

They shall not pass! Fighting infections with blood clots

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A research team at Ludwig-Maximilians-Universitaet in Munich has shown that clot formation within small blood vessels helps in the fight against pathogenic microbes. At the molecular level, clot formation turns out to be intimately connected with the innate immune system, a finding that may open up new therapeutic possibilities.

The [adaptive immune system](#) can recognize and respond specifically to particular infectious agents. But the first line of defence against pathogens is the so-called innate immune system. This system reacts to invaders by initiating unspecific inflammatory responses which attract various types of specialized cells such as neutrophils to the site of the incursion.

"Neutrophils secrete proteins that inactivate bacteria and other microbes", says LMU researcher Professor Bernd Engelmann, "but they also play a role in [blood coagulation](#)." A research team led by Engelmann has now shown that the processes of blood coagulation and antimicrobial defence are functionally coupled -- and that neutrophils provide an important link between them. "During systemic infections neutrophils induce the formation of harmless clots in small blood vessels, which inhibits the dissemination of pathogens", says Engelmann. "Taken together, our results suggest that clot formation inside blood vessels is a part of the normal physiological response to pathogens. Hence there is also a physiological form of thrombosis. However, when clot formation is erroneously induced, in the absence of pathogens and within the larger blood vessels, then there is a high risk of heart attack or stroke. Our

findings may provide new insights into the mechanisms responsible for pathological thrombosis, and suggest new ways of preventing them." ([Nature Medicine](#) online, 02. July 2010)

The [arthropods](#), which include insects and spiders, are the most species-rich division of the animal kingdom. All arthropods have in common that they are dependent on their innate immune system for protection against infections. This system mobilizes a rather unspecific set of defences, and reacts to attack by inducing inflammation at the site of infection. As part of this reaction, clots can form in the haemolymph that bathes the tissues and cells, effectively trapping invading cells and preventing the establishment of a systemic infection. Humans, like all other mammals, also have an innate immune system that reacts rapidly to invaders. It therefore seemed possible that a connection between blood coagulation and antimicrobial responses existed in humans as well

Researchers led by Professor Bernd Engelmann of the Institute of Clinical Chemistry at LMU Munich and Professor Steffen Massberg of the Technical University of Munich have just published a study in which they took a close look at the role of neutrophils in the [innate immune system](#). Together with the circulating cells known as platelets, neutrophils accumulate rapidly at wound sites, which potentially provide portals of entry for pathogens. "The neutrophils produce antimicrobial factors, but they also play a role in blood coagulation", says Engelmann. "We suspected that this dual function has been conserved during evolution, and that neutrophils could serve as a functional link between blood clotting and antimicrobial defence."

The study revealed that some of the antimicrobial proteins secreted by [neutrophils](#), in particular so-called serine proteases, also participate in the process of blood coagulation, and so facilitate the formation of clots in the blood vessels. In a systemic infection, when the invader has gained entry into the bloodstream and threatens the whole organism, bacterial

pathogens were found to be trapped in tiny clots in small blood vessels in the liver, where the thrombi presumably cause no damage. But the new work showed that they effectively prevent the microbes from penetrating into the surrounding tissue. "Overall, our findings suggest that [clot formation](#) can be a physiological weapon that helps to fight off pathogenic microbes", says Engelmann. "Indeed, activation of the blood coagulation process is probably an important and widespread antimicrobial defence mechanism."

The process becomes problematical only when it contributes to the formation of clots in large blood vessels. "Thromboses are the most important cause of heart attack, stroke and pulmonary embolism, but they are also involved in the life-threatening long-term effects of sepsis and many types of infection", says Engelmann. "Arterial thrombosis, which can result from various pathologies, is actually one of the leading causes of death worldwide". Hence the new results could be useful in the search for new therapeutic strategies. "They do, after all, demonstrate that the same molecular mechanisms underlie the formation of both physiological and pathological forms of [thrombosis](#), and they may point to new targets for treatment of the latter."

More information: "Reciprocal coupling of coagulation and innate immunity via neutrophil serine proteases" Steffen Massberg et al. Nature Medicine, 2. August [DOI:10.1038/nm.2184](https://doi.org/10.1038/nm.2184)

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