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Review Article

IMPACT OF PARASITE GENOMICS ON THE DEVELOPMENT OF NEW DISEASE CONTROL METHODS

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Abstract: The present article reviews recent advances in the area of parasite genomic technology, and summarises the application of parasitic genomics and its impact on the progress of parasitic disease control methods.
Keywords: Parasitic genomics, microarray, expressed sequence tags (EST), vaccine design, Drug targets.

Introduction

Resistance in parasitic worms is increasing at such an alarming rate that many drugs will soon be rendered useless to the livestock industry (Sangster, 2001). It is therefore not surprising that genome projects on parasitic organisms are now abundant in the hope that new methods for the control of parasites will be forthcoming. The advent of 'affordable' post-genomic technology has opened up a world of proteomic, transcriptomic and metabolomic methodologies that have been utilized to examine the host's response to parasitic infections (peacock, 2010). There is no doubt the era of the "omics" is with parasitology, and current trends in the discipline are addressing fundamental biological questions that can make best use of the new technologies, as well as the vast amount of new data being generated (Ellis *et al*., 2003). 'Omics' projects along with Ingenuity (http://www.ingenuity.com) which was a Pathway analysis tool together provided indepth insights into various types of parasitic complex immune responses.

PARASITE TRANSCRIPTOME ANALYSES

mRNA of the parasitic organisms were defined by techniques such as differential display (Lau *et al*., 2000; Cui *et al*., 2001) and serial analysis of gene expression (Patankar *et al*., 2001) which have played a role in gene discovery. Clustering of expressed sequence tags (ESTs) and the generation of a consensus sequence for each cluster, greatly facilitates the ease by which data can be rapidly assembled to generate a complete gene sequence (Lawson, 1999). It is interesting to note that many of the abundant ESTs of Apicomplexa encode

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antigens that have been well characterized in the past (Table No. 1) such as those found in the micronemes, dense granules, and rhoptries (Ellis *et al*., 2003). Similarity between different parasitic genome sequences can be detected by algorithms like BLAST inaddition to searching in "Genbank" sequence datasets.

Table 1: Representing few of the expressed sequence tags (ESTS) in three coccidian species (Courtesy: http://ParaDB.cis.upenn.edu)

Toxoplasma gondii	*Neospora caninum*	*Eimeria tenella*
GRA7	GRA2	Antigen
GRA1	GRA7	Actophorin
GRA2	Uncharacterized cluster (neo_566)	Serine protease inhibitor
GRA6	MIC1	Uncharacterized cluster (Ceimqual_264)
P22	Uncharacterized cluster (neo_617)	MIC1
P30	GRA1	Uncharacterized cluster (Ceimqual_287)
HSP30	MIC10	Uncharacterized cluster (Ceimqual_521)
NTPase	P38	Uncharacterized cluster (Ceimqual_1487)
Uncharacterized cluster (Ctoxoqual4_276)	SUL1	Uncharacterized cluster (Ceimqual–953)
GRA5	Uncharacterized cluster (neo_824)	Uncharacterized cluster (Ceimqual–926)
GRA8	MIC6	Uncharacterized cluster (Ceimqual_758)
Uncharacterized cluster (toxoqual4_4452)	Uncharacterized cluster neo_287)	Uncharacterized cluster (Ceimqual_161)

Microarrays

Expression profiling by microarray analyses (Cummings and Relman, 2000; Rathod *et al*., 2002) has been reported from a small number of taxa (Cleary *et al*., 2002) which will gain popularity in parasitology sector as the availability of resources will increase. Such studies are proving important in raising and testing hypotheses on the developmental biology of parasites, and the signalling pathways that control them (Ellis *et al*., 2003). Microarray enables to identify study the genes which are underexpressed or either overexpressed under experimental conditions. Depending on the experimental objective, different types of data analyis can be used.

Microarrays are also being used to investigate changes in gene expression of host cells during parasite infection to investigate host response mechanisms (Blader *et al*., 2001).

For example, the host's immune response to Neospora infection in cattle was investigated using mouse cDNA microarrays (Peacock, 2010). Real-time quantitative RT-PCR analyses, using fluorogenic 59 nuclease assays, or Taqman, is typically used to confirm and quantify gene expression levels (Blair *et al*., 2002).

