Poster L-3

Identification of Deuterostomia Conserved Genes in the Human Parasite Schistosoma mansoni

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Short Abstract: Schistomiasis is a health problem caused by Schistosoma mansoni. Here we describe in silico identification of 21 schistosome genes conserved in Deuterostomia and lost in Ecdysozoa. Transcription regulation, metabolism and angiogenesis genes were found. They might be related to the parasite's adaptation to host or interaction with host signaling processes.

Long Abstract:

Schistosomiasis is a public health problem in many developing countries, and Schistosoma mansoni is the most widespread species of the causative trematode parasite. Vaccine development has proven difficult owing to effective immune evasion by parasites. Schistosomes achieve immune evasion primarily by recognizing host hormones and other signaling molecules.

The Schistosoma genus is part of the platyhelminth phylum, traditionally regarded as one of the first diverging phylum of the bilaterian group in the acoelomate-pseudocoelomate-coelomate theory (A-P-C). This view is based on a gradualist scenario in which the first bilaterian ancestral was acoelomate and some of its descendants developed coelomic cavities originating the various coelomate phyla. Recently, accumulation of molecular data suggested that platyhelminths are not at the basal position of bilateria, but rather are derived from an ancestral coelomate (Jenner, 2000). According to the new Lophotrochozoa-Ecdysozoa-Deuterostomia phylogeny (L-E-D), platyhelminths are lophotrochozoans (animals with a feeding structure called lophophore) and are included in the Protostomia group together with the ecdysozoans (animals that undergo ecdysis or moulting), while chordates and echinoderms are deuterostomes. Protostomes and deuterostomes are distinguished by their embryonic development (Jones and Blaxter, 2005). This theory implies multiple events of gain or loss of the coeloma along the evolution.

Recently, the transcriptome of S. mansoni has been obtained through a large-scale sequencing effort (Verjovski-Almeida et al., 2003). This dataset is the first large repository of mRNA sequences for platyhelminth organisms. Using this dataset, here we describe the in

silico identification of 21 genes shared by schistosomes and deuterostomes, which represents an interesting set of evolutionarily conserved genes that may be related to aspects of the complex molecular host-parasite interplay.

S. mansoni nucleotide sequences generated by Verjovski-Almeida et al. (2003) and their translated protein sequences were used as the starting repository of S. mansoni sequences in this work. Vertebrate and invertebrate sequences were obtained from GenBank nr database (March/2005). BLAST was used to determine schistosome proteins that have similarity to deuterostome proteins but not to proteins from non-helminth protostome organisms. Bit scores were used to evaluate the results. Although less intuitive than e-values, this metric is database-independent, allowing comparison of hits across different databases. Alignments with bit scores higher than 100 were considered as good matches, while those with bit scores lower than 50 were discarded. Hits with intermediary scores were inspected manually. These cutoffs were empirically derived.

S. mansoni protein sequences that have hits only with deuterostome proteins were submitted to manual inspection to remove redundancy and possible false positives. Multiple alignments with ClustalW (www.ebi.ac.uk/clustalw) and manual curation were performed to produce a non-redundant dataset, which was further searched against GenBank using TBLASTN, to account for non-annotated protostome genes and ensure further elimination of false positives. In cases where the schistosome sequence was shorter than all its hits, we performed additional BLASTX and TBLASTN searches using the best hits as query against the protostome sequences in the nr database at NCBI, removing eventual false positive results that had been originated from the small size of the original query.

All sequences that passed our previous filters were mapped onto the S. mansoni genome draft sequence (available at http://www.genedb.org/genedb/smansoni/), to ensure that these sequences were not spurious contaminants. The resulting dataset was analyzed with TMHMM (Sonnhammer et al., 1998), Signal IP (Bendtsen et al., 2004) and InterProScan (Quevillon et al., 2005).

Following an extensive manual curation and literature mining, we produced a dataset of 21 schistosome genes with orthologs in several deuterostomes, but not in ecdysozoans. The most interesting genes in this set are INSIG (SmINSIG), Vasohibin (SmVas), and Interferon Regulatory Factor (IRF) (SmIRF). These three genes were further characterized by wet lab experiments, essentially to obtain their full-length transcripts. A phylogenetic analysis using the neighbor-joining method (Saitou and Nei, 1987) shows that the schistosome proteins diverge before radiation of Deuterostomia. These results argue in favor of a vertical transfer for the origin of such proteins.

INSIG has a major role in cholesterol synthesis control in mammals (Goldstein et al., 2006). Considering that schistosomes are unable to produce cholesterol, we suggest that SmINSIG could have an ancient role in metabolism such as being involved in isoprenoid metabolism or mevalonate synthesis. Microarray experiments showed that SmINSIG is overexpressed in female when compared to male adult worms (DeMarco et al., unpublished).

SmVAS is the ortholog of vasohibin, a recently described regulator of angiogenesis (Watanabe et al., 2004). Interestingly, we found that SmVAS has different splicing isoforms, similar to the human ortholog, suggesting diverse functions.

IRFs are involved in immune response in mammals (Mamane et al., 1999). The presence of a schistosome ortholog (SmIRF) suggests an ancient origin of this protein family. Additional experiments are needed to clarify whether SmIRF is involved in schistosome stress response, host-parasite interplay or both.

The lack of described genes from the above families in Arthropods and Nematodes would be

more easily explained in light of the L-E-D hypothesis, since only one event of gene loss in an ancient Ecdysozoa is necessary to explain the observed data. In contrast, using the tree resulting from A–P–C phylogeny two events of gene loss, one in an ancestral Nematode and another in an ancestral Arthropod are necessary to explain the observed lack of these genes in the phyla. Additional transcriptome data from more ecdysozoans and lophotrochozoans could possibly provide more support for this observation.

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