Journal of
Proteomics & Bioinformatics

Mandage et al. J Proteomics Bioinform 2011, 4:3
DOI: 10.4172/jpb.1000168

Research Article Open Access

A Genome Based Discovery of *S. mansoni* Secretome to Identify Therapeutic Targets

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Abstract

The motivation behind the large scale genome analysis of *S. mansoni* was to explore the possibility of discovering the secretome that is frequently secreted at the interface of parasite and host is supposed to play a crucial role in parasitism by suppressing the immune response, to aid the proliferation of infectivity. Here, we present an efficient pipeline of bioinformatics methodology to identify candidate parasitism proteins within *S. mansoni* secretome of immune responses in the infected host. The 3,700 proteins deduced from the *S. mansoni* genome were analysed for the presence or absence of secretory signal peptides. We identified 32 proteins carrying an N-terminal secreted signal peptide but deficient in extra membrane-anchoring moieties. Notably we identified proteins involved in ATP synthesis, redox balance, protein folding, gluconeogenesis, development and signaling, scavenging and nucleotide metabolic pathways, immune response modulation. Most of these proteins define their potential for immunological diagnosis and vaccine design. A systematic attempt has been made here to develop a general method for predicting secretory proteins of a parasite with high efficiency and accuracy.

Keywords: *S. mansoni*; Schistosomiasis; Secretome; Secretory signal; Therapeutic targets

Introduction

Schistosomiasis remains a neglected tropical parasitic disease with more than two hundred million human infections, and approximately 200 million people in 74 countries are infected with schistosomes; 120 million are symptomatic, and 20 million suffer severe illness [1-3]. It is the most important human helminth infection in terms of morbidity and mortality; a recent meta-analysis assigned 2 to 15% disability weight to the disease [4]. Reassessment of disability due to schistosomiasis along with recent estimates of the global incidence of schistosome infection indicates that the actual public health burden due to schistosomiasis has been greatly underestimated [4]. The pathology of infection with the helminth *Schistosoma mansoni* is surprisingly varied, ranging from a relatively mild intestinal presentation to severe hepato-splenic disease, and is dependent upon not only parasitic antigens, but also the host's genetic milieu and state of concomitant schistosome infection or concurrent infection with other pathogens [5]. There is also emerging evidence that schistosome infections may impact the etiology and transmission of human immunodeficiency virus/AIDS (HIV/AIDS) [6,7], tuberculosis [8,9], and malaria [10,11], and vice versa.

Eukaryotic cells have the unique feature of transporting proteins to the targeted site, either intra or extracellular, from their site of synthesis is mostly cytoplasm. This is performed by cellular sorting and translocation machinery that identifies the proteins to be transported through a transient "zip code" (signal peptide) present as an attachment to the N terminal of protein, which is synthesized as a pre-protein. These signal peptides are short segments of amino acids that are often degraded by signal peptidases soon after the protein is delivered at the targeted site. These transported proteins often called secreted proteins are believed to have a central part in the disease and hence their identification and depiction may help us to know the specific pattern of the disease. The major focus of research on the secreted proteins is intended to resolve the antigens that induce immune responses of diagnostic value. [12-16]. These secreted proteins might have structural harmony in their signal peptides which could be helpful in identification and validation of individual proteins. A protein may possibly show therapeutic potential in the infection without its actual role in disease development or maintaining the diseased condition. However, factors like presence and quantity of a protein in normal and diseased tissue, subcellular location, its activity and its biological role have an immense influence on the protein's potential as an effective and safe therapeutic target. Hence it is crucial to screen diverse proteins to recognise the most promising candidate for drug designing. Bioinformatics methodology could be used to predict the protein's characteristics that would enable further laboratory practices to search for the protein that could be the best possible target. In order to ease the discovery of new therapeutic and diagnostic opportunities, we present here large scale genome based discovery of *S. mansoni* secretome.

