ABSTRACT

The ribosome is an immensely important target for development of therapeutics. However, current X - ray methods for obtaining three - dimensional structures of the ribosome are slow and tedious. Methods that can be used to identify, annotate, and optimize ribosome - small molecule interactions that could enable the design of compounds that modulat e ribosome fu nction are in their infancies. We have determined the three - dimensional structures of the 40S ribosomal subunit of Plasmodium falciparum , through the structure prediction method. The structure reveals the folding of the entire 40S and all the ribosomal proteins. Our Homology Model shows the Plasmodium specific elements considerably expand the network of interactions within the ribosome and provides accurate prediction of ribosomal RNA structures. The generated three - dimensional structure gener ated using homology and de novo modeling is of high resolution comparable in quality to experimentally determined X - ray crystal structure. The model allows for identification of new rRNA target sites and the specific motifs that are essential for Plasmodi um ribosome functionality and viability. Several regions of P.falciparum rRNA that contain nucleotides essential for viability of the ribosome were identified. The sites include functionally important regions, known binding sites for antibiotics, tRNA, pr oteins, the large ribosomal subunit and initiation factors. Also identified are a number of sites that are clearly essential for ribosome function, but for which no functio nal role has been identified. The model is useful for screening compound libraries a nd to carry out structural studies of target/hit complexes, allowing optimization of hit compounds and validation of target using in silico assays. The model is useful for exploiting regions of 16S rRNA that are unlikely to mutate, thus generating anti - inf ective natural products leads that would have decreased likelihood of resistance development.