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Dengue and other haemorrhagic fevers: towards a first potential treatment

Dengue is a viral disease transmitted by mosquitoes of the genus *Aedes*. It hits 60 to 100 million people in the world. The most serious form of this disease, which is currently spreading in several tropical countries, induces plasma leakage from the blood vessels, which can lead to a shock-like syndrome possibly accompanied by haemorrhage. No treatment or vaccine exists at present and the only prevention is vector control. IRD immunovirologists and their research partners ⁽¹⁾ have determined the mechanisms involved in the occurrence of the vascular leakage triggered by the Dengue virus. They not only identified enzymes, metalloproteinases, responsible for the passage of plasma across the blood-vessel walls but also found molecules that specifically inhibit their action. These original results, validated first by *in vitro* tests then *in vivo* on a mouse model, open up the first line of attack for treatment against haemorrhagic Dengue. Further research under way should help determine if these findings can also be used in a general model for investigation and development of treatments for other viral haemorrhagic fevers such as Ebola or Hantavirus.



Young patient in intensive care suffering from haemorrhagic Dengue, special DHF paediatric unit, Pratchaburi Hospital, Muang District, Thailand.

Globally, 60 to 100 million people are hit by Dengue, a viral disease transmitted by mosquitoes of the genus *Aedes*. The most severe form of this disease, which causes blood loss, can lead to a fatal shock-like state (Dengue Shock Syndrome) with or without associated haemorrhage, and is currently increasing in tropical countries. The pathological mechanisms of Dengue are still unknown and it has not been possible to produce any treatment or vaccine. The only current prevention method is vector control.

This context brought IRD immunology and virology specialists and their research partners ⁽¹⁾ to focus on these little-known biological mechanisms that are set into operation

on infection by the virus, responsible for increasing the permeability of vascular wall endothelial cells and hence blood loss. The researchers found evidence of the role played by particular enzymes, metalloproteinases, in the occurrence of this leakage. Low concentrations of these enzymes are present naturally in the organism, and they are involved in the reconfiguration of organ tissues during human embryonic development or tissue repair, but also in the development of certain cancers. They attack specifically the intercellular cement that binds the vascular walls. The research team demonstrated, *in vitro*, that Dengue-virus infection of certain targeted cells of the immune system (the dendritic cells) triggered an inflammatory reac-

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tion, stimulating these same target cells to overproduce metalloproteinases (gelatinolytic matrix metalloproteinases – MMP-9) and secrete them into the cellular supernatant (2). The quantity of enzyme produced therefore appears to be proportional to the concentration of viral particles present.

To verify that the metalloproteinases were the only agents responsible for the increased vascular permeability, the researchers performed tests on cell cultures of endothelial tissue, of the same type as that of the blood vessel walls. The supernatant of the infected cells, consequently containing the metalloproteinases, were brought into contact with this tissue. The vascular permeability, estimated by the quantity of supernatant passing through the endothelial tissue, appeared significantly higher. Conversely, the natural permeability of the tissue was restored when a specific inhibitor of these enzymes (SB-3CT) was added to the supernatant. Fluorescence microscope images of proteins of the intercellular cement, subjected to the action of the same supernatant, revealed that metalloproteinases act on the blood vessel walls like biological "scissors": they destroy the protein bonds which maintain cell adhesion and hence keep them together. This action was, however, neutralized by specific metalloproteinase inhibitors.

A series of *in vivo* experiments following the same principle confirmed these hypotheses. A mouse model with blood circulatory system coloured blue was injected with supernatant containing these enzymes, on their own or in

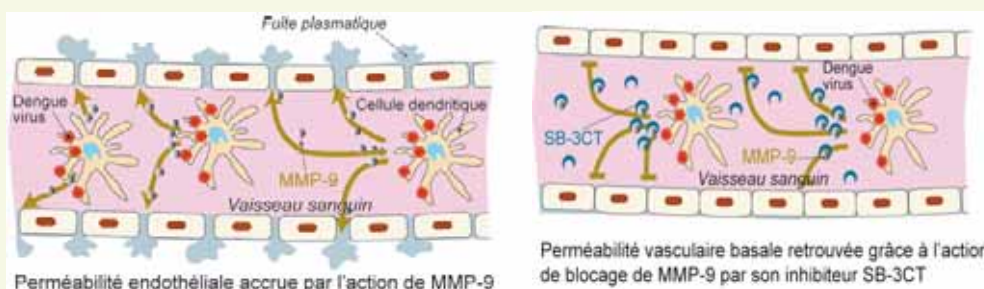
the presence of their inhibitor. This procedure not only reproduced the mechanisms of vascular rupture that originated blood leakage, but also – and more significantly – succeeded in neutralizing them.

This research sheds completely new light on Dengue's pathological strategy. The results provide a way of explaining the major role played by direct action of metalloproteinases on blood-vessel walls. The overproduction of these enzymes, linked to the viral infection and the inflammatory reaction it triggers, does not however appear to be restricted to Dengue. The mechanism described here could provide a molecular basis for a new model of the action of other known haemorrhage-inducing viruses, such as Ebola, Marburg, or Hanta. New lines of therapeutic research against these pathologies, for which no treatment yet exists, can now be envisaged. Indeed, clinical trials on Dengue are currently in preparation.

(1) These IRD investigations were conducted in partnership with research scientists from Mahidol University of Bangkok (Thailand), the company ImmunoClin Ltd (United Kingdom), research unit UMR 5535 CNRS/UM2 and unit 454 of INSERM (France).

(2) The cell supernatant corresponds to the culture medium of the infected cells.

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Translation : Nicholas Flay



Increased endothelial permeability triggered by MMP-9 action

Original baseline vascular permeability restored by blocking of MMP-9 by its inhibitor SB-3CT.

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