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Oncolytic Myxoma virus infects and damages the tegument of the human parasitic flatworm *Schistosoma mansoni*

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ABSTRACT

Schistosomiasis is a devastating disease caused by parasitic flatworms of the genus *Schistosoma*. Praziquantel (PZQ), the current treatment of choice, is ineffective against immature worms and cannot prevent reinfection. The continued reliance on a single drug for treatment increases the risk of the development of PZQ-resistant parasites. Reports of PZQ insusceptibility lends urgency to the need for new therapeutics. Here, we report that Myxoma virus (MYXV), an oncolytic pox virus which is non-pathogenic in all mammals except leporids, infects and replicates in *S. mansoni* schistosomula, juveniles, and adult male and female worms. MYXV infection results in the shredding of the tegument and reduced egg production *in vitro*, identifying MYXV as the first viral pathogen of schistosomes. MYXV is currently in preclinical studies to manage multiple human cancers, supporting its use in human therapeutics. Our findings raise the exciting possibility that MYXV virus represents a novel and safe class of potential anthelmintic therapeutics.

1. Introduction

Parasitic flatworms (Phylum Platyhelminthes) have long been a cause for concern because of their high prevalence in humans and the economically debilitating diseases they cause in livestock. Schistosomiasis is a significant, but neglected, human parasitic disease prevalent in impoverished and underdeveloped countries that is caused by flatworms (blood flukes) of the genus *Schistosoma*, most notably *S. mansoni*, *S. haematobium* and *S. japonicum*. Current estimates indicate that schistosomiasis affects over 229 million people in 78 countries worldwide (Gryseels et al., 2006; Steinmann et al., 2006; WHO, 2016). Schistosomes can survive inside human hosts for decades without being eliminated by the immune system (Basch, 1991). Immunopathological responses to parasite egg deposition, results in granuloma formation, fibrosis, and in some cases death. Currently, there is no available vaccine, and treatment and control rely on a single drug praziquantel (PZQ). Mono-therapeutic treatment of this disease with PZQ presents challenges such as inactivity against immature worms and inability to prevent reinfection (Xiao et al., 1985).

The broad and devastating impact of this disease necessitates the identification of novel anti-schistosomals and development of vaccines. Unfortunately, to date efforts to develop and identify new alternatives and synergic treatment strategies have been largely unsuccessful.

Viruses, natural or engineered, have been successfully employed as highly effective and selective therapeutics for cancer (oncolytic viruses) and antibiotic-resistant bacterial strains (phage therapy). Recent efforts have further established that parasite-associated microbes, including viruses, can impair parasite fitness and influence the pathogenesis of parasitic infection (Hahn et al., 2020). However, the therapeutic potential of viruses which infect and disable or kill schistosomes and other platyhelminth parasites, with no deleterious effects on the mammalian hosts, remains virtually unexplored.

Although no naturally occurring viral pathogens of schistosomes have been identified to date, viruses can infect parasitic flatworms. Indeed, virus-like particles have been described in other parasitic platyhelminths (Justine and Bonami, 1993; Mokhtar-Maamouri et al., 1976). The first microscopic observation of virus-like particles in a parasitic flatworm was reported by Jean-Lou Justine (Justine and Bonami, 1993). Further, Shi et al. (2016) studied the virome of a broad range of invertebrates and identified the complete genomes of *Bunyavirales* in the another schistosome *S. japonicum*. Finally, murine leukemia virus and the human HIV-1 isolate, NL4-3 pseudo-typed with vesicular

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stomatitis virus glycoprotein can integrate into the schistosome genome (Suttiprapa et al., 2016; Mann et al., 2014) indicating susceptibility to infection.

Myxoma virus (MYXV) is the type species of the *Leporipoxviruses*, a genus of *Chordopoxvirinae* double stranded DNA virus. MYXV infects leporids and squirrels, inducing cutaneous fibromas from which the virus is mechanically transmitted by arthropods. However, in the European rabbit (*Oryctolagus cuniculus*), MYXV causes the lethal disease myxomatosis.

