Exploring helminth genomes for drug and vaccine development

There are three main species of *Schistosoma* that together infect over 200 million individuals, *S. mansoni*, *S. haematobium* and *S. japonicum*. Over 200.000 deaths are related to schistosomiasis infection every year. Despite much effort, control remains essentially limited to the use of Praziquantel, the only drug available to treat the disease. It is widely recognized that new control tools such as new drugs and vaccines are needed, in additional to sanitation, education and intermediate host elimination. In addition new and more sensitive diagnostic tests are needed. The fantastic advances in the field of genomics have opened new perspectives for the development of new control tools. With this aim the genomes of the three species have been sequenced. Efforts towards making use of this resource are described for the development of new drugs and identification of drugs and vaccine targets of interest will be discussed. To make full use of the genomic data requires heavy computational resources and bioinformatics skills not available in all laboratories. The integration of large and distinct datasets readily available in a user-friendly interface is of major relevance. For this reason SchistoDB was developed. The database was structured using the Genomics Unified Schema and contains a variety of tools that permits fast analysis by similarity searches, protein characteristics, keywords, ontology annotation and other types of data such as gene transcription profiles. Metabolic analysis can also be carried out with SchistoCyc. Various drug targets were computationally identified. We have focused on the study of two families of proteins, kinases and histone modifying enzymes (HMEs). HMEs act as key protein modifiers that influence gene expression by regulating chromatin structure and are involved in a number of human diseases. As a consequence there is significant effort towards developing drug that inhibit HME activity. HME inhibitors affect parasite survival and we explored these enzymes as anti-schistosome targets. To identify targets of interest genes were invalidated by RNAi, protein structures were determined and enzymatic assays developed to test new compounds. We have developed compounds targeting different enzymes. One target is SmHDAC8. SmHDAC8 gene silencing resulted in reduced worm and egg numbers. Other targets under development are KDM1 / KDM2 e PRMT3. A second class of proteins being studied for drug development is kinases. The kinome complement of the *S. mansoni* genome was determined. Gene silencing of SmRas, SmERK1, SmERK2, SmJNK and SmCaMK2 indicated that those in the MAPK pathway are important for parasite development and reproduction.

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