Materials and Methods

Prediction of secreted proteins using SignalP

The amino acid sequences of 3,700 proteins were retrieved from the Uniprot database in FASTA format and further manually curated to exclude sequences that are previously annotated as secreted, hypothetical, putative fragments and predicted. Segments containing the NH2-terminal 70 amino acid residues of each polypeptide were analyzed for secretory signal peptides using computer programs, SignalP (http://www.cbs.dtu.dk/ services/SignalP) that predicts the presence and location of signal peptide cleavage sites in amino acid sequences from different organisms (Figure 1). The method incorporates a prediction of cleavage sites and a signal peptide/non-signal peptide prediction based on a combination of several artificial neural networks and hidden Markov models. Cutoff values for the peptide predictions

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Received December 31, 2010; **Accepted** February 21, 2011; **Published** February 23, 2011

Citation: Mandage RH, Jadhavrao PK, Wadnerkar AS, Varsale AR, Kurwade KK (2011) A Genome Based Discovery of *S. mansoni* Secretome to Identify Therapeutic Targets. J Proteomics Bioinform 4: 062-067. doi:10.4172/jpb.1000168

were selected on the basis of scores assigned to sixteen experimentally verified secreted proteins of *S. mansoni* that contain a signal peptide For these proteins, SignalP scores ranged from 0.122 0.551 We chose score cutoffs of 0.5 for SignalP. Proteins that cross the membrane via the general export pathway are released to the external environment after cleavage of the signal peptide only if they lack membrane-anchoring sequences. To eliminate from our study those proteins that contain membrane-spanning segments, proteins were analyzed with the program TMHMM ((http://www.cbs.dtu.dk/services/TMHMM-2.0/). The presence of an NH2-terminal transmembrane segment (i.e., the putative signal peptide) was confirmed TMpred (Figure 2).

Prediction of lipoprotein signal peptides using LipoP 1.0

The remaining proteins were analyzed for membrane lipoprotein (LPP) lipid attachment sites with the program LipoP 1.0 [17] that was able to distinguish between lipoproteins (SPaseII-cleaved proteins), SPaseI-cleaved proteins, cytoplasmic proteins and transmembrane proteins by means of HMM algorithm. Remaining (32 proteins) proteins were predicted as secreted on basis of presence of single transmebrane domain representing the signal peptide without membrane-spanning segments, and absent of LPP motifs (Table 1).

Results and Discussion

Length distribution of 32 predicted signal peptides had a length varying from 16 to 33 residues, with an average of 23 residues.

The frequency of 20 amino acids residues of signal peptides

A frequency analysis of the 20 amino acid was carried out to investigate sequential aspects of the amino acids that are preferred in targeting of secreted protein to specific locations. It has observed that large and nonpolar amino acid leucine (L) and valine (V) were more frequently observed as compare to other amino acids (Figure 3). The fact that the residues whose frequency is more than 5% are mostly aliphatic amino acids suggests that such residues are involved in the targeting of secreted protein to specific membrane locations in *S. mansoni*.