MYXV exhibits a very restrictive rabbit-specific tropism. It is non-pathogenic and safe in all non-lagomorphs mammals tested, including mice, rats and human (McFadden, 2005; Jackson et al., 1966; Fenner, 2000; Stanford et al., 2007; Lun et al., 2010). Indeed, MYXV species-selectivity for rabbits is so narrow that it was used to control the disastrous invasive feral rabbit population in Australia in the 1950s without any other consequences (Fenner et al., 1994).

Despite the inability to induce pathology in normal non-rabbit mammals, MYXV does exhibit oncolytic activity against cancer cells from a variety of species, including a broad range of human cancers *in vitro* (Bartee et al., 2009) (Stanford and McFadden, 2007; Sypula et al., 2004) and *in vivo* (Bartee et al., 2016; Chan et al., 2013; Rahman and McFadden, 2020). Intriguingly, schistosomes and other helminth parasites exhibit properties in common with cancer cells (Doenhoff et al., 1990; Oliveira, 2014; Ashall, 1986), including the ability to hijack and manipulate the regulatory signaling mechanisms of their hosts. Like cancer cells, schistosomes evade host immune detection, utilize simple methods of energy uptake, are dependent on proteases to facilitate migration, survival, and growth, and exploit host machinery for their own growth and development. Indeed, anti-cancer drugs often exhibit antiparasitic activity, and vice-versa (Klinkert and Heussler, 2006). Considering these factors, we asked if an oncolytic virus such as MYXV could be a promising candidate to control *S. mansoni* infections. We focused on MYXV specifically, as its genome has been sequenced and it is straightforward to engineer, its host tropism is highly restricted, no specific cell receptors are required for infection, and there is a lack of acquired immunity in human populations (Kerr and McFadden, 2002).

Here we demonstrate the infective and pathogenic potential of MYXV against different developmental stages of *S. mansoni*. We show that MYXV can infect and replicate in *S. mansoni* schistosomula, PZQ-refractory juveniles, and adult male and female worms. MYXV infection and replication disrupts the integrity of the biologically active tegumental surface, leading to death of the worm. Furthermore, MYXV infection in female worms leads to a significant reduction in the number of eggs released *in vitro*. Thus, MYXV represents a novel and promising pathogen of schistosomes and a potential anti-schistosome therapeutic.

2. Materials and methods

2.1. Ethics statement

This study was carried out in strict accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the U. S. National Institutes of Health. Animal handling and experimental procedures were undertaken in compliance with the University of Pennsylvania's Institutional Animal Care and Use Committee (IACUC) guidelines. The IACUC approved these studies under protocol number 806776.

2.2. Reagents

Construction of vMyx-GFP-TdTomato (MYXV expressing GFP under the control of a poxvirus synthetic early/late promoter and Td-Tomato under the control of a late promoter p11) and preparation of purified MYXV stocks were described previously (Bartee et al., 2009), RPMI (Thermofisher, Philadelphia PA), FBS (Gem Cell, Geminin Bio products West Sacramento, CA), penicillin/streptomycin. (Corning Life Sciences, Tewksbury, MA) were purchased from different suppliers.

2.3. Isolation of schistosomes

Biomphalaria glabrata snails infected with *S. mansoni* (NMRI strain, NR-21962) and Swiss-Webster mice infected with *S. mansoni* (NMRI strain, NR-21963) were provided by the NIAID Schistosomiasis Resource Center of the Biomedical Research Institute under NIH-NIAID contract HHSN2722010000051. Adult and juvenile worms were perfused from mice (Lewis et al., 2008; Cody et al., 2016). *S. mansoni* adults were perfused at 6–7 weeks and juvenile worms at 3–4 weeks post infection from mice as described (Tucker et al., 2013) and were maintained in standard schistosome medium consisting of RPMI (Thermofisher, Philadelphia, PA), plus 10% FBS (Gem Cell, Gemini Bio Products, West Sacramento, CA) and 100 U/ml penicillin/100 mg/ml streptomycin, (Corning Life Sciences, Tewksbury, MA) 500 ng/ml amphotericin B (GIBCO) at 37 °C and 5% CO_2. Schistosomula were obtained by *in vitro* transformation of cercariae (Tucker et al., 2013) and maintained in the same culture condition as adults (Milligan and Jolly, 2011).

