Study shows how sepsis can affect vascular smooth muscle cells on an acute and long-term basis

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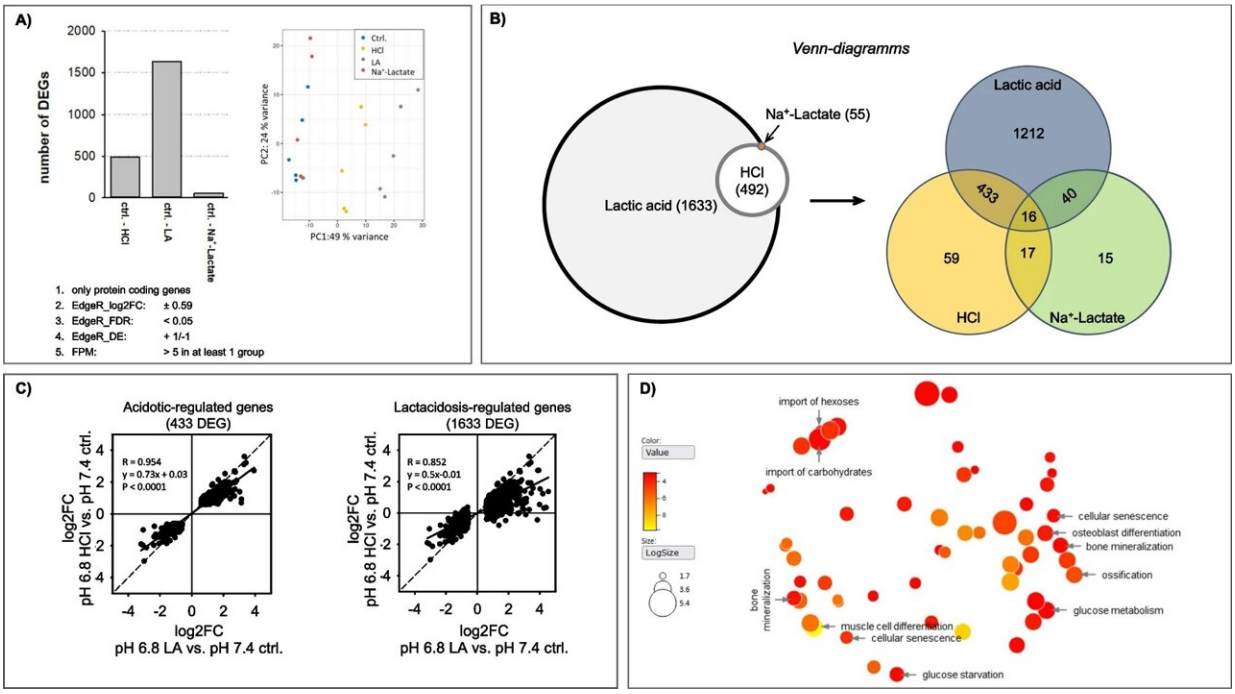

The synergism of cytosolic acidosis and reduced NAD+/NADH ratio is responsible for lactic acidosis-induced vascular smooth muscle cell impairment in sepsis. Credit: *Journal of Biomedical Science* (2024). DOI: 10.1186/s12929-023-00992-6

A recent study by University Medicine Halle shows how sepsis can lead to dysfunction of vascular smooth muscle cells. The researchers found

that elevated lactate levels and acidosis, which can occur acutely during sepsis due to metabolic derailment, only have a disrupting effect in synergistic combination.

The study, published in the *Journal of Biomedical Science*, also provides a possible explanation for why some sepsis survivors experience long-lasting impairments.

Treating sepsis poses a major challenge worldwide. Early diagnosis is crucial, as advanced stages can only be treated to a limited degree and up to half of all cases are fatal.

"Sepsis is a serious complication that often leads to multiple organ failure. Circulatory disorders play a decisive role. However, the pathogenetic mechanisms are still poorly understood," explains Dr. Stefanie Ruhs, a biochemist at University Medicine Halle and one of the first authors of the study. Sepsis is known to lead to metabolic changes. Two thirds of affected individuals have extremely high lactate levels with concurrent metabolic acidosis—a low blood pH.

At University Medicine Halle, the University Clinic and Outpatient Clinic for Anesthesiology and Operative Intensive Care and the Julius Bernstein Institute of Physiology joined forces to better understand the pathogenesis of sepsis.

"In our study, we investigated the effects that lactate, acidosis on its own, and both in combination (lactic acidosis), have on the vascular smooth muscle cells in blood vessels. The latter, lactic acidosis, is clinically associated with low survival rates," explains Ruhs.

In their experiments, the researchers used isolated vascular smooth muscle cells from the aorta, which were propagated in the laboratory. These were treated for 48 hours either with lactate at a normal pH, with

acid without lactate, and with both in combination (lactic acidosis).

Fatigue and stiffening of blood vessel cells caused by lactic acidosis

Lactate at a normal pH has shown to cause a few relevant changes in the vascular smooth muscle cells. Acidosis without lactate led to changes at the genetic level: under acidic conditions, nearly 500 genes were expressed differently. However, the cells investigated in this study were able to compensate to a large degree for any adverse effects on function.

"Only the combination of lactate and acidic conditions, i.e. lactic acidosis, led to extensive changes at the genetic level, in energy metabolism, and to the phenotype," says Philipp Terpe, Ph.D. student and first author.

"Around 1,500 genes exhibited an altered expression linked to metabolism and cell appearance. This can lead to the impairment of various processes related to energy balance that could no longer be compensated for. We were also able to demonstrate a restructuring of the vascular smooth muscle cells as a result of mineralization."

All in all, these effects indicate that, during sepsis, blood vessels partially lose their function and stiffen due to restructuring. This can restrict blood flow in both short and long term. According to the authors of the study, this lasting impairment could also explain why patients who survive sepsis continue to experience symptoms on a physical and cognitive level.

"In the future, we want to analyze further types of vascular cells and investigate whether cells undergo repeated stress once blood values normalize after sepsis. A better understanding of the underlying

mechanisms might help to develop new bio markers that could help indicate the severity of sepsis at an early stage, thereby shortening clinical response times.

"After all, every minute counts during the intensive care treatment of sepsis and septic shock. And if we succeed in identifying the long-term effects at the molecular level, we may be able to use new approaches for treating survivors," says Terpe.

Sepsis can occur after a bacterial, viral or fungal infection. The cause of this life-threatening condition is a dysregulated immune reaction. This is characterized by vasodilation and decreased systemic vascular resistance, resulting in circulatory disorders. It often leads to the failure of one or more organs.

Even if the patient receives intensive care treatment, sepsis can be fatal in 30 to 50% of all cases. Some studies have also reported a mortality rate of more than 50% in the case of septic shock.

More information: Philipp Terpe et al, The synergism of cytosolic acidosis and reduced NAD+/NADH ratio is responsible for lactic acidosis-induced vascular smooth muscle cell impairment in sepsis, *Journal of Biomedical Science* (2024). DOI: 10.1186/s12929-023-00992-6

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