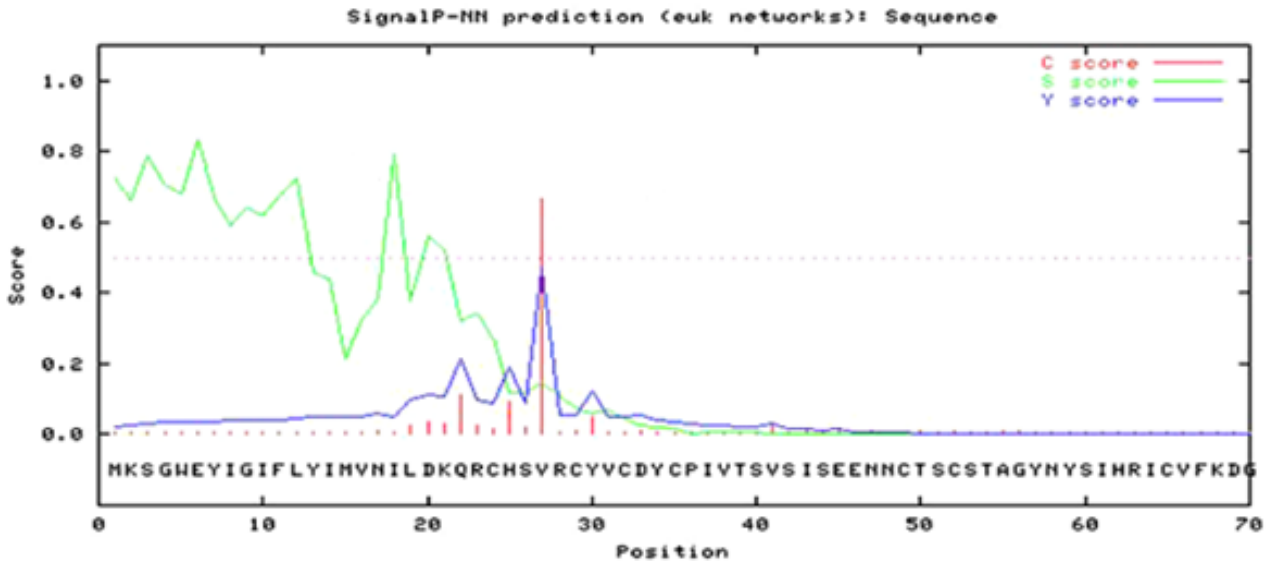

Figure 1: Signal peptide prediction using the SignalP 3.0 server. Probability of residue as the signal peptide is indicated by green line whereas blue line indicates the cleavage site.

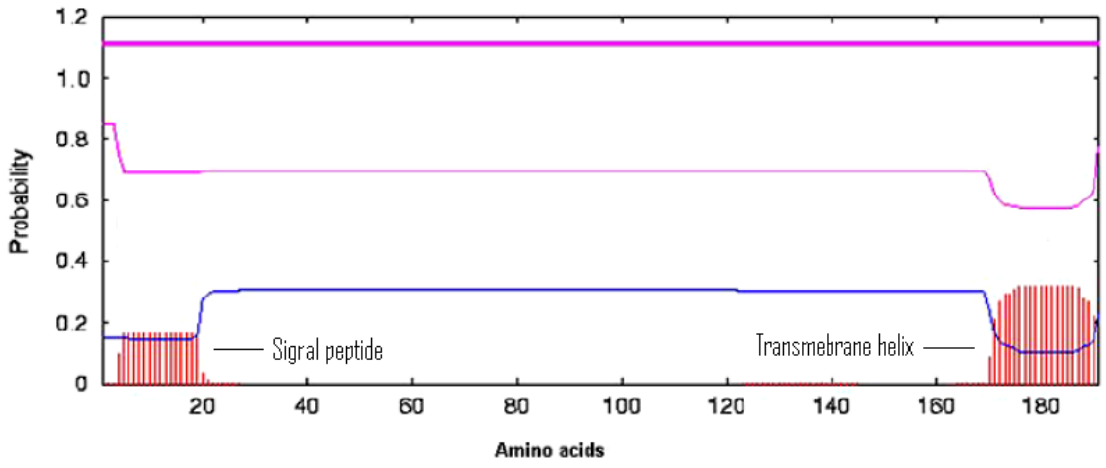

Figure 2: Putative signal peptide and transmebrane helix prediction using TMHMM.

Functions of proteins identifies as secreted (Table 2)

Several glycolytic enzymes including enolase were identified in genome based secretome discovery. Enolase, a non-classical secreted protein plays a major role in glycolysis and gluconeogenesis however it also shows diverse functions such as plasminogen receptor on the surface of hematopoetic, endothelial and epithelial cells, as a heat shock protein, a hypoxic stress protein and also as a cytoskeletal and chromatin binding protein. It is also of concern in autoimmune diseases such as lupus erythematosus, ulcerative colitis, Crohn's disease, autoimmune hepatitis, apoptosis and endometriosis [18]. The fact that enolase acts as a possible plasminogen receptor and makes this protein a promising target for therapy [19]. It has been previously studied for its possible use as a drug discovery target against Trypanosoma brucei, a protozoan organism responsible for sleeping sickness in humans [20]. Some proteins such as thioredoxin, peroxiredoxins were also identified in the secretome that are concerned with energy production, cell signaling, and maintenance of redox potential. Peroxiredoxins are important parasite antioxidant proteins involved in the detoxification of hydrogen peroxide and other hydroperoxides and are biochemically distinct from human peroxiredoxins [21,22]. They also play a crucial role in redox balance mechanisms, redox signaling processes and affect protein phosphorylation, transcriptional regulation, and apoptosis. Production of an antioxidant "firewall," which would neutralize the oxidative assault generated by host immune defenses, is one proposed

