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New model accurately predicts who will develop deadly form of dengue fever

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Researchers at the University of Texas Medical Branch have developed the first accurate predictive model to differentiate between dengue fever (DF) and its more severe form, dengue hemorrhagic fever (DHF). The breakthrough, which could vastly reduce the disease's mortality rate, was reported in related papers in The *American Journal of Tropical Medicine and Hygiene* and *Clinical and Translational Science*. These studies could lead to a personalized approach to treatment of dengue fever.

Approximately 2.5 billion people – more than 40 percent of the world's population – are at risk for dengue infection, mainly in tropical and subtropical regions. An estimated 500,000 people with DHF are hospitalized each year, a large proportion of whom are children, and about 12,500 of those affected die. Dengue is remerging in the Americas – with 1.6 million cases in 2010 – due to increasing urbanization, globalization of travel and the reduced use of DDT pesticide. In the U.S., the number of people hospitalized for dengue tripled between 2000 and 2007.

"We have long known that dengue has many manifestations, from asymptomatic to a flu-like state to a life-threatening condition. If we could figure out early a patient's susceptibility to the deadly form, we could save thousands of lives," said lead author Dr. Allan Brasier, Director of UTMB's Institute for Translational Sciences, with a multidisciplinary team of protein biochemists and bioinformatics specialists developing approaches to personalized medicine – work that will allow doctors to provide better individual diagnostics and treatments

for common illnesses.

There is no drug treatment for DHF and fatality rates can exceed 20 percent; however, early and intensive supportive therapy – such as transfusions to reduce bleeding complications and organ failure – can reduce the rates to less than one percent.

In the new papers, the researchers outline results of two separate proteomics analyses using laboratory assays that are commonly available, including in resource-poor clinics, and more complex profiling techniques to identify specific candidate protein biomarkers.

They found that the cytokine IL-10 (a protein involved in the immune response) and reduced platelet and lymphocyte counts were key predictors of DHF. Further investigation showed that the most accurate model for predicting DHF – effective in 100 percent of the cases studied – was based on IL-10 and seven distinct proteins (tropomyosin, complement 4A, immunoglobin G, fibrinogen and three forms of albumin).

"Until now, biomarkers of the disease have proved elusive. But proteomics technologies are changing the landscape and these studies are the first step toward a personalized approach to treating dengue infection," said Brasier.

For each study, the UTMB Proteomics Center team collaborated with the U.S. Naval Medical Research Unit and practicing physicians in clinics and hospitals in Maracay, Venezuela. Approximately 55 study subjects with acute dengue infection provided blood samples and observed for clinical outcome. The researchers analyzed gender; clinical signs (e.g., days of fever, diarrhea); laboratory measurements (lymphocyte/platelet counts, hemoglobin concentration, red blood cell count); and cytokine concentrations.

Looking first at the most accessible laboratory and clinical data points, they found that increased concentrations of IL-10, reduced platelet counts and, to a slightly lesser extent, reduced lymphocyte counts are major informative features of DHF – accurately predicting the disease in 86 percent of cases.

Next, multidimensional protein profiling – a more complex and in-depth proteomics analysis – was used to measure cytokines that have been associated with DHF in other studies. The researchers again identified IL-10 as a significant determining factor between DF and DHF. Additionally, seven proteins (out of 42 studied) were shown to be predictive of DHF: tropomysin, complement 4A, immunoglobin G, fibrinogen and three forms of albumin.

Further analysis indicated that any single protein would be a poor differentiator between DF and DHF, but together the proteins were 100 percent accurate in classifying the infection.

"We've proved it is feasible to identify predictive proteins associated with DHF," said Brasier. "If future research bears out these candidate proteins as firm predictors of DHF, doctors can act early to save lives – the highest hope for personalized medicine."

He added that larger validation studies will be needed to verify these findings and analyze the biological pathways affected in DHF. Most of the candidate proteins identified can be linked to the biological processes underlying DHF, including cytokine storm, capillary leakage, hepatic injury and antibody consumption, suggesting that these predictors may have biological relevance.

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