistosomiasis.

Schistosoma species	Host	Tissue	Region	Age	Sex	Time points	Publication
Schistosoma japonicum	*M. fortis*	Liver	China	Sexually mature	NS	0, 10, 20 days	Xiong *et al.*, 2021
Schistosoma haematobium	Homo sapiens	Peripheral blood	Tanzania	Adult	M & F	Not mentioned	Dupnik *et al.*, 2019
Schistosoma japonicum	*M. fortis, & C57BL/6*	Serum & Liver	China	NS	NS	0, 2, 3, 4 weeks	Hu *et al.*, 2017
S. mansoni	BALB/cJ	Liver	Maine	7 weeks	M	7 weeks	Wijayawardena *et al.*, 2016
Schistosoma japonicum	Homo sapiens	Liver biopsies	Hunan China	Adult	NS	chronic	Gobert *et al.*, 2015
Schistosoma japonicum	Bos taurus, Bubalus bubalis	Peripheral blood	Japan	15-18 months	M	0, 7weeks	Yang *et al.*, 2015
Schistosoma japonicum	*M. fortis, & BALB/c*	Liver	China	7 - 8 weeks	F	1, 2, 3, 4 weeks	Hu *et al.*, 2014
Schistosoma japonicum	C57BL/6 mice	Liver	China	6 weeks	F	4, 6 & 7 weeks	Chuah *et al.*, 2013
Schistosoma haematobium	BALB/c mice	Bladder	Maine	7-8 weeks	F	1, 3 & 5 weeks	Ray *et al.*, 2012
Schistosoma japonicum	BALB/c and CBA	Livers	Australia	6 weeks	F	4 & 9 weeks	Perry *et al.*, 2011
Schistosoma japonicum	C57BL/6 mice	Spleen	Australia	6 weeks	F	4, 6 & 7 weeks	Burke *et al.*, 2010b
Schistosoma japonicum	C57BL/6 mice	Liver	Australia	6 weeks	F	4, 6 & 7	Burke *et al.*, 2010a
Schistosoma japonicum	BALB/c	Spleen	China	8 weeks	F	0, 3, 6, 10, &13 weeks	Ji *et al.*, 2003

Table 2. Sequencing methods used for mammalian schistosomiasis gene expression studies.

Expression profiling	Number of samples	Cases	Controls	Sequencing platform	Publication
High throughput sequencing	18	6	12	Illumina HiSeq™ 2000	Xiong *et al.*, 2021
High throughput sequencing	33	11	22	Illumina HiSeq 4000	Dupnik *et al.*, 2019
High throughput sequencing	14	7	7	Illumina HiSeq™2000	Hu *et al.*, 2017
High throughput sequencing	6	4	2	Illumina HiSeq2000	Wijayawardena *et al.*, 2016
High throughput sequencing	17	13	4	Array	Gobert *et al.*, 2015
Array	12	6	6	Agilent-023647 B. taurus (Bovine) Oligo Microarray v2 (Feature Number version)	Yang *et al.*, 2015
High throughput sequencing	15	12	3	Illumina HiSeq™2000	Hu *et al.*, 2014
Array	7	4	3	Illumina BeadStation	Chuah *et al.*, 2013
Array	NS	NS	NS	standard Illumina protocols on the MouseWG-6 v2.0 chip	Ray *et al.*, 2012
Array	10	6	4	Illumina MouseWG-6 v2 arrays	Perry *et al.*, 2011
Array	25	22	3	Illumina Mouse 6 version 1.1 Whole Genome Expression Chips	Burke *et al.*, 2010b
Array	25	22	3	Illumina Mouse 6 version 1.1 Whole Genome Expression Chips	Burke *et al.*, 2010a
Array	5	5	NS	U74A GeneChip arrays	Ji *et al.*, 2003

on different sequencing platforms identifying changes in the transcriptome that may be linked to host susceptibility and resistance to infection.