Acc No	Predicted signal peptide sequence	SignalP Score					TM domain
		C	S	Y	s	D	
C4PZD0	MKKRVRISSIVIIIHT	Y	Y	Y	N	Y	0
C4Q7G8	LKNARTTLIAAAIAGTLVTTSPAGIANA	N	Y	Y	Y	Y	0
C4Q8H9	MLSPLSPSLMPQQTLAMTWTYLFE	Y	N	Y	Y	Y	1
C4QDJ7	MFSTVMVVLVLSYEVVST	Y	Y	Y	Y	Y	0
C4QF57	MKLTTMIKTAAAIATFAAPVALA	Y	Y	N	Y	Y	0
C4QFH0	VQGAVAGLVFLAVLVIFAIIVVAKSVALI	Y	Y	N	Y	N	0
C4QJ92	MITNLRRRTAMAAAGLGFSMSSFF	Y	Y	Y	Y	Y	0
C4QQR1	MRYLIATAVLVAVVLVGWPAAGAPQQTLA	Y	Y	Y	Y	Y	0
O96413	MLMYAKFLILARIMSKHMI	Y	N	Y	Y	Y	0
O97161	MPAMTARSVVLSVLLGAHPAIQVPIFI	Y	Y	N	Y	Y	1
P09792	MSRLSSILRAGAAGVATAAATTAATLGLAALG	Y	Y	Y	N	Y	0
P15964	MSSFFISAFHRNLASVKGRIFVYLSLVCSLLFI	N	Y	N	Y	N	0
P35661	MFSTYGIASTLLGVLSVAAVVLGAMIWSAHR	Y	Y	Y	Y	Y	1
P37227	MSTIFDIRSLRLPKLSGIVIMM	Y	Y	Y	Y	Y	0
P38658	MGMIGVPFIQVPIFIGIIMDRLGG	Y	N	Y	Y	Y	2
Q06814	VIIPDINLLLYAVITGFPQHRRAHA	Y	Y	N	Y	N	0
Q07167	MKHMILENMASLILQC	Y	Y	Y	N	Y	0
Q1WMM9	MSSFFISAFHLWNLALVLGGP	Y	Y	Y	Y	Y	1
Q26540	MIQIATALSAGVGAVAMSLTVGA	Y	Y	Y	Y	Y	0
Q26582	MIMKTVVSIVIMMMTWTYLFE	Y	Y	N	N	Y	1
Q26595	LTDPRHVPSAVALSLGSLAVALGSVG	Y	Y	Y	Y	Y	0
Q27877	MPFWLWNLALVLNGCS	Y	Y	Y	Y	Y	1
Q2KMJ3	MGVIARVVGVAACGLSLAVL	Y	Y	Y	Y	Y	0
Q2Y2H5	MLMPEMDRRRMMMMAGFGALA	Y	Y	Y	Y	N	0
Q7Z1I4	MTVSPSKMKKVPWTYLFEDIFDT	Y	Y	N	Y	Y	0
Q869D4	MKGTKLAVVVGMTVMLNGF	Y	Y	Y	Y	N	1
Q86QQ6	MSRLSSILRAGAAFLVLGIAAATFPQSAA	Y	Y	Y	Y	Y	0
Q8T9N5	MVLRSRKSTLGVVVCLALVLGGPLNGC	N	Y	Y	Y	Y	2
Q94747	MIIMDRLGGRHLLLLLLL	Y	Y	Y	Y	Y	1
Q962Y6	MLSPLSPRIIAAFTTAVGAAAIGL	N	Y	Y	Y	N	0
Q9BMI9	SRLSSILRAGAAFLVL	Y	Y	Y	N	Y	1
Q9XYR4	MPFWLWNILVFGGSLILFLFKSLNLT	N	Y	Y	Y	Y	0
C4QEC4	GTKLAGVVVCLRRMMVLRSRKS	N	Y	N	Y	Y	1

