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Investigating the Role of STAT1 Transcription Factor in the Regulation of Schistosome Immunopathology

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ABSTRACT

Schistosomes are parasitic trematode worms that infest bodies of water and cause the disease schistosomiasis. A portion of eggs produced by adult schistosomula lodge in the liver and induce CD4 T helper (Th) cell-mediated granulomatous inflammation and fibrosis. Milder pathology is associated with T helper 2 (Th2) cytokines while severe pathology is associated with Th1 and Th17 cells. We have previously shown that Type I Interferon (IFN-I) plays a key role in controlling disease pathogenesis by limiting inflammation. Yet, it is unknown how interferon-α/β receptor (IFNAR) signaling impacts disease severity and which transcription factors are activated downstream of IFNAR. Previous studies showed that schistosome eggs are potent inducers of signal transducer and activator of transcription (STAT1) phosphorylation in Dendritic cells but revealed no consequences to this activation. We demonstrated that mechanistically STAT1 diminishes inflammation by restraining egg-mediated inflammasome activation and inducing anti-inflammatory cytokine production. Additionally, we showed that STAT1 deficiency results in marked increase in pathology *in vivo*. These results suggest that schistosome egg mediated STAT1 activation directly curbs inflammation and immunopathology *in vitro* and *in vivo*.

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Introduction

Schistosomes are trematode helminths that contaminate bodies of freshwater particularly in South America and Africa. The larval form of schistosomes, cercariae, are released by snail intermediate hosts and penetrate human skin. In the body, cercariae transform into schistosomula and enter the vasculature to migrate to the portal system. The species *Schistosoma mansoni* lay eggs that become trapped in the liver and intestines and induce CD4 T helper (Th) cell-mediated granulomatous inflammation and fibrosis. While a mild form of the disease is developed in most individuals following schistosome infection, the disease is severe and life threatening in 5 to 10% of patients (1). As the second most devastating parasitic disease worldwide, it is essential to expand the limited understanding of immunopathology of schistosomiasis in infected patients (2).

Previous publications suggest that milder pathology is associated with T helper 2 (Th2) cytokines while severe granulomatous inflammation is mainly via Th17 cells (1, 3-6). As a model of milder pathology, C57BL/6 (BL/6) mice have been observed to exhibit stronger anti-inflammatory responses due to a protective Th2-dominated cytokine environment (1). During infection with an intestinal helminth, Th2 cytokines induce eosinophilia, immunoglobulin E (IgE) synthesis, and intestinal mastocytosis to defend against infection and promote expulsion of the parasite (7). Th2 cells also generate host-protective responses through the secretion of interleukin (IL)-4, IL-5, IL-10, and IL-13 that suppress inflammation through downregulation of Th1 responses (8, 9). IL-10 is an especially potent anti-inflammatory cytokine that reduces immunopathology in schistosomiasis and other infectious diseases (9-11).

Type I interferons (IFN-Is), including IFNα and IFNβ, are cytokines that are secreted by infected cells to activate the adaptive immune system and initiate antigen-specific T and B cell

responses. IFN-I signaling has been shown to upregulate levels of protective anti-inflammatory cytokines including IL-5, IL-12, and IL-10 in response to schistosome eggs (12-15). IFN-I signaling has also been shown to suppress inflammasome activation, specifically NLRP3, and IL-1β production (16). To cause these effects, IFN-Is bind to IFN receptors (IFNARs), which activate Janus kinase (JAK) and tyrosine kinase 2 (TYK2) that phosphorylate signal transducers and activators of transcription (STATs) which can then form homodimers or heterodimers (17). STAT1 homodimers, which have been found to be induced by schistosome eggs, bind to the gamma interferon activation site (GAS) to activate transcription of IFN stimulated genes (ISG) in nuclei (Fig. 1) (13). STAT3 homodimers function similarly to STAT1 homodimers to induce pro- or anti-inflammatory responses in schistosomiasis (18). The critical role of STAT1 in the IFN-1 pathway therefore makes the molecule an attractive target for the therapeutic manipulation of host immune responses in various human diseases including schistosomiasis.