Dynamics of gene expression during schistosomiasis

The early stages of schistosomiasis from penetration and transformation, migration of schistosomula, and maturation into adult worms, are characterized by a T-helper type (Th) 1 immune response, which involves the production of pro-inflammatory cytokines including the interleukins (IL) 1, 6 and 12, Interferon gamma (*INFG*) and tumor necrosis factor alpha (*TNFA*)(Egesa *et al.*, 2018) (Ray *et al.*, 2012) (Wijayawardena *et al.*, 2016) followed by Th2 response (Ray *et al.*, 2012)(Wijayawardena *et al.*, 2016). Studies have shown that the gene expression profiles of these processes are altered in direct proportion to the stage of infection and most likely impact the fitness of the host (Burke *et al.*, 2010a; Chuah *et al.*, 2013; Hu *et al.*, 2014). Notably, there is a temporal relationship between expression of genes in the liver (Burke *et al.*, 2010a). The expression of genes follows a coordinated manner between the liver and spleen (Burke *et al.*, 2010b) in that when one set of genes is upregulated in one organ, it is downregulated in the other at that specific time. This shows there could be distinction of gene expression in different host organs.

However, even with similarity in shift of gene expression from Th1 to Th2 response (Ray *et al.*, 2012) (Wijayawardena *et al.*, 2016), it has been noted in the non-permissive voles that Th1, Th2 and Th7 responses occur earlier than in the more susceptible mice (Hu *et al.*, 2014), which could be associated with the difference in susceptibility between these hosts. Hosts that are resistant to *Schistosoma* infection, such as reel vole and rats, generally display a stronger immune response compared to more susceptible hosts such as the mice, displaying significant levels of cytokines, complements and antibodies (Hu *et al.*, 2014; Hu *et al.*, 2017; Khalife *et al.*, 2000). These hosts display strong response to infection in the second week of infection that is mainly associated with inflammation, metabolic and immune responses (Hu *et al.*, 2014). In addition,

the resistant vole displays upregulation of apoptosis inducing genes and down regulation of development associated genes (Jiang *et al.*, 2010).

Notably, there is a low expression of genes associated with immune response in peripheral blood of less susceptible water buffalo compared with more susceptible yellow cattle infected with *S. japonicum* (Yang *et al.*, 2015), which may be responsible for the differences in pathology seen between the two hosts (Davies *et al.*, 2001). There is high expression of the *IL10* family of cytokines in the less susceptible buffalo; these cytokines are important in limiting tissue damage through promoting innate immune responses from tissue epithelia, which may contribute to the reduced susceptibility to infection of buffalo (Webster *et al.*, 2021; Yang *et al.*, 2015). The high expression of *IL10* particularly through the JAK2/STAT1-Mf-HSP90α pathway has also been suggested to be responsible to resistance to infection in M. fortis to S. japonicum infection (Xiong *et al.*, 2021). In addition, the unique genes differentially expressed in the buffalo are comparable with immune related pathways as opposed to those in the susceptible yellow cattle that are associated with inflammation linked pathways, such as cytokine–cytokine receptor interactions, neuroactive ligand–receptor interactions, chemokine signaling pathways (Yang *et al.*, 2015). Beyond the early stages of infection, there is reduced expression of metabolic genes responsible for amino acid and carbohydrate metabolism (Gobert *et al.*, 2015; Wijayawardena *et al.*, 2016), which could be linked to reduction of function of the affected organs.

In humans infected with *S. haematobium,* there is upregulation of transcription and translation genes that are involved in cell differentiation as well as genes related to the cell cycle including Notch pathway genes which may be markers of systemic inflammation associated with chronic schistosomiasis (Dupnik *et al.*, 2019).