Table 1: Predicted signal peptide sequence of *S.mansoni by* SignalP. [The SignalP algorithm uses neural networks and HMM. Output scores are presented as being above (Y) or below (N) a defined cutoff where C ="cleavage site", S ="signal peptide" score, Y = the combined C and S scores, s is the mean S score between the N-terminus and the cleavage site and D is the average of the s and Y scores].

survival mechanism of this parasite [23] therefore it may be possible to design parasite-specific peroxiredoxins inhibitors to be used in the future to control schistosomiasis. Genomic analysis reveals two abundant proteins, alpha-1 and a ribonuclease omega-1. Alpha-1 and omega-1 encourage Th2 differentiation in a cascade. IL-4 secretion by schistosome eggs is induced by Alpha-1 and hence renamed as IL-4-inducing principle of schistosome eggs (IPSE), also initiates the degranulation of human basophils that lead to development of Th2 environment [24]. It cross-links surface IgE on basophils, in an antigen independent manner. It has also been found to function as chemokine binding protein which can prevent chemokine-mediated recruitment of inflammatory cells, by sequestering ligands [25,26]. Helminth parasites are the most potent natural inducers of T helper 2 (Th2) cell–polarized responses. Infection with *S. mansoni* elicits strong Th2 responses in humans and in experimental animal models. The development of this Th2 polarization coincides with the onset of egg production by adult worms [27]. During a human infection, the *S. mansoni* worm lays its eggs, and these eggs secrete a factor, termed omega-1, which is a known RNaseT2 family member provokes a host immune response that aids in the egg's excretion [28]. Recently, two groups showed that omega-1 is the major component in priming dendritic cells for Th2 polarization of CD4+ T cells during infection [29,30]. NPC1, a ubiquitous essential protein was also detected in the secretome that is concerned in cholesterol trafficking out of lysosomal/endosomal compartments [31]. This protein was identified as a potential candidate by a search of expressed sequence tag databases by presence of a sterol-sensing domain (SSD), a plasma membrane secretion signal. These results may lead to a better understanding of the molecular mechanism of cholesterol transport and the design of even more potent cholesterol-absorption inhibitors [32]. Purine-nucleoside phosphorylase (PNP), a enzyme which requires inorganic phosphate during cleavage and α-ribose-1-phosphate for synthesis of adenosine from adenine in nucleotide metabolic pathway, is also an attractive target for the discovery of potential antischistosomal agents as crystallographic studies provided important structural insights for rational inhibitor design, revealing consistent structural differences in the binding mode of the inhibitors in the active sites of the S. mansoni PNP and human PNP structures [33]. The molecular information gathered in this work should be useful for future medicinal chemistry efforts in the design of new inhibitors of purine-nucleoside phosphorylase. Since egg secreted proteins profoundly influence the Th1/Th2-cytokine environment and serve as the focus of the host immunoinflammatory response, the discovery of such proteins secreted by *S. mansoni* is of original interest. Now that a comprehensive list of secretome is accessible, future investigate may reveal their explicit role in the immunobiology and pathogenesis of schistosomiasis. However plentiful proteins in the secretome still require experimental charactorisation [34].

Conclusion

Genome based discovery of S. mansoni novel secretome enables the study of their subcellular location and to define their potential for immunological diagnosis and vaccine design. Developing anti-schistosome vaccine is quite possible with the advances in molecular and computational methods. These tools provide rapid and efficient gene identification, in silico characterization, exploring therapeutic candidates against this complicated parasite. Interactions between