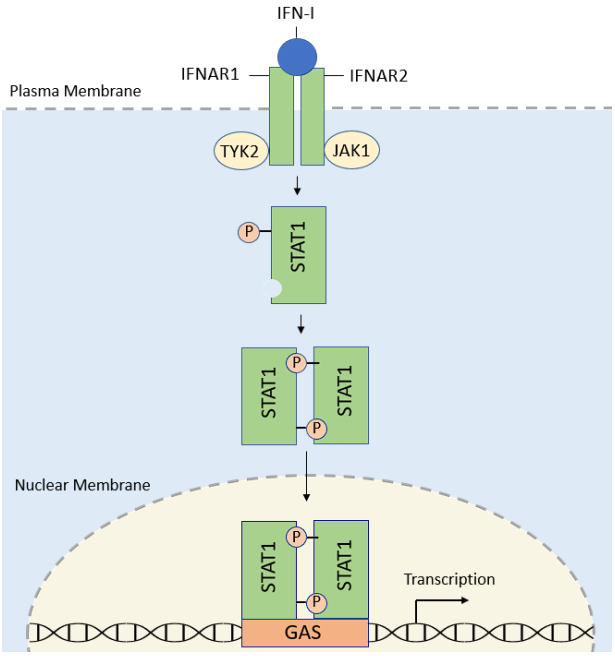


Figure 1. Type 1 Interferon induced JAK/STAT1 signaling pathway and subsequent transcription of IFN stimulated genes.

Inflammasomes are innate immune system sensors that play an essential role in inducing inflammation in response to infection. An inflammasome complex is composed of a sensor protein, an adaptor, and pro-caspase-1 (19). Initiation of inflammasome complex assembly is achieved through sensors including nucleotide-binding domain, pyrin, and leucine-rich repeat receptors, which are also known as NOD-Like receptors (NLRs) (19, 20). The pyrin domain-containing 3 (NLRP3) belongs to the NOD-like receptor family and associates with apoptosis-associated speck-like protein containing a CARD (ASC) adaptor to recruit pro-caspase-1 and ultimately induce inflammation (19-21). Oligomerization of pro-caspase-1 proteins results in the production of activate caspase-1, which functions to cleave pro-IL-1β to its active form IL-1β (19-21). Schistosome antigens have been well established to activate the NLRP3 inflammasome and upregulate the production of inflammatory IL-1β (22, 23). The function of STAT1 as a suppressor of inflammasome activation will be investigated to better understand the immunopathology of schistosomiasis.

Schistosome eggs have been reported to stimulate Dendritic cells (DCs) to produce Type I Interferon (IFN-I), which then induces an Interferon Receptor (IFNAR)1-dependent Th2 response (13-15). Our previous studies using STAT1 inhibitor fludarabine phosphate (FP) suggest that STAT1 is activated and required for egg-mediated IFNβ production in bone marrow-derived dendritic cells (BMDCs) (15). In the study, pharmacological inhibition of STAT1 led to a significant increase in proinflammatory cytokine IL-1β and T-cell activating IL-17 secretion in BMDCs but did not affect TNFα production in these cells. We also showed that STAT1 activation by egg-mediated IFN-I was able to trigger the suppression of CD209a transcription (15), a molecule that has a critical role in inducing inflammation during schistosome infection (6). The impact of STAT1 on disease severity, however, has not been previously studied. Based on these

data and existing literature, it can be hypothesized that STAT1 plays a critical role in regulating schistosome immunopathology during schistosome infection. The molecular mechanisms by which IFN-I suppresses schistosome immunopathology through STAT1 *in vitro* was examined. Preliminary findings of increased egg-induced granulomatous inflammation as a result of STAT1 deficiency *in vivo* were also examined.

Materials and Methods

Experimental Design

To conduct *in vitro* experiments, bone marrow derived dendritic cells (BMDCs) from BL/6 and STAT1 knock-out ($STAT1^{-/-}$) mice were cultured. As a model of milder pathology, BL/6 mice served as the control group while $STAT1^{-/-}$ mice served as the experimental group. BMDCs were treated with STAT1 inhibitor fludarabine phosphate (FP) or IL-10 receptor (IL-10R) blocking antibody followed by lipopolysaccharide (LPS) and schistosome eggs. FP was used to treat BL/6 BMDCs to observe the immunological effects of inhibiting STAT1. IL-10R blocker was also used to treat BL/6 BMDCs to further investigate the mechanistic effects of IL-10. LPS served to activate dendritic cells (DCs) in preparation for stimulation with schistosome eggs. The concentrations of IL-10 or IL-1β in cell supernatants were measured using sandwich enzyme-linked immunosorbent assay (ELISA). Levels of STAT1, ASC, and GAPDH proteins in cell lysates were measured using Western Blot. As an adaptor protein for inflammasomes, ASC protein levels served as a representative for inflammasome activation. GAPDH served as a loading control.

