A dengue virus protein alters the blood vessel surface and makes it leaky

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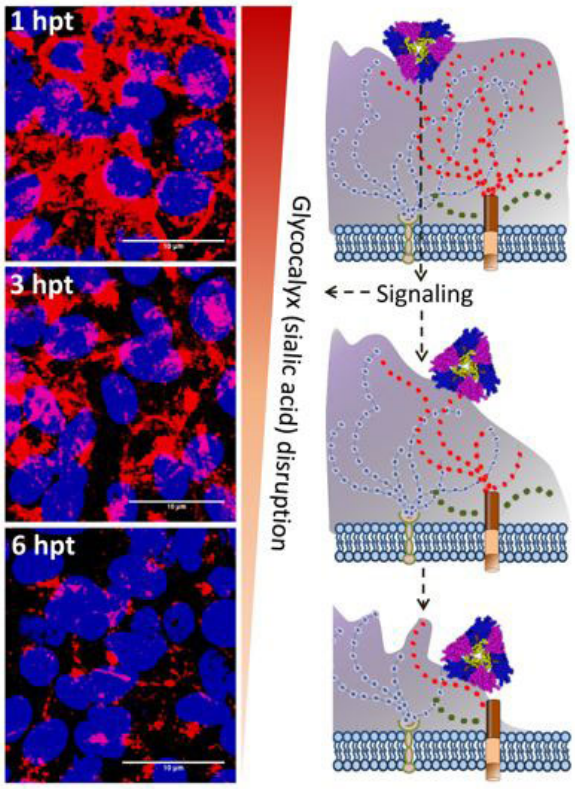

Exposure to DENV NS1 (magenta/blue/yellow in the schematic panels) causes loss of Sia chains (red) from EGL attached to endothelial cells (blue on left). Credit: Puerta-Guardo H et al., (2016)

The major symptom of severe dengue disease is leakage of blood plasma out of small blood vessels, which can lead to shock and death. A study published on July 14th in *PLOS Pathogens* suggests that the dengue virus (DENV) protein NS1 can disrupt the innermost layer of blood vessels and make them more permeable.

DENV nonstructural protein 1 (NS1) is the only viral protein secreted from infected host cells, with high concentrations found in the blood of patients with severe dengue disease. NS1 has multiple functions in virus replication and its interaction with the human immune system. More recently, several research teams have found that NS1 can make blood vessels more permeable and cause blood vessel (or 'vascular') leakage.

One of these groups, led by Eva Harris of the University of California in Berkeley, USA, conducted the present study to investigate how NS1 disrupts the blood vessel barrier. Because in severe dengue disease, major accumulation of fluid occurs in the lung, the researchers studied the interaction of soluble NS1 with cultured human lung endothelial cells.

Endothelial cells form blood vessels and generate an extracellular layer, the endothelial glycocalyx layer (EGL). The EGL consists of a network of membrane-bound molecules on the surface of the endothelial cell layer in direct contact with the blood. Recent studies have shown that the EGL plays an important role in regulating blood vessel permeability.

Cultured endothelial cells form an EGL on their surface, and the researchers show that binding of DENV NS1 to the cells can disrupt the integrity of the EGL, causing breakdown and shedding of key components. For example, NS1 exposure led to removal of sialic acid (Sia for short), the part of EGL molecules that sticks out furthest into the vessel lumen and is known to influence permeability. NS1 was also shown to disrupt the EGL by altering the expression and shedding of molecules called heparan sulfate proteoglycans, such as syndecan-1.

NS1 doesn't mess with the EGL molecules directly, but induces human enzymes to carry out the EGL alterations. The researchers were able to show that drugs that block these enzymes prevent both EGL disruption and endothelial permeability, despite the

presence of bound NS1.

To see whether the effects on the EGL and vessel permeability were specific to dengue, the researchers tested NS1 proteins from different members of the DENV group as well as NS1 from the related West Nile Virus. They found that NS1 from all four DENV serotypes produced consistent EGL alterations and leakage, but West Nile Virus NS1 showed no such effects.

The researchers explain that their results were observed following treatment with amounts of DENV NS1 similar to levels reported in patients with severe dengue disease, but acknowledge that they need to be followed up with studies in whole organisms. More comprehensive studies, they say, are under way to understand the relative contribution of these endothelial-intrinsic mechanisms in the context of dengue disease.

"Our study", the researchers conclude, "suggests a novel role for DENV NS1 in inducing EGL disruption to increase fluid leakage during severe dengue disease". More broadly, they hope that the results "may contribute to future advancements in dengue treatment and diagnostics".

More information: Puerta-Guardo H, Glasner DR, Harris E (2016) Dengue Virus NS1 Disrupts the Endothelial Glycocalyx, Leading to Hyperpermeability. *PLoS Pathog* 12(7): e1005738. DOI: 10.1371/journal.ppat.1005738