Genes expressed in schistosomiasis

With these differences in study models and types, the two major processes affected during schistosomiasis infection are the immune (Burke *et al.*, 2010a) (Burke *et al.*, 2010b) and metabolic processes (Gobert *et al.*, 2015; Wijayawardena *et al.*, 2016; Wu *et al.*, 2010) at different stages of infection. Importantly, expression levels of the immune related genes in mice are lower in less susceptible host compared to the susceptible hosts (Yang *et al.*, 2015), which may play a role in the notable profiles of schistosomiasis infection and host reaction to infection (Wijayawardena *et al.*, 2016). These gene expression changes are in direct proportion of the stage of infection and may also be associated with the observed phenotype at each stage of infection (Burke *et al.*, 2010a) (Burke *et al.*, 2010b) and (Wijayawardena *et al.*, 2016). Expression levels of immune genes before infection of the mammalian host may be associated with the level of susceptibility to infection by the worm. IL10 family cytokines have been shown to be upregulated in less susceptible hosts before infection. IL10 plays an important role in eliciting the innate immune response to limit damage of the epithelial tissues on infection by schistosomes. This therefore may be directly linked to the observed difference in pathology between susceptible and the less susceptible hosts (Yang *et al.*, 2015). This transcriptome profiling has led to identification of genes upregulated early in the infection, consistently up-regulated during infection, up-regulated late in the infection and those genes down-regulated during the infection genes (Burke *et al.*, 2010a) (Burke *et al.*, 2010b) (Perry *et al.*, 2011) (Hu *et al.*, 2014).

Genes upregulated in early stages of infection

In the early infection, genes up-regulated are mainly associated with immune function, among which are cytokines (Th1, Th2 and Th17), along with serine protease inhibitor genes (Burke *et al.*, 2010a) (Burke *et al.*, 2010b) (Perry *et al.*, 2011) (Hu *et al.*, 2014). Th1 associated genes [Il1a, *INFG*, *TNFA*, IFNG-induced GTPase (*Igtp*), *Cxcl9* and Signal Transducers and Activators of Transcription 1 (*Stat1*)] as well as Th2 associated genes [IL4 induced (*Il4i*), *Ccl24* and *Ccl7]* are upregulated in these initial stages of infection (Burke *et al.*, 2010a) (Perry *et al.*, 2011). Of note, IFN-inducible genes (*Igtp*, *Tgtp*, *Lrg47*, *Irg47*, *Iigp*, and *GtpI*) are expressed earlier in the infection before expression of *IFNG,* which may be linked to a possible method of interfering with schistosomiasis pathology by inducing an early and strong *IFNG* response (Ji *et al.*, 2003) (Burke *et al.*, 2010a) (Burke *et al.*, 2010b). The expression of *IFNG* decreases as the infection progresses while Th2 increases, but is sustained through the infection (Ji *et al.*, 2003) underscoring the role of *IFNG* in schistosomiasis. A significant number of genes associated with antigen presentation and cell recruitment reflected by T- and B- cell markers are upregulated early in *S. japonicum* infection (Burke *et al.*, 2010a). Among these are *Cxcl13*, *Cxcl9* and *Cxcl16,* which play a critical role in recruitment of B and T- cells and *Ccl24* which is associated with recruitment of eosinophils in the liver. The acute phase is characterized by a transition from Th1 to Th2, which is driven by deposition of schistosome eggs (Pearce & MacDonald, 2002). This transition is implied when expression of Th1 related genes such as *INFG* decline in *S. mansoni* infection (Pearce & MacDonald, 2002) and plateau in *S. japonicum* infection (Ji *et al.* 2003). Early upregulation of *Il10* and plateauing at the same time but with higher production levels than *IFNG* indicates its regulatory role in switching from Th1 to Th2 response (Ji *et al.*, 2003) (Wijayawardena *et al.*, 2016). The Th2 response is associated with granuloma formation during *S. japonicum* infection (Burke *et al.*, 2010a).