2.4. Visualization of GFP and tRFP through confocal spinning disk microscopy

Green (GFP) and tomato red (TdTomato) fluorescence signals were acquired on a Yokogawa CSU-X1 spinning disk confocal attachment (Yokogawa, Sugarland TX). Through a 20× objective (NA 0.70) with a 16-bit cooled EMCCD camera (C9100-13, Hamamatsu, Bridgewater, NJ) with appropriate excitation lasers (488 nm for GFP, 561 nm for TdTomato) and emission filters (505–552 nm for GFP, 583–650 nm for TdTomato).

3. Results and discussion

We exposed different life cycle stages of *S. mansoni* to vMyx-GFP-TdTomato, a wild type recombinant MYXV construct expressing green fluorescent protein (GFP) driven by a synthetic early/late (sE/L) poxvirus promoter and tomato red fluorescent protein (tRFP) driven by poxvirus p11 late promoter (Bartee et al., 2009). This recombinant MYXV allowed monitoring both early (GFP) and late (tRFP) viral gene expression, indicating MYXV infection and replication. Thus, MYXV infection in *S. mansoni is* detected by expression of GFP in the worm while MYXV replication is marked by expression of tRFP. As described below, we find that MYXV infects schistosomula, juveniles, and adult male and female worm stages of the parasite life cycle, establishing a remarkably long-lived persistent infection that caused disruption of the parasite tegumental surface and worm death.

3.1. vMyx-GFP-TdTomato infects and replicates in S. mansoni schistosomula

While schistosomula naturally develop from cercariae following their penetration into the host skin (Protasio et al., 2013; Gobert et al., 2007), they can also be generated from cercariae *in vitro*. To determine their susceptibility to MYXV, schistosomula (~10^3-10^4) transformed from cercariae *in vitro* (Brink et al., 1977) were cultured in schistosome medium and exposed to 1.6×10^7 FFU/ml of intact or UV inactivated vMyx-GFP-TdTomato (Bartee et al., 2016; Rinaldi et al., 2011) (Mann et al., 2010; Madlambayan et al., 2012). MYXV infection and replication in schistosomula were confirmed by presence of GFP and tRFP respectively (Fig. 1a). An evident fluorescence signal was detected using spinning disk confocal microscopy. As expected, vMyx-GFP-TdTomato inactivated by UV-irradiation was unable to infect schistosomula. Although autofluorescence was evident in schistosomula (Fig. 1(a) A and B), the fluorescence was distinct and readily distinguished in Fig. 1 (a) C and D.