PARASITE GENOME SEQUENCING

The approaches being adopted are similar in structure for each, concentrating on sequence assembly from whole genome shotgun sequencing approaches (Gardner, 2001). Initially, parasite genome sequencing began on a chromosome by chromosome basis, with different groups taking responsibility for individual chromosomes (Bowman *et al*., 1999). However, the power of shotgun sequencing realistically has made approaches based on individual chromosomes redundant for protozoa and more dependent on the tools of bioinformatics for compiling and annotating the genome sequences generated (Ellis *et al*., 2003). Several genomic projects which were conducted by Sanger Centre (U.K.) and TIGR (The Institute for Genome Research -USA) were represented in Table No. 2. Genomic survey of *Schisotosoma mansoni* is still under process.

Table 2: representing parasitic genomic projects conducted by Sanger Centre (U.K.) and TIGR (Ellis *et al*., 2003)

Species	**Number of chromosomes, genome size Species (Mb)**	**Comments**	**Useful Web-sites**
Plasmodium falciparum	14, 30	whole genome	www.plasmodb.org
Theileria annualata	4, 10	whole genome	www.sanger.ac.uk/Projects
Toxoplasma gondii	11, 80	whole genome	http://ToxoDB.org/ToxoDB.shtml
Eimeria tenella	14, 60	whole genome	www.sanger.ac.uk/Projects
Trypanosoma cruzi	35, 40	Partial genome	www.dbbm.fiocruz.br/genome/tcruzi/tcruzi.htm
Leishmania major	36, 33.6	whole genome	www.genedb.org
Entamoeba histolytica	18, 20	whole genome	www.nematode.net/

COMPARATIVE GENOMICS

This methodology aids in the identification of homologous genes amongst species (Thompson *et al*., 2001). Comparisons of parasite genomes from closely related species is

now providing valuable information not only on genome organization but also on gene function (Thompson *et al*., 2001; Waters, 2002). For example, eventhough *N. Caninum* and *T. gondii* are closely related species; information regarding *N. Caninum* was scanty. Genomic sequencing of *N. Caninum* and its comparison to *T. gondii,* aids in knowing information regarding the organism. Although there is much to learn about the H. contortus organism (genome, gene expression and protein function), many assumptions about its physiological and metabolic processes were obtained from the model organism *Caenorhabditis elegans* (Peacock, 2010).

PARASITE PROTEOME ANALYSES

The key technologies behind the core of proteome analyses, namely two-dimensional gel electrophoresis and mass spectroscopy and data base searching, have been described in detail elsewhere (Ashton *et al*., 2001). Recently, large-scale analyses on parasite proteomes have been reported (Jefferies *et al*., 2001; Cohen *et al*., 2002). Identifying immunogenic proteins that elicit protective responses in resistant animals can also help identify potential vaccine candidates (Peacock, 2010). For example, Glycosylphosphatidylinositols have been extensively studied in protozoa for their role as membrane anchors and in cell signalling (Schofield and Tachado, 1996), and more recently their role in activating a Toll-like receptor recognition system may have important implications for vaccine design (Campos *et al*., 2001). Categorization of parasitic proteomes based on their function can be done by Parasite Proteome Server

IDENTIFICATION OF NEW DRUG TARGETS

Investigations into the genomes of parasitic protozoa have also identified many new, potentially exciting targets for chemotherapeutic treatment, such as enzymes of folate metabolism, the mannitol cycle, and polyamine biosynthesis, for example (Coombs and Muller, 2002). For example, genomic characterization of the apicoplast which is essential for parasite survival (Ralph *et al*., 2001) can be selectively targeted by drugs like Ciprofloxacin (Fichera and Roos, 1997). The identification of the shikimate pathway in Apicomplexa is also worth noting, since this pathway is missing in mammals and is a target for herbicides in plants (Roberts *et al*., 2002). Glyphosphate, which targets 5 enolpyruvyl shikimate 3-phosphate synthase, shows antiparasitic activity (Roberts *et al*., 1998).

Still, very little information is known regarding metabolic pathways of parasites implying that further research is required and it is highly likely that new drug targets will be identified in the future (Fairlamb, 2002).

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