Two distinct pathways leading to the development of septic shock pave the way for personalized medicine in sepsis

- Researchers have published new insights into the causes of mortality in sepsis
- Loss of endothelial function is induced through two different pathophysiological processes and is a major driver of septic shock, a life-threatening drop in blood pressure
- The first pathway originates in the loss of the endothelial barrier triggering an increased production of the repair hormone bioactive Adrenomedullin (bio-ADM), which also has the undesired side effect of vasodilation
- The second threat acting on the endothelial function is the release of the protease DPP3 into the bloodstream which degrades angiotensin II, a process resulting in decreased vascular tone and cardiac output
- The different pathways require different treatment strategies thus opening new approaches for personalized medicine in sepsis
- New diagnostics for quantification of bio-ADM and DPP3 are available as laboratory and near-patient rapid tests
- Biomarker-guided approaches for therapies targeting these pathways are showing promising results

Hennigsdorf/Berlin, Germany, February 18, 2021 – Diagnostics company SphingoTec GmbH (SphingoTec) announced today that two distinct processes are involved in the development of septic shock and that SphingoTec's biomarkers for endothelial function (vascular integrity) and cardiovascular depression allow early identification of these underlying mechanisms requiring different interventions. Sepsis, a global burden with nearly 50 million cases worldwide, is a life-threatening condition that is diagnostically and therapeutically underserved. With the availability of such pathway-specific biomarkers, new avenues for diagnosing and monitoring sepsis are opened and biomarker-guided trials for personalized therapies targeting these mechanisms are enabled.

Researchers have summarized the available evidence (1) on two distinct pathophysiological processes leading to endothelial dysfunction and the subsequent development of shock and organ failure in sepsis. The two biologically active molecules acting on the vasculature and influencing patient outcomes are bioactive Adrenomedullin (bio-ADM) and Dipeptidyl peptidase 3 (DPP3). One distinct pathway originates in the loss of endothelial barrier integrity, causing edema and the loss of intravascular volume. To compensate for this leakage, the production of the repair hormone bio-ADM is increased. But bio-ADM has also the second function of vascular relaxation, therefore the increased production leads to a dangerous side effect of vasodilation, generating a loss of tissue resistance which ultimately culminates in shock. Data from the observational study AdrenOSS-1 show (3) that elevations of bio-ADM levels reflect the loss of endothelial function and translate into poor outcome in sepsis. Furthermore, the results of the biomarker-guided AdrenOSS-2 trial (2) confirm that this pathway is a valid therapeutic target. According to the second underlying mechanism accountable for the loss of the endothelial function, the depletion of angiotensin II affects the renin-angiotensin-aldosterone system (RAAS), ultimately leading to a cardiovascular depression (4,5) and reduced vascular tone, a deadly combination in need of selective treatment strategies. The main process generating the depletion of the cardiovascular stimulating hormone angiotensin II is the release of the protease DPP3 into the bloodstream through sepsis-induced cell damage (6).

Personalized medicine has shown significant progress in areas such as oncology or cardiology, but in intensive care units, it has remained challenging to identify biomarkers that facilitate personalized treatments. In the context of a life-threatening condition such as septic shock, taking therapeutic decisions is time-critical, aiming to respond in the best possible way and especially on a patient-specific basis. The review (1) summarizes that the biomarkers bio-ADM and DPP3 can identify these pathways, supporting an early and precise diagnosis and monitoring of sepsis patients. Moreover, data from the biomarker-guided interventional study AdrenOSS-2 show that clinical trials can benefit from the use of biomarker as an enrichment strategy. Within the AdrenOSS-2 study, patients with sepsis-associated endothelial dysfunction were identified by increased bio-ADM to receive therapy with placebo or Adrecizumab (2), an antibody targeting the loss of vascular integrity by maintaining protective bio-ADM concentrations in the blood. When excluding patients with additionally high DPP3 blood concentrations, outcomes could further be improved. Therapies blocking DPP3-activity have also been shown to improve outcomes in various preclinical models. (7)

Dr. Andreas Bergmann, founder of various companies fighting sepsis mortality and CEO of critical care diagnostics company SphingoTec commented: “Following a deep understanding of the disease biology, we have developed diagnostic solutions that can now unravel the etiology of the mortality drivers in sepsis. The evidence confirms the utility of our biomarkers in supporting clinicians make more informed decisions and ultimately improve patient management. “

The new diagnostics for quantification of bio-ADM and DPP3 are available as microtiter plate assays as well as point-of-care tests on the Nexus IB10 immunoassay platform. The Nexus IB10 analyzer provides test results on whole blood samples in only 20 minutes and can be flexibly deployed in emergency departments, intensive care units, and any laboratory setting.

References

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About SphingoTec

SphingoTec GmbH ("SphingoTec"; Hennigsdorf near Berlin, Germany) develops and markets innovative in vitro diagnostic (IVD) tests for novel and proprietary biomarkers for the diagnosis, prediction and monitoring of acute medical conditions, such as sepsis, acute heart failure, circulatory shock, and acute kidney injury in order to support patient management and provide guidance for treatment strategies. SphingoTec's proprietary biomarker portfolio includes bioactive Adrenomedullin (bio-ADM), a biomarker for real-time assessment of endothelial function in conditions like sepsis or congestive heart failure, Proenkephalin (penKid), a biomarker for real-time assessment of kidney function, and Dipeptidyl Peptidase 3 (DPP3), a biomarker for cardiac depression. IVD tests for SphingoTec's proprietary biomarkers are made available as sphingotest® microtiter plate tests as well as point-of-care tests on the Nexus IB10 immunoassay platform by SphingoTec's subsidiary Nexus Dx Inc. (San Diego, CA, USA) alongside a broad menu of established and commonly used tests for acute and critical care.

About bio-ADM®

sphingotest® bio-ADM® measures bioactive Adrenomedullin (bio-ADM), a hormone maintaining endothelial function. The endothelium contributes to blood pressure and separates blood from the surrounding tissue. Elevated blood levels of bio-ADM® predict blood pressure break down and leaky vessels resulting in oedema. Imbalanced endothelial function is the major cause of shock ultimately resulting in organ dysfunction and death. Early identification of an imbalance in endothelial function allows guidance of vasopressor and diuretic therapy in critically ill patients to improve outcomes. Learn more about bio-ADM® at www.sphingotec.com

About DPP3

sphingotest® DPP3 measures Dipeptidyl peptidase 3 an active enzyme which, when released into the blood, inactivates angiotensin II, a hormone that is important for heart function. The depletion of angiotensin II affects the renin-angiotensin-aldosterone system (RAAS), ultimately leading to cardiovascular depression and reduced vascular tone, a deadly combination in need of selective treatment strategies. The DPP3 release is a newly identified disease mechanism explaining short-term organ failure in critically ill patients. Early identification of DPP3 release may allow better patient stratification and earlier therapy escalation to improve outcomes. www.sphingotec.com

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