For *in vivo* experiments, BL/6 and $STAT1^{-/-}$ mice were infected with cercariae of *S. mansoni* to examine differences in immunopathology in the presence and absence of STAT1. Organ sizes and weights were compared between the BL/6 control and the $STAT1^{-/-}$ experimental groups.

Infection of Mice

BL/6 and $STAT1^{-/-}$ mice were purchased from The Jackson Laboratory. Six- to eight-week-old female BL/6 and $STAT1^{-/-}$ were infected by intraperitoneal injection with 85 cercariae

of *S. mansoni.* After 7 weeks of infection, when egg-induced granulomatous inflammation was at its peak, the mice were sacrificed and examined for immunological parameters.

Primary Bone Marrow Derived Dendritic Cell Culturing

BL/6 and STAT1$^{-/-}$ mice from 3 months – 6 months old were euthanized by carbon dioxide inhalation for tibia and femur bone extraction. Extracted bones were kept in RPMI-1640 complete culture medium (cRPMI) supplemented with 10% fetal bovine serum (FBS), 1% L-glutamate, 1% sodium pyruvate, 1% HEPES, 1% NEAA, 0.1% 2-ME, and 20% Penicillin/Streptomycin. Bone marrow was collected by flushing bones with cRPMI using a 10-ml syringe with a 25G needle. Cell suspensions were filtered to remove any tissue debris and centrifuged at 1200 rpm for 5 minutes. Supernatants were removed and cell pellets were lysed in 1 mL of red cell lysis buffer on ice for 10 minutes. Lysis buffer was neutralized with media and cell suspensions were centrifuged at 1200 rpm for 5 minutes. Supernatants were removed and cells were resuspended in fresh cRPMI. Cells from the same mouse strain were combined to bring total cell suspension volume to 4 mL of cRPMI. 1 mL of cells and 9 mL of cRPMI were added to 4 plates for each mouse strain. Granulocyte-macrophage colony-stimulating factor (GM-CSF) was added to each plate for a concentration of 10 ng/mL. Plates were incubated at 37 °C. On day 3 following bone marrow extraction, 10 mL of cRPMI and GM-CSF was added for a concentration of 10 ng/mL to each plate. On day 5, the number of plates was doubled. 15 mL of media were collected from each plate and 5 mL of fresh media was returned to each original plate. The collected media was centrifuged at 1200 rpm for 5 minutes. Supernatants were removed and cell pellets were resuspended in cRPMI. Cells were plated in the same fashion as on day 0. On day 7, media was collected from all plates. The collected media was centrifuged at

1200 rpm for 5 minutes and supernatant was removed. Cell pellets were resuspended in cRPMI. 10 mL of 2mM pH 8.0 ethylenediaminetetraacetic acid (EDTA) was added to each plate and plates were incubated for 10 minutes. Plates were washed with EDTA by pipetting EDTA up and down on each plate. Cells were collected and centrifuged at 1200 rpm for 5 minutes. Cells were resuspended in cRPMI and combined with cells from the same mouse strain to bring each mouse strain cell suspension to a total of 5 mL. Cells were counted and plated. 50,000 cells or 1,000,000 cells were seeded per well in 96-well or 6-well plates respectively and left to incubate overnight at 37°C.

Dendritic Cell Treatments

BMDCs were generated and seeded as described above. Cells in 96-well plates were treated with 10 ug/mL of FP (Sigma-Aldrich) for 1 hour followed by 100 *S. mansoni* eggs for 24 hours. Additional treatments included IL-10R blocking antibody (BioXCell) at final concentrations of either 5 µg/mL or 10 µg/mL for 1 hour followed by 10 ng/mL of LPS for 2 hours and then 100 *S. mansoni* eggs for 24 hours. Cells in 6-well plates were primed with 100 ng/mL of LPS for 2 hours followed by stimulation with 300 eggs for 24 hours. Supernatants and cell lysates were then obtained and frozen at -20°C.

Western Blot

BMDCs were washed with cold 1x phosphate buffered saline (PBS). Cells were lysed with radioimmunoprecipitation assay (RIPA) buffer (Thermo Fisher Scientific) with 1:10 dithiothreitol (DTT) (Thermo Fisher Scientific) and 1:100 Halt Protease Inhibitor (Thermo Fisher Scientific) added according to manufacturers' instructions. Samples were run on native

PAGE 4-20% Mini-Protean precast gels (BioRad) and transferred to a nitrocellulose membrane (BioRad). A solution of 1000 mL of PBS with 0.5 mL of Tween 20 (PBST) was prepared. The membrane was blocked in a solution of PBST with 5% powdered milk. The membrane was probed for antibodies specific for ASC (22514, Santa Cruz), STAT1 (9172, Cell Signaling), and GAPDH (365062, Santa Cruz).

