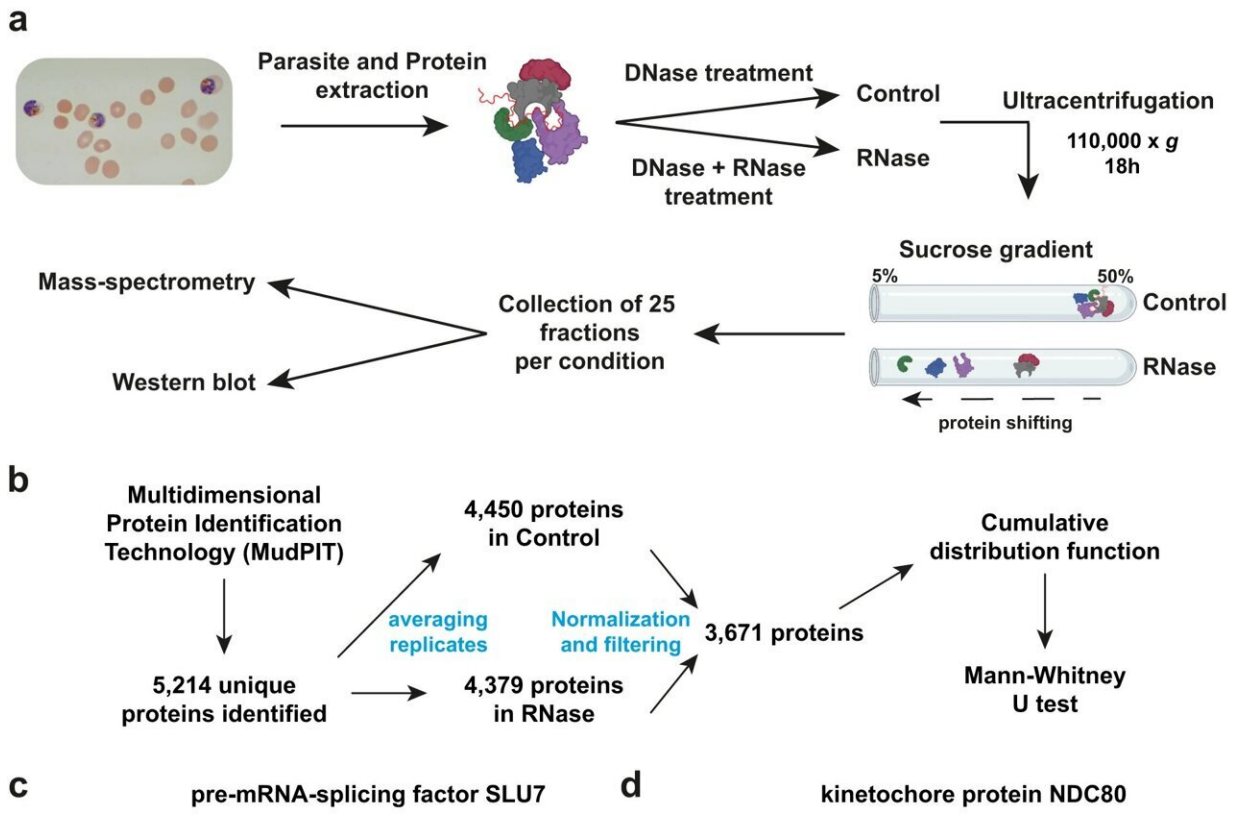
RNA-dependent protein research advances the fight against malaria

February 15 2024



R-DeeP approach to identify RNA-dependent proteins in P. falciparum. a Schematic overview of the R-DeeP method. NF54 parasite protein lysates were treated with DNase (Control) or DNase + RNases (RNase) and loaded on a sucrose gradient. After ultracentrifugation, 25 fractions were collected and further processed by mass spectrometry and western blot analysis. Created with BioRender.com. b Bioinformatics workflow for the mass spectrometry data analysis. After multiple filtering (see Methods), a final list of 3671 proteins was obtained, and a cumulative distribution function (CDF) was calculated for each

protein. CDF profiles of pre-mRNA-splicing factor SLU7 (c) and kinetochore protein NDC80 (d) illustrate an RNase-shifted and non-RNase-shifted protein, respectively. e The graph shows the number of left-shifted, right-shifted, and non-shifted proteins detected in this R-DeeP. f GO enrichment analysis of the 898 left-shifted proteins. The significance of Biological Process terms is shown by –log10 (adjusted P-value) (Fisher's exact test with Bonferroni adjustment). Credit: *Nature Communications* (2024). DOI: 10.1038/s41467-024-45519-1

New work by a team led by scientists at the University of California, Riverside, has taken research one step closer to designing new therapies to fight and eradicate malaria thanks to a lab technique called R-DeeP.

The team is studying RNA-dependent proteins—assemblies of RNA molecules and proteins that are critical for cell survival. These RNA-protein complexes play fundamental roles in many cellular processes.

In Plasmodium falciparum, the deadliest human malaria parasite, however, scientists have been able to identify and characterize only a limited number of RNA-dependent proteins due to the complexity of the parasite life cycle progression and limited tools available to edit the parasite genome efficiently.

Now, using a comprehensive "molecular search tool" called R-DeeP, Karine Le Roch, and her colleagues have identified and characterized 898 RNA-dependent proteins in P. falciparum, including uncharacterized and parasite-specific proteins, which could lead to novel therapeutic targets against malaria. Study results appear in *Nature Communications*.

"We also validated that one novel parasite-specific RNA-binding protein, PF3D7_0823200, interacts with various Plasmodium transcripts involved in controlling virulence," said Le Roch, a professor of

molecular, cell and systems biology and director of the UCR Center for Infectious Disease and Vector Research. "This RNA-binding protein could be targeted by new drugs and is, therefore, of interest in the fight against malaria."

During transcription, a gene's DNA sequence is copied by enzymes to make an RNA molecule. Of the 898 RNA-dependent proteins the researchers identified, only 39% of them had already been identified as associated with RNA.

"Our study provides the first snapshot of the Plasmodium protein-protein and protein-RNA interaction network in the parasite," Le Roch said. "These generated R-DeeP results highlight the importance of RNA in many biological pathways in the parasite and identify new targets for combating malaria."

More information: Thomas Hollin et al, Proteome-Wide Identification of RNA-dependent proteins and an emerging role for RNAs in Plasmodium falciparum protein complexes, *Nature Communications* (2024). DOI: 10.1038/s41467-024-45519-1

Provided by University of California - Riverside