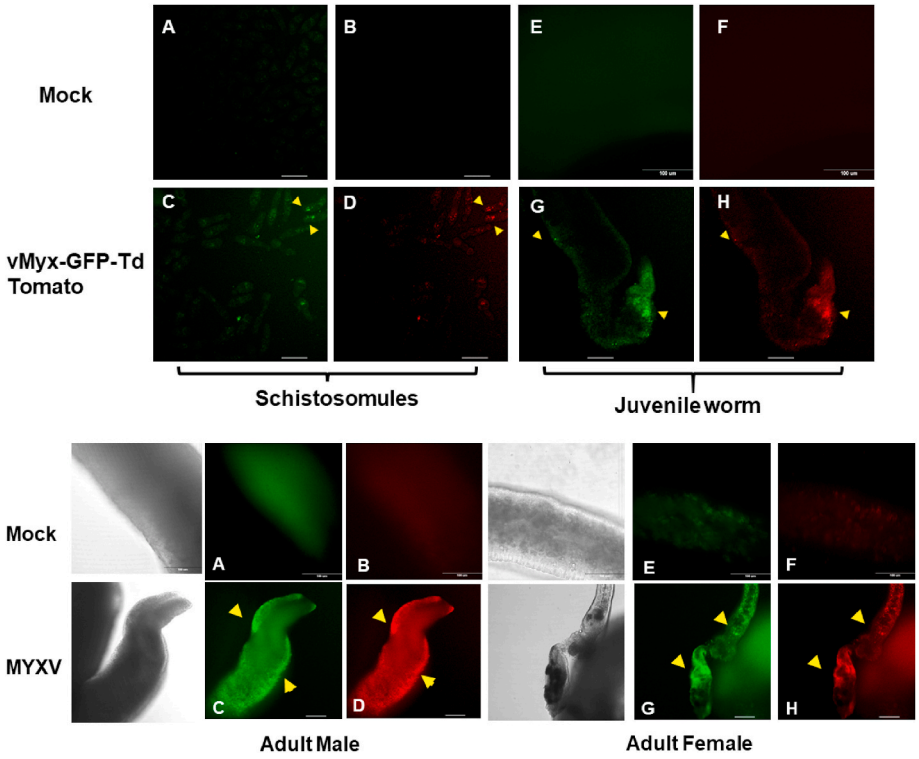

Fig. 1. (a)**MYXV infects and replicates in *S. mansoni* schistosomula and juvenile worms.** Expression of GFP and Tomato red tRFP in *S. mansoni* schistosomula and juvenile worms, indicating respectively infection and replication of MYXV in these organisms. Arrows show evidence for infection (green fluorescence) and replication (red fluorescence). Mock infection is with inactivated (UV-irradiated) vMyx-GFP-TdTomato. Scale bar = 100 μm. (b) MYXV infects and replicates in *S. mansoni* adult male and female worms. Adult worms were exposed to1.6 × 10^6 FFU/ml vMyx-GFP-TdTomato for 24 h and examined after 120 h. Arrows indicate virus infection (green fluorescence) and replication (red fluorescence). Scale bar = 100 μm.

3.2. *vMyx-GFP-TdTomato infects and replicates in juvenile S. mansoni*

Juvenile schistosomes (3–4 weeks post-infection) are refractory to PZQ, a major limitation of the drug, and a confounding factor in evaluating field studies of PZQ efficacy (Vale et al., 2017; Kasinathan et al., 2014; McManus et al., 2018). Importantly, we find that juvenile worms are readily infected by MYXV, and the virus replicates efficiently in these juveniles. 100% of juveniles were positive for GFP and tRFP after exposure to 1.6 × 10^6 FFU/ml of vMyx-GFP-TdTomato, indicating highly efficient MYXV infection of and replication in schistosomes at this stage (Fig. 1(a)). On the other hand, juvenile worms subjected to mock infections with UV-inactivated vMyx-GFP-TdTomato showed no infection. Although autofluorescence was evident in juvenile worms (Fig. 1 (a) E and F), the fluorescence was distinct and readily distinguished in Fig. 1(a) G and H. Significantly, following MYXV infection the tegument of juvenile worms exhibits signs of shredding and blebbing (Fig. 2).

3.3. *vMyx-GFP-TdTomato infects and replicates in adult S. mansoni*

We next asked if adult worms are susceptible to MYXV, and if different sexes exhibit differences in susceptibility. We exposed adult male and female schistosomes (6–7 weeks post infection) to intact or

