New point-of-care diagnostic test may revolutionize early diagnosis of Mediterranean rickettsiosis spotted fever

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Rickettsiae are bacteria that cause severe, potentially lethal human infections, including Mediterranean spotted fever (MSF) and Rocky Mountain spotted fever. Delays in diagnosing and treating MSF can cause significant morbidity and mortality, due in part to the lack of a test for early detection. A new study in the *American Journal of Pathology* reports the discovery of a sensitive and specific marker that may enable early diagnosis, treatment, and accurate public health notification of spotted fever rickettsial infections including MSF.

The assay currently used to diagnose rickettsial diseases lacks sensitivity, especially during the first week of infection, which can lead to mis- and under-diagnosis.

Researchers used a quantitative proteomics pipeline to identify a biomarker for rickettsial infection, rickettsial putative N-acetylmuramoyl-L-alanine amidase (RC0497), for the diagnosis of MSF. After identifying rickettsial RC0497 protein from the culture medium of primary human umbilical vein endothelial cells infected with the MSF-causing pathogen *Rickettsia conorii*, assays were developed for the detection of RC0497 in blood. The presence of RC0497 was confirmed in the blood of a mouse model of *R. conorii* and the serum samples from a cohort of humans presenting with acute rickettsioses.

This study shows that RC0497 can significantly differentiate infected

individuals from healthy controls, and that the circulating levels of RC0497 are proportional to the severity of infection. Many species of the spotted fever group rickettsiae were also found to express proteins with sequence highly homologous to RC0497.

"The detection of RC0497 has the potential to diagnosis a wide variety of rickettsial spotted fever infections, including Rocky Mountain spotted fever," stated co-lead investigator Yingxin Zhao, Ph.D., the Department of Internal Medicine and Sealy Center for Molecular Medicine, University of Texas Medical Branch (UTMB), Galveston, TX, USA. Differences in RC0497 levels between infected patients and healthy controls were most striking during the acute phase of infection, although levels of RC0497 were still elevated during convalescence.

"It is our long-term goal to convert this into a point-of-care diagnostic test that will revolutionize the diagnosis of spotted fever rickettsioses, making it available as therapeutic decisions are being made," commented co-author David H. Walker, MD, Director, UTMB Center for Biodefense and Emerging Infectious Disease, Department of Pathology, UTMB, Galveston, TX, USA.

If validated with a larger cohort, this biomarker will enable early detection and timely treatment for rickettsia patients and advance the epidemiological study of spotted fever rickettsial infections.

"This discovery opens the door for a deeper understanding of the spectrum and epidemiology of this re-emerging tick-borne disease. Importantly, the work is the product of an interdisciplinary team of infectious disease specialists, experts in tick-borne diseases, advanced proteomics/analytical chemists, and informaticists who collectively combined their skills to advance this field," noted co-lead investigator Allan R. Brasier, MD, who participated in the study while affiliated with the Department of Internal Medicine and Sealy Center for Molecular

Medicine, University of Texas Medical Branch (UTMB), Galveston, TX, USA .

"The rickettsioses represent an important unmet need in human and veterinary medicine. Rickettsioses are a spectrum of potentially lethal diseases whose diagnosis and definitive treatment require a high index of suspicion," explained Drs. Zhao and Brasier.

MSF, one of the most severe diseases caused by rickettsiae, is prevalent throughout the Mediterranean basin, Africa, the Middle East, and India. It presents as an eschar (dry, dark scab), acute fever, headache, and maculopapular rash. After entering the body, rickettsiae can cause vascular leakage, such as pulmonary or cerebral edema.

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