Enzyme-Linked Immunosorbent Assay (ELISA)

Cytokine protein measurements were performed by sandwich ELISA in culture supernatants for IL-1B using mouse ELISA kits from R&D Systems according to the manufacturer's instructions. Data was analyzed for statistical significance by conducting unpaired t-tests using GraphPad Prism 9 software.

Results

Schistosome Egg-Induced DC IL-10 Production Depends on STAT1

Previous studies from our lab have shown that treatment of BMDCs from BL/6 mice with STAT1 inhibitor fludarabine phosphate (FP) led to increased levels of pro-inflammatory cytokines including IL-1B and IL-17 (15). To investigate the protective function of STAT1 in response to eggs, levels of anti-inflammatory cytokine IL-10 secreted by BMDCs treated with STAT1 inhibitor FP were examined. IL-10 released by BMDCs stimulated with eggs significantly decreased with FP treatment, suggesting that IL-10 release is mediated by STAT1 activation in BMDCs (Fig. 3).

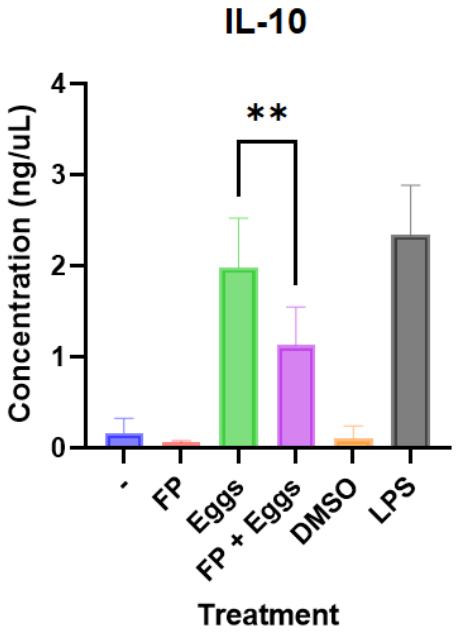


Fig. 3. BMDCs from BL/6 mice were treated with 10 ug/mL STAT1 inhibitor fludarabine phosphate (FP) and then stimulated with 80 eggs for 24h. IL-10 levels were measured in the supernatants by ELISA. Error bars represent the mean ± SD cytokine levels from one representative experiment of 2 with similar results. *$P \leq 0.05$, **$P \leq 0.005$.

Inhibition of IL-10 Receptor Results in Decrease of IL-1β

To further understand the protective mechanistic pathway of STAT1, the role of secreted IL-10 was examined. IL-1β was measured in supernatants of BL/6 BMDCs treated with various concentrations of IL-10 receptor (IL-10R) blocking antibody followed by LPS and 100 eggs. Concentrations of IL-1β significantly increased with IL-10R blocker treatment preceding LPS and egg stimulation (Fig. 4). Concentrations of IL-1β also increased with increasing concentrations of IL-10R blocker from 5 µg/mL to 10 µg/mL. These data suggest that IL-10 plays a significant role in regulating IL-1β production.

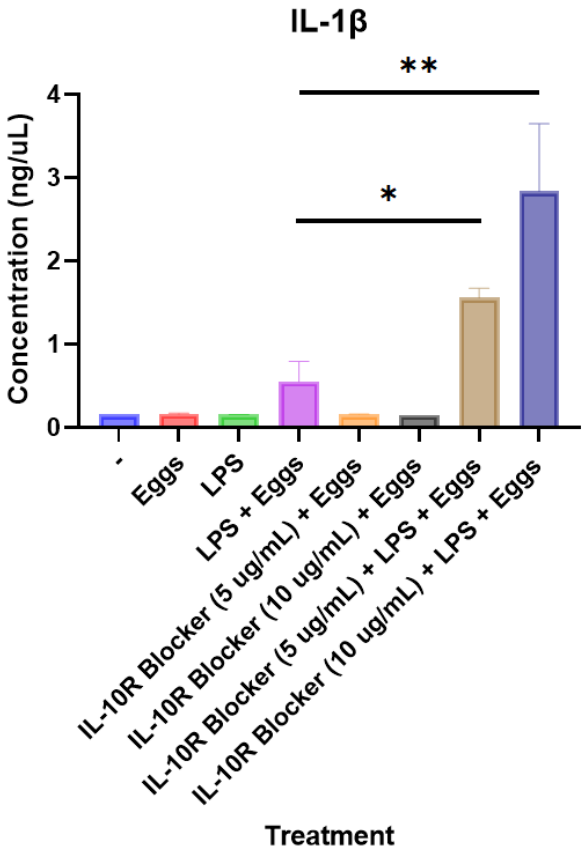
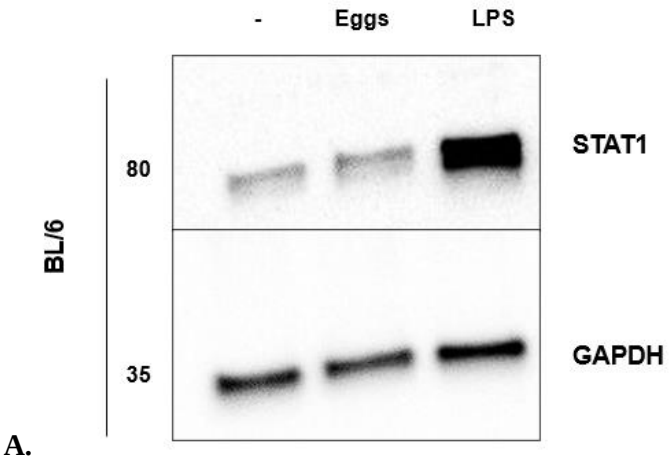


