O-GlcNAcylation, and various enzymes involved, and biological parameters (urea, creatinine, pH, PCO2, PO2).

Cardiovascular function was strongly modified with a reduction in blood pressure (~25%) in LPS injected rats, while no improvement was reported neither after GLCN nor NbutGT treatment. An increase in global O-GlcNAcylation was only obtained under GLCN and NbutGT treatment. GLCN led to an increase in two enzymes involved in HBP regulation (GFAT and O-GlcNAase). LPS injected rats presented a lactate acidosis associating an increase in lactate (3.38±0.7 mmol/L vs 6.37±0.66) and drastic reduction in HCO3–. Urea and creatinine were increased suggesting an acute renal failure. Treatment with NbutGT but not GLCN corrected biological parameters (lactate: 2.6±1.00 mmol/L, pH: 7.41±0.03, HCO3–: 27.66±2.24 mmol/L).

Our study demonstrates the putative beneficial effect of O-GlcNAc stimulation during sepsis, especially by NbutGT. It remains to be determined whether the improved biological parameters are associated with a reduced mortality of rats.

0321
PTP1B gene deletion or pharmacological inhibition improves glucose metabolism and limits cardiovascular dysfunction in experimental septic shock

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Hyperglycemia is a feature of septic patient and has been associated with poor outcome and higher mortality. In contrast insulin has been shown to decrease mortality and to prevent the incidence of multi-organ failure but is often associated with deleterious hypoglycemia. Protein Tyrosine Phosphatase 1B (PTP1B) is a negative regulator of insulin signaling and NO production. Recently we showed that PTP1B gene deletion improves cardiovascular dysfunction during endotoxemia. However, the effect of PTP1B inhibition on glucose metabolism and cardiovascular insulin resistance during sepsis is unknown.

Thus, in order to address this question, we developed a Cecal Ligation and Puncture (CLP) model of sepsis which is known to reproduce metabolic disorder of clinical sepsis. Impaired glucose metabolism was found in mice 16 hours after CLP induction as shown by the disruption of glucose intake and insulin response during glucose (GTT) and insulin (ITT) tolerance tests. PTP1B–/– mice showed improved GTT and ITT (GTT 120min: CLP WT 20.1±2.1, CLP PTP1B–/– 12.5±2.4 mmol/L, p<0.001; ITT 120min: CLP WT 2.4±0.2, CLP PTP1B–/– 0.60±0.03 mmol/L, p<0.001) demonstrating an improvement of glucose metabolism. Insulin- and flow-mediated dilatation assessed in isolated-perfused mesenteric arteries was abolished by CLP and was improved by ex vivo PTP1B inhibition (% dilatation: Ins10-5M, CLP 7±2, CLP+PTP1B 18±4%, p<0.01; 200 µmin flow, CLP ± CLP+PTP1B 13±3%, p<0.01). Arteries isolated from PTP1B–/– mice were protected against TNF-α induced impairment of dilation to insulin. We found that PTP1B–/– mice subjected to CLP had a higher survival rate compared to WT.

Thus, PTP1B gene deletion or inhibition limits sepsis-induced hyperglycemia and insulin resistance associated with reduced vascular dysfunction and increased survival. PTP1B inhibition may represent a new strategy in the treatment of septic insulin resistance with hyperglycemia.

0129
Pharmacological modulation of microparticle-mediated vascular response in a rat model of septic shock

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Introduction: Circulating procoagulant microparticles (MPs) take part in septic shock vascular dysfunction through pro-inflammatory and procoagulant detrimental effects. Aims were to study how circulating procoagulant MPs are involved in the vascular dysfunction of septic shock and to examine if the pharmacological modulation of MP could be beneficial.

Methods: In a first set of experiments, MPs were isolated from sham or septic rats obtained by cecal ligation and puncture, resuscitated and treated by activated protein C (aPC). Then, healthy recipients were inoculated with septic MPs and hemodynamic parameters were recorded during 4 hours. At the end of the record, blood and organs were harvested.

Results: Treating septic rats with aPC significantly reduced norepinephrine needs to reach the mean arterial pressure goal and leukocyte-derived MPs (6.2±2.1 vs 2.9±1.7 nM PhldSer, p<0.05, n=16). MPs from septic rats significantly decreased the mean arterial pressure of healthy recipients (85±9 vs 107±2 mmHg), a deleterious hemodynamic effect also prevented by aPC treatment (120±6 mmHg). Possibly through the elevation of MP thromboxane content (77.1±11.4 pg/mL vs 39.8±4.5 pg/mL in sham-NaCl MPs, p<0.05, n=12), a decreased arterial inflammation in mesenteric resistance arteries and heart was observed (evident (40±5) western blotting of global reduction in NF-κB and pIκB-α staining). Of note, inoculation of MPs from aPC-treated septic rats altered MP phenotype. Recipients had elevated circulating levels of platelet and endothelial MPs.

Conclusions: During sepsis, MPs modulate the inflammatory response in cardiac and vascular tissues and contribute to septic hemodynamic dysfunc-
Circulating markers of vascular endothelial dysfunction in obese patients

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Obesity is a major worldwide health problem associated with several metabolic, inflammatory and oxidative troubles which represent major cardiovascular risk factors. The endothelial dysfunction plays a central role in the physiopathology of cardiovascular diseases. This critical function is generally evaluated through in vivo functional assessment, but emerging new biomarkers, like cell-derived microparticles (MPs) reflecting alteration of the endothelium are increasingly studied. The aim of this study was to assess the level of circulating MPs in normal weight and obese patients and their relation with different oxidative, inflammatory and endothelial function parameters.

Normal weight subjects (n=29, BMI<25 kg/m²) and obese patients (n=53, BMI>30 kg/m²), were recruited at F. Hached Hospital (Sousse, Tunisia). Vascular endothelial function was assessed by the exploration of the endothelium-dependent vasodilatation by Laser Doppler Flowmetry and flow cytometry analysis was used for the quantification of circulating MPs. Obese subjects presented an endothelium-dependent vasodilatation significantly lower (21.26±2.89) than in normal weight patients (32.40±6.35) (p=0.008), characteristic to a vascular endothelial dysfunction. Furthermore, obese patients displayed a significantly higher number of circulating MPs (37579±4766 MPs/μl) in comparison to normal weight subjects (12099±934 MPs/μl) (p<0.001). Circulating MPs were positively correlated with anthropometric parameters BMI (r=0.504; p=0.02) and waist-hip ratio (WHC) (r=0.476; p=0.14). A positive correlation was also observed with parameters of inflammation (C-reactive protein (CRP) r=0.374; p=0.045) and oxidative stress (advanced oxidation protein product (AOPP) r=0.487; p=0.04 and total thiols r=0.551; p=0.01).

These data demonstrated that circulating MPs could be a good biomarker of vascular endothelial dysfunction in obese patients, however the precise role of MPs in inflammation and oxidative stress has still to be clarified in further studies. Obesity, endothelial dysfunction, microparticles,