Genes upregulated during the course of infection

During the course of infection, particular IFN-inducible genes (*mGBP1* and *mGBP2*) (Ji *et al.*, 2003) and *IFNG* (Burke *et al.*, 2010a) are upregulated, suggestive of the sustenance of Th1 response through *S. japonicum* infection, implying a mixed Th1/Th2 immune response (Ji *et al.*, 2003) (Burke *et al.*, 2010a). Profibrotic cytokines such as *IL4*, Interleukin 10 Receptor Alpha (*Il10ra*), Interleukin-33 (*Il33*) and Interluekin-4-inducible 1 (*Il4i1*) expression increases over time with *S. japonicum* infection in mice (Burke *et al.*, 2010a) (Perry *et al.*, 2011). There is however variation between time of increase in expression between susceptible and less susceptible mouse strains (Perry *et al.*, 2011). Neutrophil infiltration associated genes, such as

Neutrophil granule protein (*Ngp)* and Myeloperoxidase (*Mpo),* could play an important role towards susceptibility of CBA mice in which expression of these molecules declines with time while expression in maintained in the less susceptible BALB/c mice in *S. japonicum* infection (Perry *et al.*, 2011). The *Ccl24* gene that is essential for eosinophil chemotaxis is also seen to be significantly upregulated in CBA mice over time of the infection unlike in BALB/c mice where it is not upregulated at any time point (Perry *et al.*, 2011).

Genes upregulated in later stages of infection

Later in the infection the genes upregulated are associated with wound healing and chemotaxis (*Cxcl1*, *Cxcl4, Cxcl7*, *Ccl21*, *Ccl7*, *Ccl8* and *S1008a8*) fibrosis, glycolysis and peroxidase activity (Burke a, b). To note, there is late upregulation of *Ccl3* chemokine, *Tlr Il13* and *Tgfb,* which are thought to be involved in *S. japonicum*-induced fibrogenesis (Burke *et al.*, 2010a) (Perry *et al.*, 2011). Fibrosis associated genes upregulated late in the infection include matrix metalloproteinases *(Mmps)* and tissue inhibitors of matrix metalloproteinases (*Timps*). Importantly the *Mmp:Timp* ratio may play an important role in the outcome of the severity of schistosome induced fibrosis (Burke *et al.*, 2010a). *Mmp2, Mmp9, Mmp13, Timp1* and *Timp2* are commonly expressed in *S. japonicum* and *S. mansoni* unlike *Mmp8* and *Mmp12,* which are only expressed in *S. mansoni* infection and *Mmp23* and *Mmp25* only recently reported in *S. japonicum* infection (Burke *et al.*, 2010a). Contrary to the previous observation, *Mmp12* was also upregulated during *S. japonicum* infection and only *Timp1* was expressed in higher amounts in the susceptible CBA compared to the BALB/c mice (Perry *et al.*, 2011). The upregulation of *Cxcl14*, *Ccl6*, *Ccl7* and *Ccl8* indicates a possible mechanism for alternatively activated macrophage involvement in schistosome granuloma induction (Burke *et al.*, 2010a). Genes associated with recruitment of alternatively activated markers; Chitinase 3-like 3 (*Chi3l3*), Resistin-like alpha (*Retnla*), Mannose Receptor C Type 1 (*Mrc1)* are seen to be significantly expressed in more susceptible CBA compared to BALB/c in *S. japonicum* infection (Perry *et al.*, 2011). Other upregulated genes include neutrophil markers such as *NgP*, *Ne*; eosinophil markers (*Epx, Ear1 – 3,6,10*), Annexin a 1 (*Anxa1*) and Cathelicidin Antimicrobial Peptide (*Camp*) (Burke *et al.*, 2010a) (Burke *et al.*, 2010b) *Eas11* (Perry *et al.*, 2011).