Fig. 4. BMDCs from BL/6 mice were treated with various concentrations of IL-10 receptor blocking antibody for 1h followed by treatment with LPS for 2h and 100 eggs for 24h. IL-1β levels were measured in supernatants by ELISA. Error bars represent the mean ± SD cytokine levels. *$P \leq 0.05$, **$P \leq 0.005$.

STAT1 Deficiency Results in Increased Activation of Inflammasomes

Given the importance of inflammasomes in schistosome immunopathology (30, 31), the role of STAT1 in suppressing inflammasome activation was also examined. BMDCs from BL/6 and STAT1$^{-/-}$ mice were treated with LPS for 2 hours and then eggs for 24h. Protein levels of STAT1 and ASC in cell lysates were measured using Western Blot. STAT1 levels in BL/6 DCs increased following egg and LPS treatments (Fig. 5.A.). Using STAT-/- BMDCs, we showed that ASC levels increased following egg and LPS treatments in the absence of STAT1 (Fig. 5.B.) suggesting that STAT1 decreases IL-1B production in response to eggs by suppressing inflammasome activation.



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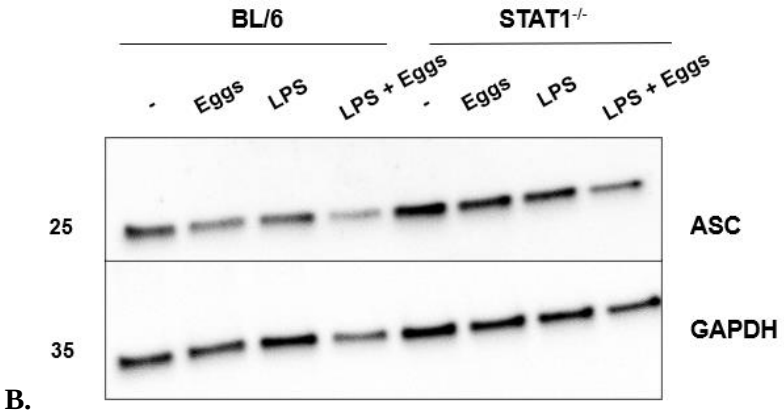

B.

Fig. 5. *(A)* Western blots for 1 x 10^6 BL/6 BMDC cell lysates following treatments with LPS for 2h and eggs for 24h. Antibodies against STAT1 and GAPDH were used. *(B)* Western blots for 1 x 10^6 BL/6 and $STAT1^{-/-}$ BMDC cell lysates following treatments with LPS and eggs. Antibodies against ASC and GAPDH were used.

STAT1 Deficiency Induces Increased Egg-Induced Granulomatous Inflammation

To investigate the immunological role of STAT1 *in vivo,* BL/6 and $STAT1^{-/-}$ mice were infected with *S. mansoni* and killed after 7 weeks. $STAT1^{-/-}$ livers, spleens, and mesenteric lymph nodes (MLN) showed greater levels of egg-induced inflammation based on their significantly larger sizes compared to the BL/6 control organs (Fig. 6). $STAT1^{-/-}$ livers appeared more grey and granular in appearance as a result of increased granulomatous lesions. Liver, spleen, and MLN weights were also measured. Organs from $STAT1^{-/-}$ mice were significantly greater in weight compared to those from BL/6 mice (Fig. 7).

