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Pathogenic bacteria adhering to the human vascular wall triggers vascular damage during meningococcal sepsis

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Researchers at the Paris Cardiovascular Research Center (PARCC) have shown how adhesion of *Neisseria* (*N.*) *meningitidis* to human microvessels in a humanized mouse model leads to the characteristic cutaneous lesions of meningococcal sepsis. This work, published on January 24 in the Open Access journal *PLOS Pathogens*, is an important demonstration of the direct role of adhesion, specifically Type IV pili mediated adhesion, plays in the development of the disease.

Meningococcal sepsis is a rapidly developing and often fatal infection. Cutaneous lesions, often presenting clinically as purpuric or petechial skin rashes, are a hallmark feature of the infection hence the term purpura fulminans to describe this severe form of sepsis. Understanding the mechanisms behind the development of these lesions is important to understand disease progression because it reveals the underlying mechanisms of the pathological process. From the experimental point of view the strict human specificity of *N.* meningitidis has long been a limiting factor in the development of relevant in vivo models of this infection and for understanding how the bacteria interact with the blood vessels. It was previously thought that that the large number of circulating bacteria was responsible for the vascular damage through the release of LPS in particular.

In this research, investigators utilized a humanized mouse model, where human skin, containing an abundance of human microvessels, was

grafted onto immunocompromised mice. Grafted mice thus had a hybrid vasculature, part mouse, and part human. In this context, *N. meningitidis* associated exclusively, and in significant numbers, with the human vessels. Once associated with the human vessels the bacteria rapidly led to an endothelial inflammatory response with expression of the human pro-inflammatory cytokines IL-6 and IL-8 and the infiltration of inflammatory cells. Vascular events such as clotting, thrombosis, congestion and vascular leak were all observed in the infected human vessels, mimicking the clinical pathology. The combination of these factors led to the development of a purpuric rash in 30% of the infections. The association of the bacteria with the human vessels was shown to be dependent on the adhesive properties of the bacterial Type IV pili, filamentous structures found at the surface of many pathogenic bacteria. Importantly, bacterial mutants deficient for these adhesive structures do not lead to any distinctive pathology despite normal numbers of circulating bacteria.

This work thus leads to a change in the paradigm in our understanding of the disease mechanism, with local adhesion events now considered central to the disease process. Because it recapitulates key features of human infection, the described experimental model opens new avenues of research to further understand the mechanisms of disease and to design new prevention and treatment strategies.

More information: Melican K, Michea Veloso P, Martin T, Bruneval P, Duménil G (2013) Adhesion of Neisseria meningitidis to Dermal Vessels Leads to Local Vascular Damage and Purpura in a Humanized Mouse Model. PLoS Pathog 9(1): e1003139. doi:10.1371/journal.ppat.1003139

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