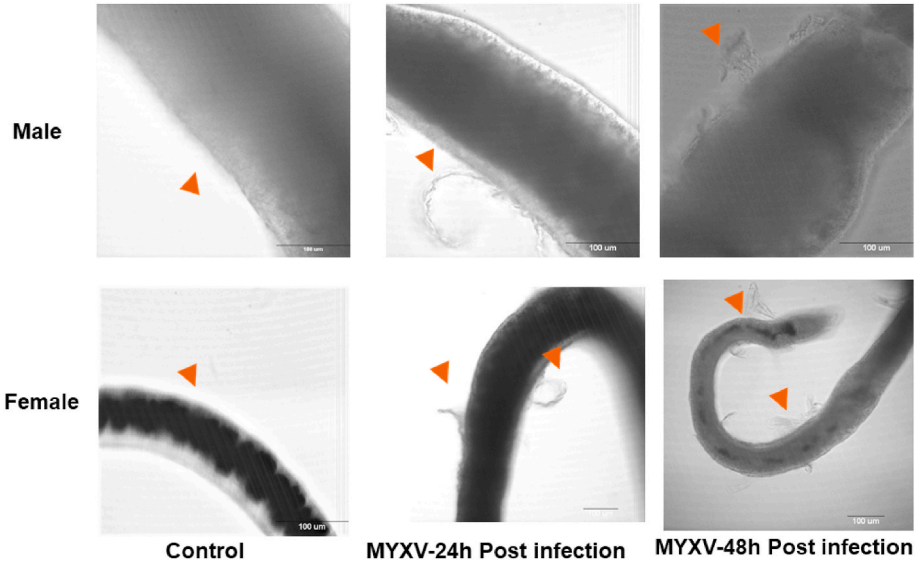

Fig:2. MYXV infection of adult *S. mansoni* produces extensive damage on the tegument of the parasite Shown are adult male and female *S. mansoni* exposed to 1.6 × 10^6 FFU/ml vMyx-GFP-TdTomato for 24 h and observed at 24 h and 48 h under spinning disk confocal microscopy. The parasite tegument is "shredded" as indicated by arrows.

UV-inactivated vMyx-GFP-TdTomato. (1.6×10^6 FFU/ml). We found all worms are susceptible to MYXV infection and permissive for MYXV replication, regardless of sex (Fig. 1(b)). Although, autofluorescence was evident in adult worms (Fig. 1(b) A, B, E and F), the fluorescence was distinct and readily distinguished (Fig. 1(b) C, D, G and H). Infection was again highly efficient, as 100% of tested worms showed evidence of infection and replication. In addition, infection and replication of MYXV continuously increased until the worm ultimately died. Infected worms of both sexes exhibited tegumental damage, which was evident by 24 h post exposure and the fluorescence intensity of both GFP and tRFP continued to increase over a period of 3 days post treatment.

3.4. Infection with vMyx-GFP-TdTomato results in extensive damage to the schistosome tegument

MYXV-infected juvenile and adult *S. mansoni* worms exhibit signs of shredding and blebbing on the worm tegument (Fig. 2). In adults, MYXV-infected worms of both sexes exhibited tegumental damage which became apparent by 24 h following exposure. Damage included extensive tegumental disruption, with blebbing, peeling and erosion of the tegument. Worms exposed to MYXV showed 68% death within 120 h, suggesting that MYXV may be acting as a "schistolytic agent".

3.5. Infection of female worms with vMyx-GFP-TdTomato affects release of eggs in vitro

When female *S. mansoni* are exposed to 1.6×10^6 FFU/ml vMyx-GFP-TdTomato, the number of eggs released *in vitro* is significantly lower at 48 h and 72 h (Fig. 3). This reduction of egg release suggests that MYXV might play an important role in regulating egg production or release, a significant factor in reducing the pathology in schistosomiasis.

Although virus-like particles have been identified in the outer layer and in the cytons of the tegument in monogenean flukes (Justine and Bonami, 1993; JTA Depierreux et al., 2020), this study provides the first demonstration of MYXV infection and replication in platyhelminths. Further, we show that MYXV infection significantly impacts the tegument of schistosomes and causes shredding of the worm tegument. This is critical as schistosomes must adapt to changing and harsh host and external environments which depends upon an intact tegument (Wendt and Collins, 2016) (Van Hellemond et al., 2006). The tegument of intra-mammalian stage schistosomes is a unique double membrane structure that is of crucial importance for modulating the host immune response and promoting parasite survival (Van Hellemond et al., 2006) (Shaw and Erasmus, 1988) (Faghiri et al., 2010; Liu et al., 2018). In schistosomes, 80–100% of nutrient absorption occurs via the tegument (Asch and Read, 1975).