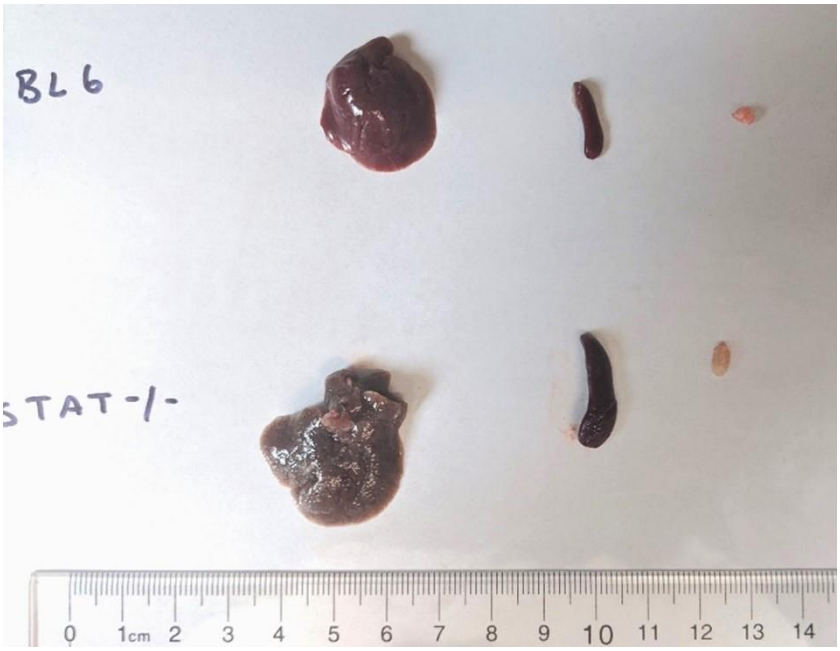

Fig. 6. Representative images of livers, spleens, and MLNs from BL/6 and STAT1$^{-/-}$ mice infected with *S. mansoni* and killed 7 weeks post infection (n=4).

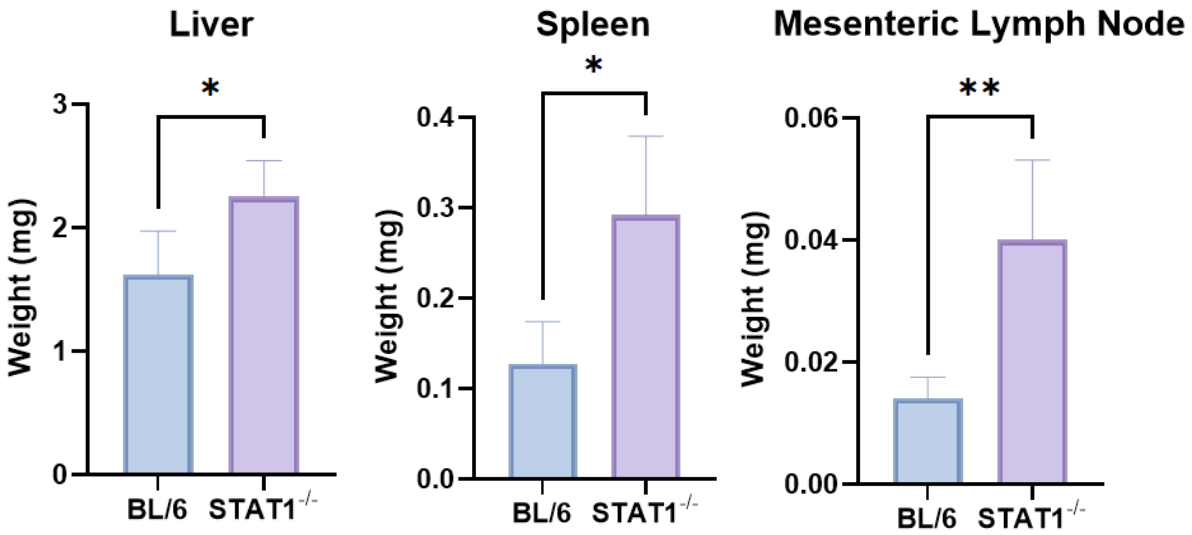

Fig. 7. Weights of livers, spleens, and MLNs from BL/6 and STAT1$^{-/-}$ mice infected with *S. mansoni* and killed 7 weeks post infection. Error bars represent the mean ± SD (n=4). *$P \leq 0.05$, **$P \leq 0.005$.

