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Birmingham researchers identify how Salmonella infections can lead to life-threatening thrombosis

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Researchers from the University of Birmingham have, for the first time, identified how Salmonella infections that have spread to our blood and organs can lead to life-threatening thrombosis.

These systemic infections trigger the development of inflammation, which in turn leads to thrombosis. Crucially, the maintenance of the sustained threat from thrombosis is independent of the continued presence of infection and instead parallels the regulation of inflammation within the host.

The findings, published in the *Journal of Clinical Investigation*, shed light on a poorly understood area of clinical medicine. The team believe that the identification of the pathway will offer new therapeutic opportunities that can control the devastating consequences of infection-driven thrombosis, without increasing the risk of life threatening side-effects such as bleeding.

Whilst some of the mechanisms that underpin the process of infection-driven thrombosis are known, particularly for Gram-positive organisms such as staphylococci or streptococci, they are not universally applicable. This is evidenced by the limited efficacy of current treatments available for modulating thrombosis. Moreover, during sepsis the causative pathogen is often never isolated or identified. This work helps to explain why this is the case.

The study demonstrated that thrombi developed within the liver of murine models infected with Salmonella Typhimurium, and these thrombi persisted for many weeks.

The infection caused inflammation in the liver tissue, which then triggered thrombosis within vessels via the ligation of C-type lectin-like receptor-2 (CLEC-2) on platelets by podoplanin, a molecule which is ordinarily absent in blood vessels but is expressed by macrophages responding to the infection.

The regulation and amplification of thrombosis, which causes dangerous clotting involving platelets, was triggered by TLR4, a protein essential for the activation of the inflammatory cascade and the control of infection during its early stages.

Critically, thrombosis remained at peak levels even when bacteria were absent from the blood and largely cleared from the infected organs.

Uncontrolled thrombosis is a common, life-threatening consequence of systemic infection caused by many types of bacteria, and is a typical component of sepsis, where the death rate can be 30% or higher. Clots can develop, break off and move throughout the body - to the brain or heart - where they become immediately more dangerous.

Professor Adam Cunningham, from the University of Birmingham, explained, "For all of the advances we've made in this field it is not always clear why people die from infection, we think complications of thrombosis may be one reason. In Salmonella infections, severity is typically associated with the presence of bacteria in the blood, called bacteraemia, even though the actual numbers of bacteria in the blood are very low. This suggested to us that the host response was crucial in determining the outcome."

BHF Professor Steve Watson, also from the University of Birmingham, added, "A little, controlled thrombosis is probably a good thing as it helps to clear bacteria from the blood. Therefore, any intervention would need to control, rather than deny, the host response. The problem only comes when it develops into a clot."

"Most of the current approaches to counter the development of these life-threatening thrombi do not account for the non-classical mechanism that we have shown to be at work."

The team are now working to further understand how to manipulate and control this response, and how it can contribute to the complications of other infections and diseases.

Subreena Simrick, Research Adviser at the British Heart Foundation, which part-funded the research, said, "Uncontrolled clotting within blood vessels, known as thrombosis, can be a life threatening complication of severe infection. This study led by BHF Professor Steve Watson and Professor Adam Cunningham at the University of

Birmingham, has identified a previously unknown pathway linking the activation of the immune system which is caused by a bacterial infection, with thrombosis. This insight into novel mechanisms involved in thrombosis could help develop new approaches to regulate blood clotting in sepsis."

Source:
University of Birmingham