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Role of protein tyrosine phosphatases PTP1B & TC-PTP in inflammation mediated insulin resistance and skeletal muscle atrophy

Charlotte Wulfert [1,2], Björn Brinschwitz[1,2], Jens Fielitz[1,2]

Background

- 50% of critical ill patients in ICU develop skeletal muscle atrophy (ICUAW)
- Systemic inflammation and sepsis leads to therapy resistant hyperglycemia and therefore insulin resistance, which serves as a risk factor for ICUAW
- Patients that survive the initial septic event often have impaired muscle functioning, low quality of life, and prolonged immunosuppression resulting in increased risk of death for years to come
- Insulin acts as an endogenous anabolic hormone on skeletal muscle protein synthesis
- PTPs act as post receptor modulators mainly by dephosphorylating tyrosine residues on the INSRβ subunit itself and on downstream targets

Skeletal muscle insulin signaling

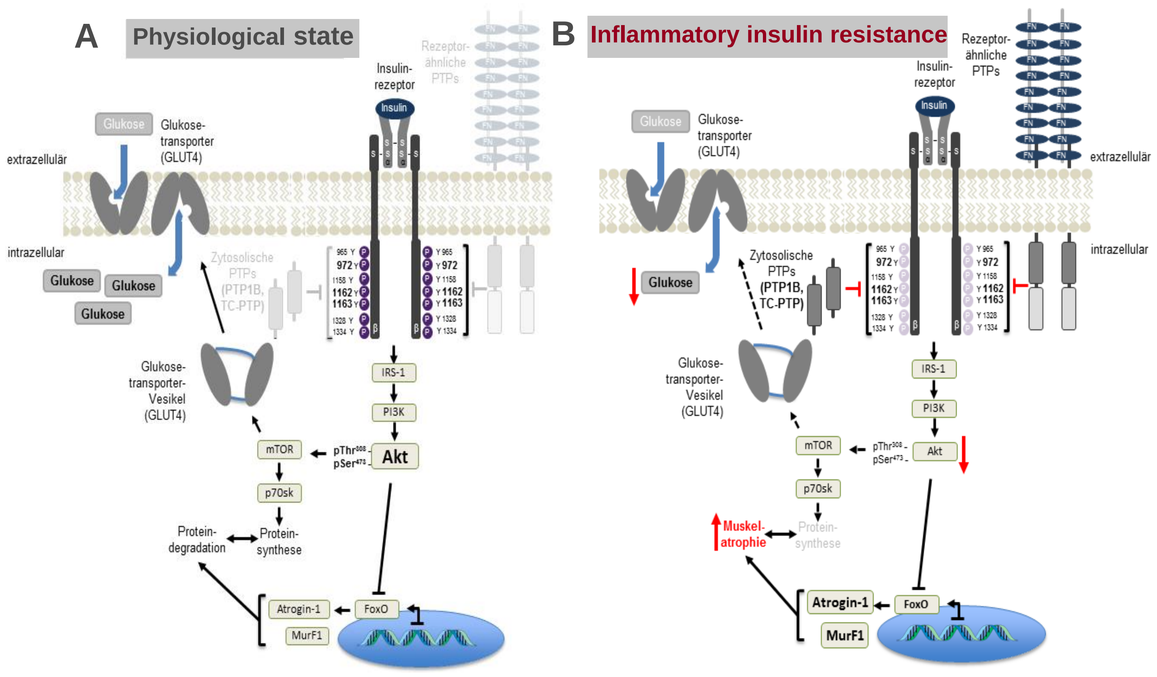

Fig.1 Insulin signaling pathway in skeletal muscle form Insulin receptor to protein synthesis and glucose uptake under physiological conditions (A) and in an hypothized inflammatory state (B)