Discussion

Previous studies examining the role of STAT1 have demonstrated its function in providing innate immunity against viral, bacterial, and parasitic infections in murine models (24-26). To exert its function, STAT1 has been found to downregulate inflammation through inhibition of the NLRP3 inflammasome and IL-1β production (16). The mechanistic pathway of STAT1 in the immunopathology of schistosomiasis, however, has not been well studied. STAT1 may be an essential regulator in immune responses to shistosome infection, as studies have established that NLRP3 inflammasome is activated by schistosome eggs (22, 23, 27, 28). To investigate gaps in current literature, this study reveals possible mechanistic pathways of STAT1 in schistosomiasis *in vitro* and *in vivo*.

Our results suggest that the IFN-I induced JAK/STAT1 pathway may be significantly involved in promoting anti-inflammatory responses in schistosomiasis by regulating IL-10 production. BL/6 BMDCs treated with STAT1 inhibitor FP showed a significant reduction in IL-10 levels. This reduction in IL-10 concentration was more prominent as FP concentration increased, which suggests that production of IL-10, a highly protective Th2 cytokine, is dependent on STAT1 (29, 30). To further understand the mechanistic pathway of STAT1 following IL-10 modulation, IL-10R was blocked in BL/6 cells. As IL-10R activation was inhibited, concentrations of IL-1β significantly increased. This novel finding reveals that STAT1-induced production of IL-10 decreases production of pro-inflammatory IL-1β in the context of schistosomiasis.

In addition to upregulation of IL-10, STAT1 exerts its protective role by suppressing inflammasome activation. In the absence of STAT1, ASC adaptor protein, which helps comprise the inflammasome complex (19-21), was highly expressed in comparison to the BL/6 control

group. STAT1 deficiency was noted by the absence of STAT1 protein expression in STAT1$^{-/-}$ BMDCs. Based on these results, it can be understood that STAT1 suppresses inflammasome activation.

Based on these results, a mechanistic pathway is outlined. As described above, IFN-I induced JAK/STAT1 signaling activates transcription of ISGs and production of IL-10. IL-10 then binds to the IL-10R which inhibits inflammasome activation and the subsequent production of IL-1β (Fig. 8). To inhibit inflammasome activation, STAT3 may be involved, as STAT3-mediated inflammasome suppression downstream of IL-10R was observed in a previous study assesing the effects of IFN-I in bone marrow derived macrophages (16). Protein levels of STAT3 in response to schistosome eggs in BL/6 and STAT1$^{-/-}$ BMDCs must be measured to evaluate this hypothesis. This investigation demonstrates novel findings of the IFN-I/STAT1/STAT3 pathway specifically in schistosomiasis.

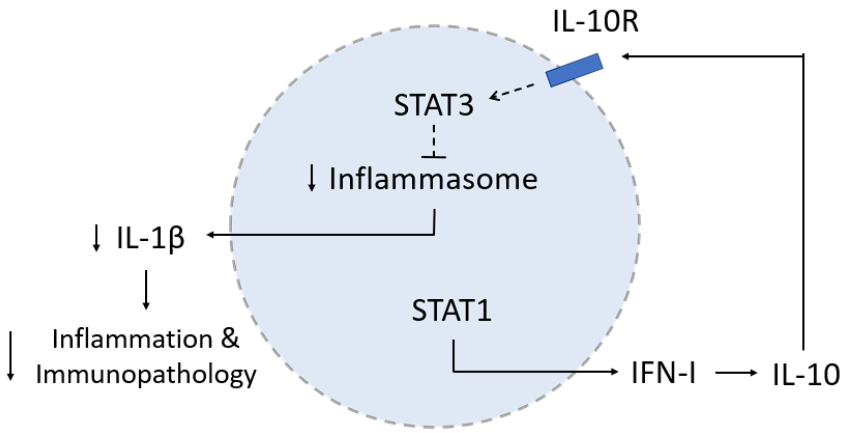

Fig. 8. STAT1 has a central role in suppression of inflammation by inducing IL-10 production and suppression of inflammasome and IL-1β production, leading to the suppression of inflammation and immunopathology in schistosomiasis.