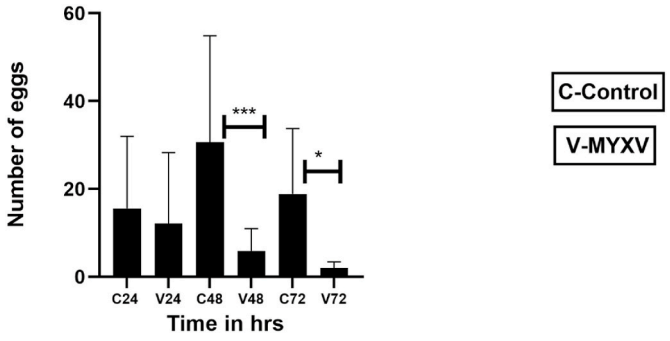

Fig:3. Infection of females with vMyx-GFP-TdTomato causes reduction in egg release in culture. Female *S. mansoni* exposed in culture to 1.6×10^6 FFU/ml vMyx-GFP-TdTomato, caused significant reduction in release of eggs at, 48 h and 72 h. Relative to controls. C (control) represents females exposed to UV inactivated vMyx-GFP-TdTomato (n = 18), and V represents females exposed to intact vMyx-GFP-TdTomato (n = 18.). *, ***, represents $p < 0.05$ and $p < 0.0001$ respectively.

MYXV-mediated disruption of the tegument could potentially compromise its ability to evade or suppress the host immune response, and the unmasking of tegument antigens may cause these worms to be more easily detected by the host immune system in *in vivo*. Our data show that MYXV may disrupt the worm life cycle and likely disease pathogenesis by suppressing egg production. Such a result could stem from the effects of the virus on the tegument or could be an independent consequence of infection.

Finally, our identification of MYXV as a novel pathogen of schistosomes provides new insights into the host range and evolution of this oncolytic MYXV. MYXV has been regarded as a rabbit-specific virus that is incapable of infecting non-cancerous cells from other species (including humans) (Wang et al., 2004). Indeed, despite its narrow host range in nature, MYXV has been shown to productively infect various classes of human cancer cells. It is currently being developed as a potential therapeutic for several cancers such as pancreatic cancer, glioblastoma, ovarian cancer, melanoma, and hematologic malignancies (Chan et al., 2013). Reports of treating murine allogenic bone marrow containing a mouse myeloma cell line with MYXV and transplanting into recipient mice dramatically ablated pre-seeded residual myeloma *in vivo* (Stewart et al., 2021). Notably, in all these studies, there has never been any evidence for alteration of MYXV host range to infect neighboring non-malignant cells.

Our results suggest a broader host range for this oncolytic MYXV virus and could potentially offer a novel point of attack against parasitic flatworm diseases such as schistosomiasis. Unlike rabbits, however, schistosomes are not a natural host for virus spread. Instead, we believe that undefined properties of schistosome cells have similarity to those of malignant mammalian cells, which can also act as hosts for MYXV. Beyond that speculation, the evolutionary genetics of host-pathogen interaction is unknown for schistosomes and MYXV. Furthermore, since no specific cell surface receptors for cell entry by poxviruses have been reliably reported (McFadden, 2005), it is not yet possible to search for receptor orthologs in schistosome genomes. Future efforts will be focused on determining how MYXV impacts schistosome biology, parasite vigor, and immune evasion within the host.

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Disclosure

G.M. is co-founder and stakeholder, and M.M.R. is consultant for OncoMyx Therapeutics, a biotech company engaged in the clinical development of armed MYXV for clinical trials.

CRediT authorship contribution statement

Masmudur M. Rahman: Conceptualization, Methodology, Resources, Writing – review & editing, Supervision, Funding acquisition. **Grant McFadden:** Conceptualization, Methodology, Validation, Resources, Writing – review & editing, Supervision, Funding acquisition. **Gordon Ruthel:** Software, Formal analysis, Writing – review & editing. **De'Broski.R. Herbert:** Writing – review & editing. **Bruce D. Freedman:** Software, Writing – review & editing. **Robert M. Greenberg:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Swarna Bais:** Conceptualization, Methodology, Validation, Formal

analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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