

Virulence factors of schistosomes

R. Alan Wilson*

Centre for Immunology & Infection, Department of Biology, University of York, Heslington, York YO10 5DD, UK

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Abstract

This review considers whether the products of schistosomes in the mammalian host can be considered as virulence factors. These include: the cercarial secretions used in infection, those of the migrating schistosomulum, surface-exposed proteins of adult worms in the portal system and their gut vomitus in the context of immune evasion, secretions of the egg facilitating its escape from gut tissues and micro-exon gene products. © 2012 Institut Pasteur. Published by Elsevier Masson SAS. All rights reserved.

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1. Introduction

The concept of virulence factors first came to prominence in the 1970s, applied almost exclusively to pathogenic bacteria. The term encompasses microbial products, generally macromolecules, which facilitate establishment and maintenance of an infection, contributing to its pathogenicity. They include cell surface components essential for infection and evasion of the immune response, as well as secreted toxins that are directly linked to virulence. The purpose of this article is to evaluate whether the ‘virulence factor’ concept is applicable to macroparasitic helminths, specifically the blood dwelling schistosomes of humans. It has only been used overtly with the helminth parasite *Schistosoma mansoni* in a single paper published in 2011 [1]. The task is not straightforward because, apart from scale, there is a major difference between microbes and helminths. Once a microbe has established it undergoes replication, usually rapid, until it is checked by the immune system or the host is overwhelmed. Conversely, helminths do not multiply in the mammalian host, each invasion being a singular event. Thus, the parasite burden accumulates and may be terminated acutely or persist chronically according to helminth species. The recent advances in proteomics, coupled

with sequencing of the genomes and transcriptomes of the major schistosome species have made it possible, for the first time, to define the major constituents of the schistosome–mammalian host interface, and the secretions of the larval and adult stages associated with the host tissues and bloodstream [2]. Can these constituents be termed or represented as virulence factors?

2. Schistosomes and the mammalian host

The schistosomes parasitic in humans are threadlike and about 1 cm long, the adults living as paired males and females in the hepatic portal vasculature (*S. mansoni* and *Schistosoma japonicum*) or the vessels of the bladder wall (*Schistosoma haematobium*). The eggs laid by the females in the tissues of the gut or bladder wall are the main pathogenic agents. In the intestinal infections they may dislodge and travel downstream to embolise in the liver; in the case of *S. haematobium* they have a direct effect on the tissues of the urogenital tract. The adult worms are remarkable for living, apparently unprotected, in the host bloodstream for decades so must clearly deploy sophisticated means of immune evasion. The infective agents are microscopic cercaria larvae, shed from fresh water snail intermediate hosts, which directly penetrate the skin to reach dermal blood vessels and begin migration to the portal system. The dramatic physiological transition from fresh water to the human body is accompanied by loss of the cercarial tail and

* Tel.: +44 1904 328600; fax: +44 1904 328505.

E-mail address: raw3@york.ac.uk.

metamorphosis into the schistosomulum. Coincident with this, the parasite replaces its surface membranes and becomes invulnerable to killing by antibody-dependent killing mechanisms (ADCC) [3]. The cercaria possesses five pairs of acetabular glands to assist skin penetration, and a minute head gland that facilitates parasite entry into a blood vessel. It is apparent that the schistosome eggs, deposited in host tissues, have their own system for secreting proteins required for exit from the host. Production of factors essential for onward transmission is not an aspect of virulence that has been applied to microbes but it seems apposite for schistosomes.

3. Host invasion

We are on safe ground in suggesting that the secretions used by cercariae to penetrate host skin are directly analogous to bacterial virulence factors. However, while the work on schistosomes has focused largely on proteases, with little information on adhesion molecules, the situation is reversed in bacteria with the emphasis placed on adhesion proteins. Additionally, bacteria secrete a whole range of exotoxins; schistosomes may produce the equivalent, but data on their function is lacking at present. The three pairs of cercarial post-acetabular glands were shown decades ago to produce mucins [4] that enabled the cercaria to make firm adhesions to the stratum corneum of the skin, preparatory to penetration. However, no attempt to date appears to have been made to characterise their molecular composition. Instead, researchers have focused on the soluble proteins packaged in vesicles in the two pairs of pre-acetabular glands.