The protective function of STAT1 is further supported by *in vivo* data of schistosome infected BL/6 and STAT1$^{-/-}$ mice. Compared to BL/6 livers, spleens, and MLNs, STAT1$^{-/-}$ organs were larger and heavier due to more severe infection. STAT1$^{-/-}$ livers appeared to have more granulamatous lesions, as indicated by their granular surfaces as opposed to the smooth and firm BL/6 livers. STAT1$^{-/-}$ organs were also significantly heavier in weight than BL/6 organs. The increased weight of STAT1$^{-/-}$ organs was likely caused by an increase in the infiltration of immune cells to the liver and development of large granulomas. To confirm this hypothesis, granuloma count and area must be measured. In line with *in vitro* findings, absence of STAT1 resulted in severe immunopathology based on the appearance and weight of organs. Further cytokine and chemokine profiling must be conducted to better understand the impacts of STAT1 deficiency in schistosomiasis on a molecular level.

This investigation examines current gaps in the understanding of pathways to protect against severe schistosome egg-induced immunopathology. Currently, praziquantel is the primary post-infection treatment for schistosomiasis. Through research on STAT1 and other regulators of inflammation, preventative measures targeting early stages of schistosome infection can be developed. Our findings suggest that IFN-I-mediated STAT1 activation decreases inflammation by upregulating IL-10 that suppresses inflammasome activation. STAT1 activation may be an effective therapeutic intervention to attenuate schistosomiasis immunopathology. As STAT1 becomes more comprehensively understood, a better understanding of inflammatory pathways will lead to further avenues of research in both schistosomiasis and other diseases in the future.

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ACADEMIC VITA

Sara Yi

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EDUCATION

Pennsylvania State University, Schreyer Honors College **Expected: May 2023**

- Bachelor of Science in Biology, Vertebrate Physiology Option
- Minor in Film Studies
- Dean's List for 6 semesters

Anatomy in Italy Embedded Study Abroad **Jan. 2022 - May 2022**

- Investigated the intersection of biology and history with a focus on the Italian Renaissance in SC 475N
- Studied basic Italian and culture in IT 175
- Traveled to Italy over spring break of 2022 to engage in cultural experiences and interact with Italian medical students

HONORS & AWARDS

Student Engagement Network Grant **Spring 2022**

- Awarded to applicants for engagement opportunities (Anatomy in Italy Study Abroad)

Tsui Honors Scholarship **Fall 2021 - Spring 2023**

- Awarded to Asian American Scholars for academics

RESEARCH EXPERIENCE

Dr. Kalantari Laboratory | *Research Assistant* **Apr. 2022 - Present**

- Investigate the inflammatory pathway of the infectious disease Schistosomiasis
- Independently perform molecular biology and immunological techniques, including cell culturing, ELISA, and Western Blot to identify the role of STAT1 transcription factor
- Collaborate with research team to perform *in vivo* infection and sacrifice of infected mice

Noll Microvascular Laboratory | *Research Assistant* **Jun. 2021 - Aug 2021**

- Participated in the Summer Translational Cardiovascular Science Institute Program
- Designed a protocol for measuring platelet aggregation following exercise trials
- Analyzed the effects of aspirin supplementation on regulation of human core body temperature and platelet aggregation

LEADERSHIP EXPERIENCE

Students Teaching Students **Aug. 2022 - Present**

***Director of Outreach,* Jan. 2023. - Present**

- Contact potential student instructors to increase engagement in the program
- Facilitate communication between student instructors, executive members, and faculty

***Co-Instructor,* Aug 2022. - Present**

- Created a semester-long curriculum for Bioethics in Media course
- Teach weekly lectures for undergraduate students in Spring 2022 and 2023
- Communicate with co-instructor, advisors, and students to develop course ideas and solve conflicts

Remote Area Medical **Oct. 2019 - Present**

***Volunteer Member,* Oct. 2019. - Present**

- Fundraise for and volunteer at non-profit mobile health clinics in medically underserved areas

***Promotions Committee Member,* Aug 2022. - Present**

- Advertise the first clinic hosted by the Penn State chapter of Remote Area Medical in Spring Mills, PA
- Reach out to community leaders and patients to increase public awareness of the Spring Mills, PA clinic

Eberly College of Science Student Council | *Secretary* **Aug. 2022 - Dec. 2022**

- Effectively maintained records of meeting minutes, meeting agenda, and event attendance of all members
- Created and maintained biweekly newsletters to members of the student council

University Ambulance Service | *Volunteer EMT-B* **Jul. 2021 - Dec. 2021**

- Respond to emergency medical calls on campus and transported patients to surrounding hospitals
- Worked standby at university events including football games, concerts, and social events

WORK EXPERIENCE

Mid-State Literacy Council | *Federal Work Study* **Jun. 2020 – May 2021**

- Synthesized teaching plans and tutored adults in areas including English, computer skills, US citizenship exam preparation, and health literacy
- Interviewed students and tutors to write corresponding blog posts