Genes downregulated in schistosomiasis infection

IFN-inducible gene expression is reduced in *S. japonicum* chronic infection (Ji *et al.*, 2003), which could affect effective response to *S. japonicum* through impairment of signal transduction as well as causing dysfunction of antigen recognition between APC and T cells as a way of parasite evasion of the immune system (Ji *et al.*, 2003). In contrast to the liver, in the spleen expression of chemokines decreases, including *Cxcl13*, *Ccl21* and *Ccl19* in *S. japonicum* infected mice and may be more associated to migration than to apoptosis (Burke *et al.*, 2010b). Downregulated clusters of genes during *S. japonicum* infections include oxidoreductase activity, ion and vitamin binding, biosynthesis and metabolic processes (Perry *et al.*, 2011). Also, owing to significant damage to the liver during schistosomiasis, notable under-expression of enzymes involved in the production of acyl COA (acyl-COA synthetase, acyl-COA Co-enzyme and acyltransferase) is observed along with downregulation of enzymes involved in amino acid synthesis and catabolism (Wijayawardena *et al.*, 2016). Networks of genes expressed in human peripheral blood are associated with development, cell death and survival, cell signaling and immunological disease pathways (Dupnik *et al.*, 2019). Most genes that are expressed later in the infection are associated with fibrosis processes, glycolysis and peroxidase activity.

Conclusion

Transcriptomics studies have played a major role in understanding the major host-parasite molecular interactions. Different technologies such as SAGE (Verjovski-Almeida *et al.*, 2003), microarray technologies (Fitzpatrick *et al.*, 2009) (Burke *et al.*, 2010a) (Burke *et al.*, 2010b) (Perry *et al.*, 2011) (Chuah *et al.*, 2013) and recently next generation sequencing (NGS) using pyrosequencing (Anderson *et al.*, 2015) and Illumina technologies (Hu *et al.*, 2014) (Wijayawardena *et al.*, 2016) (Wangwiwatsin *et al.*, 2019) (Dupnik *et al.*, 2019) (Xiong *et al.*, 2021 have been employed to study transcriptome changes in both the parasites and hosts. The mammalian host studies conducted are mainly using *S. japonicum* species (Burke *et al.*, 2010a) (Burke *et al.*, 2010b) (Perry *et al.*, 2011) (Chuah *et al.*, 2013) (Gobert *et al.*, 2015) one using *S. mansoni* (Wijayawardena *et al.*, 2016) and two *S. haematobium* (Ray *et al.*, 2012) (Dupnik *et al.*, 2019). The studies done in humans were on people infected with *S. japonicum* and *S. haematobium* and none on *S. mansoni.* Moreover, different hosts species respond to infection differently (Yang *et al.*, 2015) (Perry *et al.*, 2011) and different *Schistosoma* species may have different effects on the host.

But even with these host variations, the immune processes and metabolic processes have been shown to be the most affected. There is generally upregulation of immune related genes at particular time points which correspond to the stage of infection although some studies have shown upregulation of energy and purine metabolism linked metabolites in early infection (Osakunor *et al.*, 2020). It is important to note that less susceptible hosts may express immune genes before infection, as seen in murine hosts (Yang *et al.*, 2015). The greater number of the genes differentially expressed are among candidate genes for schistosomiasis infection (Mewamba *et al.*, 2021). Moreover, some of the genes that are expressed such as *MMPs*, *TIMPs*, *STATs* and Histone deacetylase have been identified as potential therapeutic targets among others (Latronico & Liuzzi, 2017).

Whilst studies in humans are potentially much more informative about human disease, there are substantial difficulties involved. Firstly, humans from the same population have diverse life histories and environments; secondly, they are genetically heterogenous unlike laboratory mice which are inbred; thirdly, it is difficult to obtain appropriate samples, blood is

useful for studying the response to the parasite but most of the pathology is in other tissues such as the liver and spleen; lastly, there are significant sex differences in gene expression which make it harder to detect responses to the infection (Bongen *et al.*, 2019). A recent analysis of immune genes expressed in non-human primates (baboons) infected with *S. mansoni* (Melkus *et al.*, 2020) showed the changes in expression of cytokine genes that can direct the transcriptomic changes in humans infected with *S. mansoni*. However, it is notable that there have been no studies of the transcriptome of humans infected with *S. mansoni*. It will be important to carry out such studies to discover the differentially expressed genes in humans with different *S. mansoni* infection intensities and how these impact the physiology and clinical outcomes of infection in these individuals.

Data availability

No data is associated with this article.

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