# Blood-clotting protein linked to cancer and septicemia

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In our not-so-distant evolutionary past, stress often meant imminent danger, and the risk of blood loss, so part of our body's stress response is to stock-pile blood-clotting factors. Scientists in the Molecular Medicine Partnership Unit (MMPU), a collaboration between the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany, and the University of Heidelberg Medical Centre, have discovered how stressed cells boost the production of the key blood-clotting factor, thrombin. Their work, published today in *Molecular Cell*, shows how cancer cells may be taking advantage of this process, and opens new possibilities for fighting back, not only against cancer but also against septicaemia, where increased blood clotting is still one of the leading causes of death.

Blood clots tend to form more often in the veins of people with cancer, a syndrome first described almost 150 years ago by French physician Armand Trousseau. In recent years, doctors have also come to realise that people with activated blood coagulation are more likely to develop cancer. Accordingly, recent studies have shown that anti-coagulants may help treat and prevent cancer, but exactly how blood-clotting and cancer progression are linked was unclear – until now.

"For the 1st time, we have something in hand that might explain this enigmatic relationship between enhanced pro-coagulatory activities and the outcome of cancer," says Sven Danckwardt, who carried out the research within the MMPU.

The amount of thrombin our cells produce is controlled by two sets of

proteins: proteins that slow thrombin production, and proteins that speed it up. Both types of protein act by binding to the cellular machinery that synthesises thrombin, and, under normal conditions, the production-slowing proteins keep thrombin levels low. But Danckwardt and colleagues discovered that, when our cells come under stress from inflammation, another protein, called p38 MAPK, reacts by adding a chemical tag to those production-slowing proteins. That tag makes it harder for the production-slowing proteins to bind to the thrombin-synthesising machinery, allowing the proteins that speed up production to take over. So inflammation caused by cancer could lead to increased thrombin levels and, as thrombin is a blood-clotting agent, this could explain why cancer patients are more likely to suffer from blood-clots. The scientists believe this new mechanism of gene regulation may apply to other genes, too.

"Knowing the exact molecules involved, and how they act, has implications for treatment, especially as drugs that inhibit p38 MAPK are already being tested in clinical studies for other conditions," says Matthias Hentze, Associate Director of EMBL and co-director of MMPU, adding: "those drugs could be good candidates for potential cancer or septicaemia therapies."

The Heidelberg scientists found that p38 MAPK also influences thrombin production during septicaemia. Also known as blood poisoning, septicaemia occurs when bacteria or other pathogens enter the bloodstream, leading to widespread infection and to blood-clotting problems. When they analysed liver samples taken from septicaemic mice and from cancer patients, the scientists discovered that thrombin production increases in response both to widespread inflammation during septicaemia and to localized inflammation at the tumour's invasion front, where cancer cells are spreading into nearby tissue.

Aside from its role as a blood-clotting agent, thrombin is also involved in

creating new blood vessels, and it is able to degrade the extracellular matrix that keeps cells together. So it's possible that the cancer cells are increasing thrombin production to help the tumour spread, by making it easier to invade healthy tissue and creating blood vessels to supply the new tumour cells. This, the researchers believe, could explain why people with blood-clotting problems seem to have a higher risk of developing cancer.

"This study shows the benefits of partnerships like the MMPU, which bridge the gap between clinical and basic research," Andreas Kulozik from the University of Heidelberg Medical Centre, co-director of MMPU, concludes.

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