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Review

# The helminth parasite proteome at the host–parasite interface – Informing diagnosis and control

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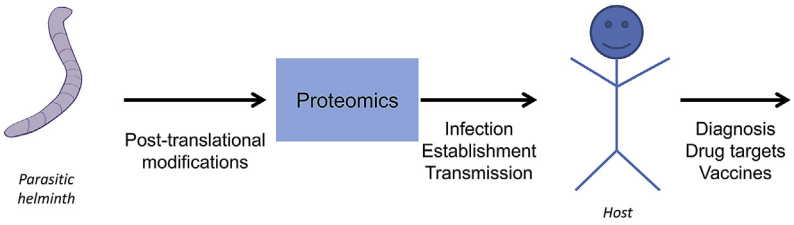
## HIGHLIGHTS

- Proteomics combined with other approaches gives insight in host–parasite interplay.
- Proteins at the host–parasite interface are potential vaccine or drug candidates.
- Proteomics is important in identifying diagnostic biomarkers or vaccine candidates.
- An information gap exists in the transmission phase of infection with helminths.

## GRAPHICAL ABSTRACT

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## ABSTRACT

Helminth parasites are a significant health burden for humans in the developing world and also cause substantial economic losses in livestock production across the world. The combined lack of vaccines for the major human and veterinary helminth parasites in addition to the development of drug resistance to anthelmintics in sheep and cattle mean that controlling helminth infection and pathology remains a challenge. However, recent high throughput technological advances mean that screening for potential drug and vaccine candidates is now easier than in previous decades. A better understanding of the host–parasite interactions occurring during infection and pathology and identifying pathways that can be therapeutically targeted for more effective and 'evolution proof' interventions is now required. This review highlights some of the advances that have been made in understanding the host–parasite interface in helminth infections using studies of the temporal expression of parasite proteins, i.e. the parasite proteome, and discuss areas for potential future research and translation.



*Abbreviations:* 2D, two-dimensional; DIA, differential in-gel analysis; DIGE, difference gel electrophoresis; EF, elongation factor; ESP, excretory-secretory proteins; GPCR, G protein-coupled receptor; GST, glutathione S-transferase; HSC, hepatic stellate cells; HSP, heat shock protein; JAK, Janus-activated kinase; PTMs, post-translational modifications; SEA, soluble egg antigen; SOD, superoxide dismutase Cu/Zn; STAT6, signal transducer and activator of transcription 6; STH, soil-transmitted helminth.

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## 1. Introduction

According to the World Health Organization, more than 1.5 billion people, or 24% of the world's population are infected with soil-transmitted helminths (STH) and more than 200 million people worldwide are infected with schistosomes (World Health Organization Media Centre, 2014a; World Health Organization Media Centre, 2014b). The infections are widely distributed in tropical and subtropical areas, with the greatest numbers occurring in sub-Saharan Africa, the Americas, China and East Asia where co-infection with schistosomes and STHs is common (World Health Organization Media Centre, 2014a; World Health Organization Media Centre, 2014b). STHs are caused by hookworms, *Ascaris lumbricoides* or *Trichuris trichiura* that live in the intestines, where they cause a loss of blood and proteins (World Health Organization Media Centre, 2014a). This can lead to serious problems such as anaemia and impaired cognitive and physical development in children (World Health Organization Media Centre, 2014a). In contrast, schistosomes settle in the veins of the host in the urinary tract or intestine, depending on the species and cause significant pathology such as inflammation in surrounding tissues. Inflammation in the urinary tract can cause scarring of the tract resulting in difficult and/or painful urination (dysuria). Chronic infections can lead to bladder cancer. And in children who are repeatedly infected, schistosomiasis can lead to severe anaemia, malnutrition and learning difficulties. Symptoms of intestinal schistosomiasis are abdominal pain, diarrhoea and blood in the faeces. Chronic infections of intestinal schistosomiasis can lead to liver fibrosis, accumulation of fluid in the peritoneal cavity and hypertension in the abdominal blood vessels (World Health Organization Media Centre, 2014b).