Acc No	Protein Name	Biological Activity
C4PZD0	Glycogenin-related	Transferase activity, transferring glycosyl groups
C4Q7G8	ATP synthase beta subunit	Hydrogen ion transporting, ATP synthase activity
C4Q8H9	fructose 1,6-bisphosphate aldolase	Glycolysis, fructose-bisphosphate aldolase activity
C4QDJ7	Transketolase	Transferase, transketolase activity
C4QF57	Heat shock protein 70	Stress response, binding
C4QFH0	Retinaldehyde binding related	Not available
C4Q7T0	Niemann-pick C1 (NPC1)	Hedgehog receptor activity
C4QQR1	Major egg antigen (P40)	Egg-induced immunopathology
O96413	Polyubiquitin	ATP-dependent degradation of cellular proteins
P09792	Glutathione S-transferase	Central role in the parasite detoxification system
P15964	Sm26/1 antigen	Role in increasing the solubility of haematin in the parasite gut
P35661	Sm26/2 antigen	Central role in the parasite detoxification system
P37227	Malate dehydrogenase	TCA cycle, malate metabolic process
P38658	ERP60	Cell redox homeostasis, protein disulfide isomerase activity
Q06814	Calreticulin	Molecular calcium-binding chaperone promoting folding
Q07167	Egg antigen SME16	Calcium ion binding
Q1WMM9	Venom allergen-like protein 3	Function unclear
Q26540	14-3-3 protein homolog 1	Capable of changing the conformation of its bound ligand
Q26582	Heat shock protein 86	Stress response
Q26595	Alpha tubulin	Microtubule-based movement, GTPase activity
Q27877	Enolase	Glycolysis, phosphopyruvate hydratase activity
Q2KMJ3	Secretory glycoprotein k5	Mmmunopathology of schistosomiasis
Q2Y2H5	ribonuclease omega-1	Ribonuclease T2 activity
Q7Z1I4	Beta-tubulin	Microtubule-based movement, GTP binding
Q869D4	IL-4-inducing protein	Skewing the immune response toward Th2
Q86QQ6	Peptidylglycine alpha hydroxylating mono-oxygenase	Catechloamine metabolic process, copper ion binding
Q8T9N5	Thioredoxin	Cell redox homeostasis, electron carrier activity
Q94747	Elongation factor 1-alpha	Protein biosynthesis, translation elongation factor activity
Q962Y6	Thioredoxin glutathione reductase	Cell redox homeostasiss, electron carrier activity
Q9BMI9	Purine-nucleoside phosphorylase	Nucleoside metabolic process
Q9XYR4	Phosphoenolpyruvate carboxykinase	Gluconeogenesis, GTP binding
C4QEC4	Peroxiredoxins	Cell redox homeostasis, oxidoreductase activity

Table: 2 List of *S. mansoni* secreted proteins with probable biological activity.

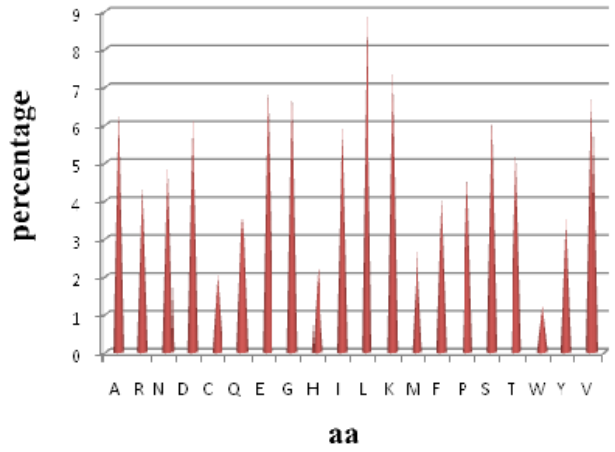

Figure 3: Distribution of 20 amino acids in signal peptide seq sequences..

the parasite and host immune system could be demonstrated using immunomodulators, and this can be studied using such computational methods. Most parasites target similar host pathways, particularly with innate immunity, but the mechanism differs for each helminth species as they have evolved their own strategy to combat host defense. Identifying such mechanisms may reveal the way to develop neutralizing vaccines. The secreted proteins by schistosome eggs function in protection of eggs from immune mediated destruction, tissue transit and granuloma formation. Well characterization of such secreted proteins will bring clear insight into the basic biology of schistosomes. The identified functions of secreted proteins would upgrade us to the development of novel diagnostic methods, drugs and vaccines. Thus a genome based discovery approach may be the best of the several strategies in therapeutic development.

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