Ptpn1 and *Ptpn2 knockout* improves cardiac function under septic conditions

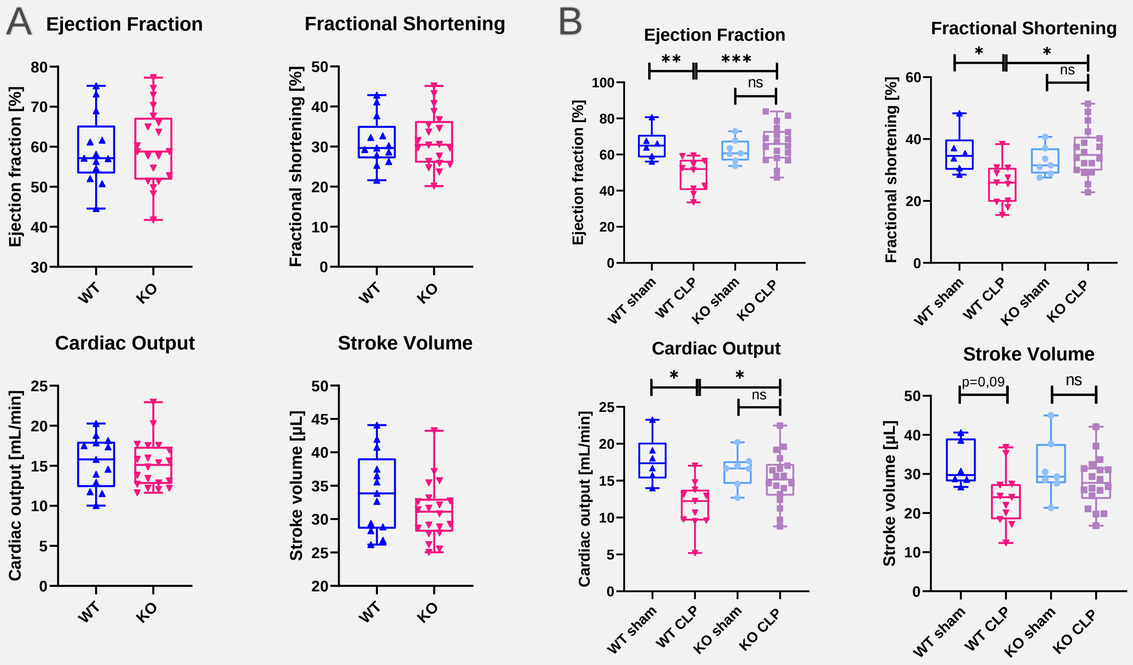

Fig.2 10-16 week old C57BL/6N Ptpn1/2$^{loxP/loxP\ \alpha MHC\ cre}$ (KO) or Ptpn1/2$^{loxP/loxP}$ (WT) (A) were subjected to either CLP or sham surgery and were sacrificed after 24 h. Before the surgery a baseline echo were performed (A) and compared to 24h after surgery (B)

Proof of CLP induced inflammation

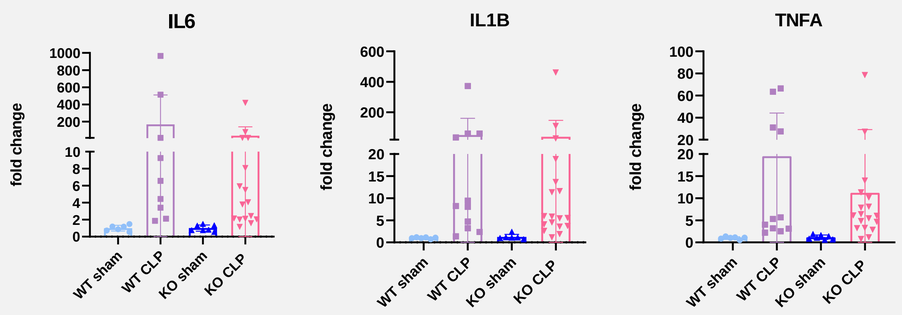

Fig.3: Investigation of the left ventricle, Genexpression

Hypothesis

PTP1B & TC-PTP mediate inflammation induced skeletal muscle insulin resistance by imparing muscle insulin signaling which leads to reduced glucose uptake, skeletal muscle protein synthesis and consequently muscle weakness and atrophy

Methods

Real-time quantitative PCR and Western blot

- Investigation of Insulin downstream targets *in vitro* and *in vivo* (INSR,IRS1,IRS2,AKT, AS160, GLUT4) and corresponding AKT downstream targets of the protein synthesis and UPS apparatus (FoxO1, MurF1, Atrogin1, p70S6K, mTOR) *in vivo & in vitro*

- Expression of cardiac stress and remodeling factors (*Nppa, Nppb, Col1a1*, *Col1a3, Fn1, Ctgf*) *in vivo*

Caecal ligation and puncture: a polymicrobial sepsis model

- The mice receive generel isofluran anesthetic

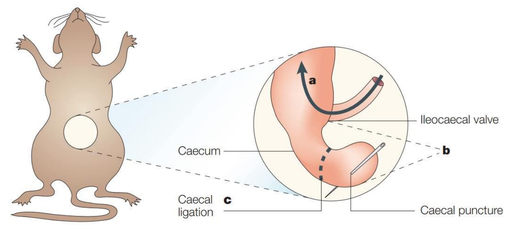

Fig.4 CLP diagram adapted from Buras et al.,2005. Mice receive general isoflurane anesthetic. Midline laparotomy, exteriorization of the caecum, ligation of the caecum (c) distal to the ileocaecal valve (a) and puncture of the ligated caecum (b). Fecal material gets manually extruded before closing peritoneum and skin.