The soluble serine proteases of *S. mansoni* cercariae have been well characterised over the last 20 years. They are generally referred to as elastases [5] but this has provoked controversy because the acetabular gland cells where they are synthesised have disappeared before the vast majority of schistosomula enter the dermis where elastin fibres are situated [6]. At least three of these serine proteases have been biochemically characterised from the acetabular gland secretions [7] and their transcripts identified in the precursor germ balls of the daughter sporocyst stage in the snail host [8]. (The latest version (v5) of the *S. mansoni* genome lists seven homologues but gives no information on the stage where each is expressed.) Since the majority of *S. mansoni* parasites do not enter the dermis for at least 48 h after penetration, the substrate of the characterised serine proteases is likely to be the proteins of the stratum corneum and the epidermis where the incoming cercarial body creates a penetration tunnel (<http://www.york.ac.uk/cii/media-library/cercariae/>). The cercarial tail and the thick protective glycocalyx are shed as the parasite enters the epidermis.

A proteomic analysis of the soluble secretions released by the schistosome cercariae during artificial transformation *in vitro* [9] identified a hitherto unsuspected major component as a metalloprotease. This is now classified in the *S. mansoni* genome database as an invadolysin (Smp_090100). Whilst tandem mass spectrometry pinpointed only a single protein, v5 of the *S. mansoni* genome lists seven homologues [10].

Furthermore, a microarray analysis of the infection process indicates that five of them were the most highly-upregulated metalloprotease genes in the germ ball stage, when cercarial proteins are being synthesised [8]. Given the role of mammalian metalloproteases in degradation of tissues matrices, a thorough investigation of these enzymes in the context of skin invasion is warranted. Why up to seven elastases and five metalloproteases, representing 34% and 13% respectively of the material released from the pre-acetabular glands, are needed for skin invasion is unclear, unless they have very fine distinctions in substrate specificity. It has been suggested that expressing multiple copies of genes for abundant secretory proteins might itself be part of an evasion strategy [8]. It is noteworthy that skin penetration by cercariae of *Trichobilharzia regenti* (a bird schistosome) and *S. japonicum* appears to be facilitated by a cysteine peptidase, cathepsin B2, so there may be some latitude in the enzymes involved in establishment among different schistosomes [11,12]. Finally, experiments *in vitro* suggest that the serine proteases secreted by cercariae can cleave host immunoglobulins such as IgE [13] and interfere with complement-mediated lysis [14]; such properties deployed *in vivo* could well enhance parasite establishment in the host.

It is possible that the acetabular gland secretions also contain the schistosome equivalents of bacterial toxins. Curwen et al. [9], identified three proteins with SCP (sperm coat protein) domains that have since been classified as part of a 28-member family of VAL (venom allergen like) proteins, approximately two thirds of which are secreted by different stages. The three constituents of the cercarial secretions are SmVAL4, SmVAL10 and SmVAL18, collectively representing 3% of released protein. Similar proteins have been identified in other helminth secretions, e.g. *Heligmosomoides polygyrus* [15]. The problem is that no clear function has yet emerged for any VAL in any helminth species. The same is true of another enigmatic constituent of the cercarial secretions, Sm16 (SmSLP/SPO-1), originally ascribed anti-inflammatory properties [16], and more recently a caspase-dependent apoptotic function [17]. Its presence in extruded material may simply reflect the fact that acetabular glands release their contents by holocrine secretion. Indeed, the localisation of Sm16 transcripts to numerous internal tissues of the cercaria by WISH [18], plus the absence of a signal peptide suggests that it has an internal function in the newly penetrated parasite. Potentially, if it is pro-apoptotic, this could be in the tissue remodelling that accompanies transformation to the schistosomulum.

The final constituents of cercarial secretions that merit attention as virulence factors are the glycans. Both the proteins in soluble cercarial secretions and those in the soluble egg secretions are heavily glycosylated [19,20]. A plethora of both N- and O-linked glycan structures have been identified by mass spectrometry and many proved to be shared between the two transmission stages, suggesting a commonality of function by the stages entering and leaving the host [19,20]. Moreover, these glycans are highly immunogenic [21,22], but there is no evidence that the responses invoked are protective. This has

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