Immunomodulation by avian schistosomes: preliminary attempts to exploit species causing human cercarial dermatitis against autoimmune diseases and allergies

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BACKGROUND

A growing body of research has shown the beneficial role of helminths and their products in the course of autoimmune diseases and allergies. However, the avian schistosomes of the genus *Trichobilharzia* spp. have been overlooked despite their worldwide occurrence and frequent human infections in temperate areas. Indeed, they cause cercarial dermatitis (or swimmer's itch). Mammals eliminate schistosomula mostly in the skin, but some of them proceed with somatic migration in experimentally infected mice (Fig. 1). Our preliminary data suggest that *Trichobilharzia* species should be considered as novel and relevant-to-human models in the field of helminth-induced immunomodulation.

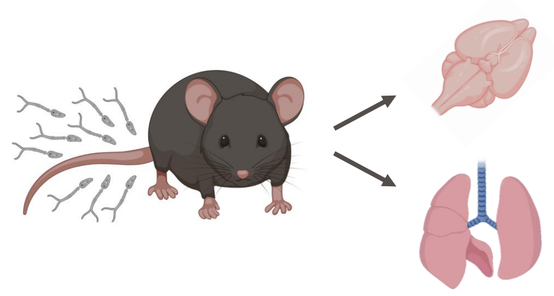

Fig. 1. Organs affected by somatic migration of *Trichobilharzia* spp. schistosomula in infected mice.

PRELIMINARY RESULTS AND HYPOTHESES

Trichobilharzia regenti, the invader of the central nervous system

The transcriptomic analysis of the spinal cord infected by *T. regenti* revealed a strong M2 phenotype represented by upregulated *Arg1, Chil3, Il4, Il10, Il13,* or *Tgf-b* (Fig. 2A). Arginase-1 was localised strictly in the close vicinity of the schistosomula (Fig. 2B). The shift towards anti-inflammatory M2 macrophages/microglia was confirmed by the absence of NO production [1]. Additionaly, *T. regenti* infection diminished the capacity of splenocytes to produce the pro-inflammatory cytokine IL-17 after treatment by concanavalin A [2].

Infection of mice with *T. regenti* induces local and systemic anti-inflammatory milieu. Could it mitigate symptoms of experimental autoimmune encephalomyelitis?

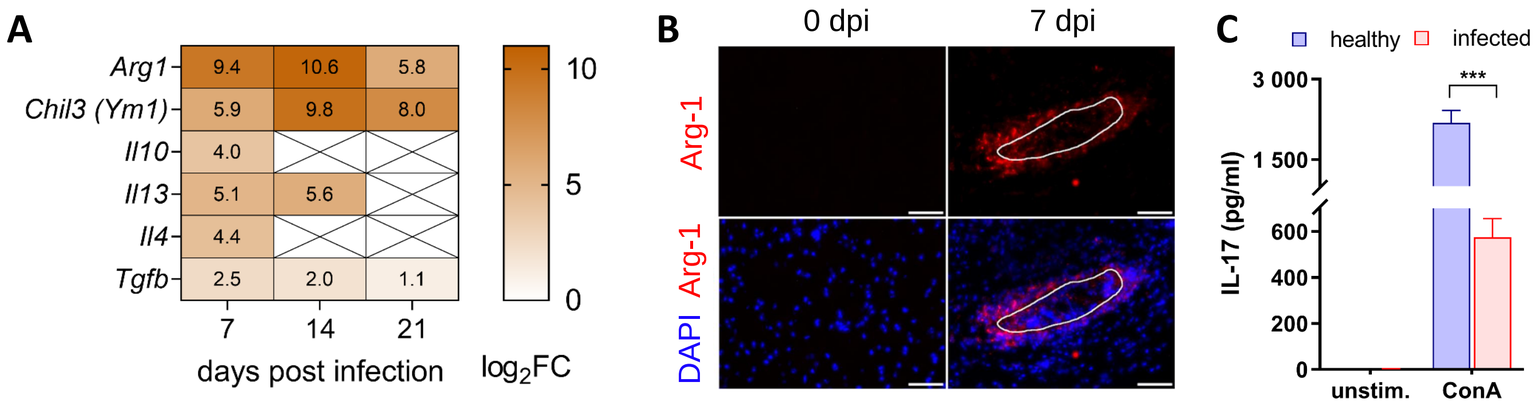

Fig. 2. (A) A heatmap showing expression of M2-associated genes in the *T. regenti*-infected spinal cord compared to naive mice. **(B)** Immunohistochemical detection of arginase-1 around *T. regenti* schistosomula in the spinal cord. Scale bar: 50 µm. **(C)** Production of IL-17 by splenocytes isolated from naive and *T. regenti*-infected mice after 72 hours *in vitro*. ConA = concanavalin A (1.25 µg/mL).

Trichobilharzia szidati, the invader of the lungs

Invasion of the lungs by *T. szidati* caused mild oedema and hyperaemia/heamorrhage (Fig. 3A). However, no significant leucocyte infiltration, tissue eosiniphilia or mucus overproduction were noticed. Accordingly, no accumulation of inflammatory cells was observed even in the schistosomula surroundings (Fig. 3B).

Invasion of the lungs by *T. szidati* causes mild tissue pathology, but not inflammation. Could *T. szidati*-derived molecules exhibit lung specific effects against asthma?