Human helminth infections are less prevalent in Europe, but nonetheless have an impact on human health. There have been recent reports of focal transmission of urogenital schistosomiasis in Corsica, France (Holtfreter et al., 2014; Schistosomiasis – France, 2014) following the case of a 12-year old German boy who presented with symptoms of haematuria. Upon clinical examination, the presentations found were a thickened bladder wall, granulomatous inflammation and viable *Schistosoma haematobium* eggs in the urine. In the father's urine non-viable *S. haematobium* eggs were found, but the mother and his siblings were negative. But after serological examination his siblings and father were found to be positive for schistosome antibodies. The family had only been to Corsica and the mother was the only family member who had not swam in the Cavu river (Holtfreter et al., 2014). In 2014 more cases of urogenital schistosomiasis were reported in Corsica in people who had swam in the Cavu river (Schistosomiasis – France, 2014). Zoonotic helminth infections occur in some developed countries including Italy, France, The Netherlands and Scandinavia (Robinson and Dalton, 2009). Recently, the zoonotic nematode *Angiostrongylus cantonensis* has become an emerging parasite, being recorded in China in 2006, with additional reports from South East Asia, Africa, India, Caribean, Australia and North America (Huang et al., 2013). Other cases of helminth infections such as schistosomiasis have been recorded in non-endemic countries in travellers who have visited endemic countries and present with clinical symptoms upon return (Karcher et al., 2008; Million et al., 2008).

Helminth infection is associated with considerable economic losses in the veterinary world. Studies from developing and developed countries show that the cost of deworming and the health impact of worms on the livestock results in major economic losses. Gastrointestinal nematodes (*Ostertagia ostertagi, Cooperia oncophora*) and the blood flukes, schistosomes (*Schistosoma bovis, Schistosoma matheii*) and liver flukes (*Fasciola hepatica*), which are related to human schistosomes are the major causes of loss of productivity in ruminants, with lungworms also important in some cases. Although the economic cost of helminth disease are difficult to quantify, particularly in developing countries where several of these infections go undiagnosed in subsistence farming systems, some data exist from commercial farming in Europe (Morgan et al., 2013). For example, in the United Kingdom the cost of parasitic nematodes of sheep is estimated to be in the order of € 99 million per year (Nieuwhof and Bishop, 2005) and the cost of liver fluke disease in Switzerland has been estimated at € 52 million per year in cattle (Schweizer et al., 2005). Within the EU the annual cost of anthelmintic drugs is estimated to be approximately € 400 million and this does not include the labour costs for administering the anti-helminths (Selzer and Selzer, 2009).

Given the medical and veterinary public health importance of helminth infections, there is urgent need for expanding significant research activity on developing more effective interventions, which can be applied on a large scale while minimizing the emergence of intervention resistant strains, i.e. evolution proof interventions. In order to develop these, it is necessary to have a comprehensive knowledge of the parasite's biology and the interaction between the parasite and the host. One approach that is being used to characterize the proteins expressed by the parasites (proteome) is proteomics. In the current review, we will focus on the helminth parasite proteome at the host–parasite interface. Proteomic approaches are used to get an insight into parasite biochemistry and physiology, in addition to investigating the immune response of the host to the parasite and the modulation of the immune response by the parasite. The information gained by proteomic approaches can be used for identification of vaccine candidates, diagnostic antigens and drug targets.

In the last 10 years the field of proteomics has expanded to allow high throughput analysis of the proteins expressed by the parasites (Boersema et al., 2015; Malik et al., 2010). More sensitive procedures and gel free methods have been developed to allow the use of small amounts of protein preparations. Difference gel electrophoresis (DIGE) allows high throughput comparative analysis of two or more protein samples, requires the use of 50% fewer gels and the imaging of gels is faster (Zhou et al., 2002). Using DIGE, two samples are bound to different cyanine dyes, the samples are mixed and run on the same conventional two-dimensional (2D) gels (Zhou et al., 2002; Unlu et al., 1997). Two images are visualized from the fluorescence of the dyes and an overlay is made, which allows a direct quantitative comparison of the samples (Zhou et al., 2002; Unlu et al., 1997). This minimizes variation overcoming reproducibility problems experienced with conventional 2D gel electrophoresis (Zhou et al., 2002; Unlu et al., 1997). In addition, quantification of proteins is possible by measuring the fluorescence intensity (Zhou et al., 2002). With differential in-gel analysis (DIA) it is possible to measure the fluorescence of the two dyes at the same time, which makes the comparison of every protein more accurate (HealthcareLimited, 2007). DIA automatically reduces the background, performs normalization, which means that it corrects for differences in the dyes, and it performs a quantitative analysis (HealthcareLimited, 2007). Advances in protein separating/extraction, e.g. intravascular biotinylation (de la Torre-Escudero et al., 2013) and enzymatic shaving (Wilson, 2012) approaches to extracting and enriching the tegument proteins of schistosomes, have allowed sub proteomes to be investigated in detail to give functional information on the different parasite compartments.

The availability of genome sequence data of key helminth parasites (for example *S. haematobium*, *Schistosoma mansoni* and *Schistosoma japonicum* genomes published in 2012 (Young et al., 2012), 2009 (Berriman et al., 2009) and 2009 (The Schistosoma japonicum, 2009) respectively, and genomes of the nematodes *Trichinella spiralis*, *Brugia malayi* and *Necator americanus* published