Echocardiography: Quantification of heart structure and function

- different views of the heart: parasternal long and short axis view, apical four/five chamber view, infrasternal four chamber view, suprasternal view

- By measuring the different heart structures in systole and diastole, parameters describing cardiac function can be calculated (e. g. Ejection fraction, Fractional Shortening, Cardiac Output)

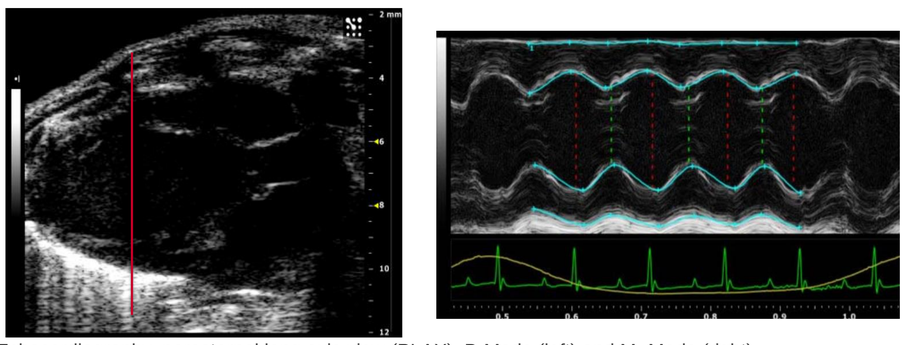

Fig.5 Echocardiography, parasternal long axis view (PLAX), B-Mode (left) and M- Mode (right)
The resulting B-mode image shows a long section through the heart, depicting the left and right ventricles with their outflow tracts, the left atrium and the aortic bulb with ascending aorta.The M- Mode image shows the changes in diastole and systole. For this purpose, an axis (red line) was placed in the B-mode image (left) and the temporal changes were derived (right)

Protein level of PTP1B and TC-PTP is elevated in the WT CLP mice

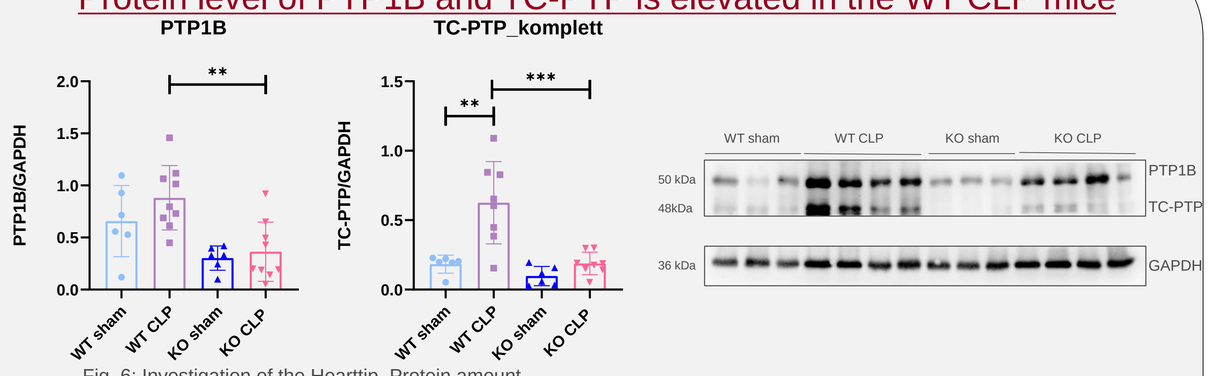

Fig. 6: Investigation of the Hearttip, Protein amount

Investigation of the Insulin signaling

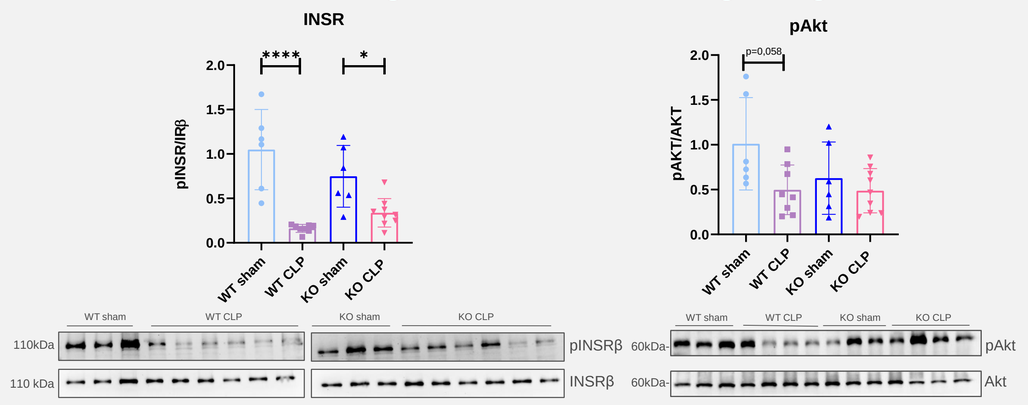

Fig. 7: Investigation of the hearttip, Protein amount

Cand. med. Charlotte Wulfert
Universitätsmedizin Greifswald
Klinik und Poliklinik für Innere Medizin B
Forschungscluster III - AG Prof. Fielitz
Fleischmannstr. 41, 17475 Greifswald
E-Mail: charlotte.wulfert@stud.uni-greifswald.de

[1]DZHK (German Centre for Cardiovascular Research), partner site Greifswald, Germany;
[2]Universitätsmedizin Greifswald, Department of Cardiology, Germany

Declaration of interest
No conflicts of interest, financial or otherwise, are declared by the authors.