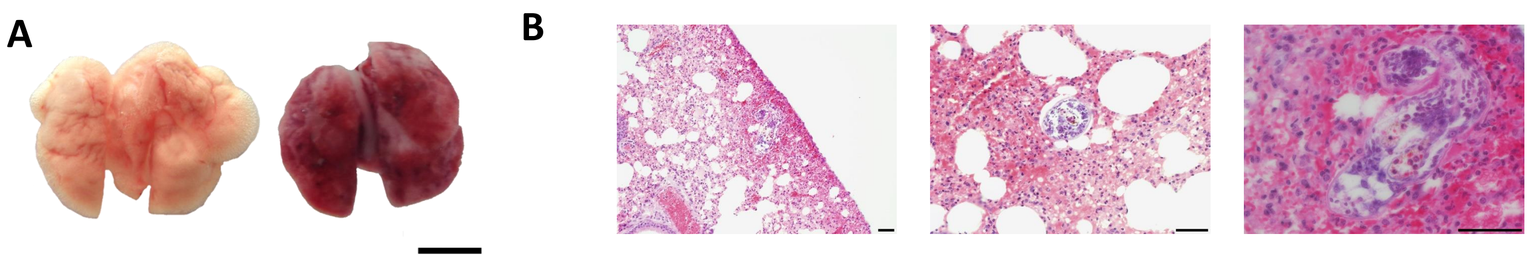

Fig. 3. (A) Lungs from naive (left) and *T. szidati*-infected (right) mice. Scale bar: 5 mm. **(B)** Histological sections of *T. szidati*-infected lungs showing no inflammation around schistosomula. Scale bar: 50 µm.

Cercarial dermatitis and eosinophilia in early phase of infection

Infected humans develop maculo-papular itching rash (cercarial dermatitis), exacerbated in repeated infection (Fig. 3A) [3]. In mice, *T. regenti* increased total IgE [4] and induced strong eosinophilia (Fig. 3B). Cysteine peptidases, the skin penetration enzymes, could be one of the potent antigens with allergenic potential [5].

Eosinophilia and elevation of total IgE accompany *Trichobilharzia* spp. infections in mammals. Could cercarial dermatitis have detrimental effects on asthma?

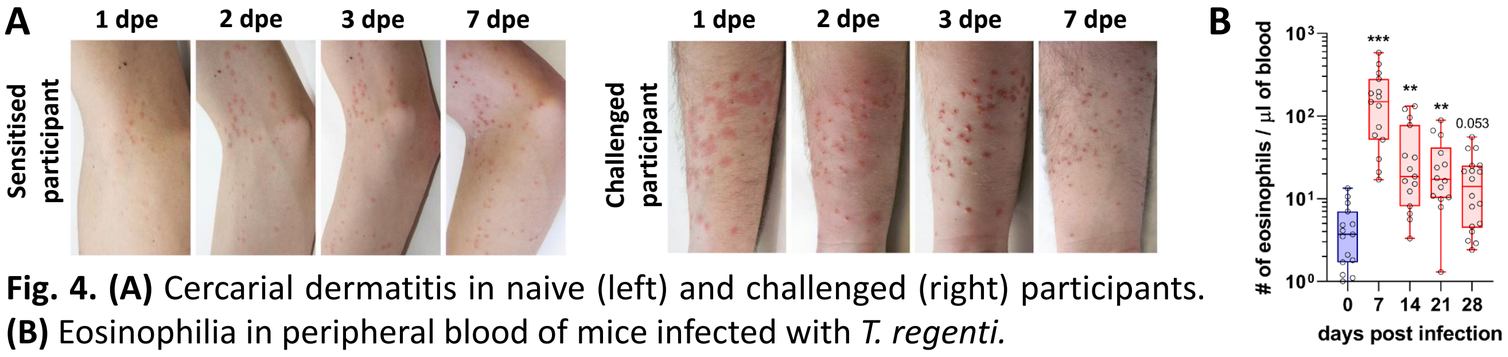

Fig. 4. (A) Cercarial dermatitis in naive (left) and challenged (right) participants. **(B)** Eosinophilia in peripheral blood of mice infected with *T. regenti.*

FUTURE PLANS AND GOALS

(1) To evaluate the anti-inflammatory effects of *T. regenti* infection/antigens on the course of experimental autoimmune encephalomyelitis (the model of multiple sclerosis) in mice, focusing on the role of M2 populations.

(2) To test the regulatory effects of *T. szidati* infection/antigens on the course of OVA model of asthma.

(3) To examine potential detrimental effects of cercarial dermatitis on the course of asthma (OVA model).

References: [1] Macháček T. *et al*. Nitric oxide debilitates the neuropathogenic schistosome *Trichobilharzia regenti* in mice, partly by inhibiting its vital peptidases. Parasit Vectors. 2020, 13(1):426. **[2]** Majer M. *et al*. The peripheral immune response of mice infected with a neuropathogenic schistosome. Parasite Immunol. 2020, 42(6):e12710. **[3]** Macháček T. *et al*. Cercarial dermatitis: a systematic follow-up study of human cases with implications for diagnostics. Parasitol Res. 2018, 117(12):3881-3895. **[4]** Lichtenbergová L. *et al*. Antibody responses induced by *Trichobilharzia regenti* antigens in murine and human hosts exhibiting cercarial dermatitis. Parasite Immunol. 2008, 30(11-12):585-595. **[5]** Kouřilová P. *et al*. Cercarial dermatitis caused by bird schistosomes comprises both immediate and late phase cutaneous hypersensitivity reactions. J Immunol 2004, 172(6):3766-3774.

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