Mitochondrial dysfunction governs immunometabolism in leukocytes of patients with acute-on-chronic liver failure

1Biochemistry and Molecular Genetics Service, Hospital Clinic-IDIBAPS, Spain
2European Foundation for the Study of Chronic Liver Failure (EF-Clif), Barcelona, Spain
3Department of Biomedical Sciences, University of Barcelona, Spain

INTRODUCTION

Acute-on-chronic liver failure (ACLF) was first defined as a distinct clinical syndrome in 2013 in the context of the EASL-CLIF Acute-on-Chronic Liver Failure in Cirrhosis (CANONIC) study, a prospective European investigation in 1,343 hospitalized patients with cirrhosis (Moreau et al., 2013). Systemic inflammation (Claria et al., 2016) is a well recognized driver from mere acute decompensation (AD) to ACLF. A follow-up study using untargeted metabolomics could identify disturbances in mitochondrial pathways, such as alternative utilization of glucose and reduced mitochondrial β-oxidation (Moreau et al., 2019).

AIM

The aim of this study was to demonstrate that mitochondrial dysfunction is a hallmark of ACLF development, and that inadequate energy output is the basis for organ failures and high mortality rate inherent in this disease. We assessed our hypothesis by two approaches. The first was of descriptive nature, comprising the examination of mitochondrial ultrastructure and evaluation of possible biomarkers of mitochondrial dysfunction. The second approach was aimed at the analysis of the metabolic phenotype of circulating leukocytes of patients with acutely decompensated (AD) cirrhosis and ACLF.

METHODS

1. Assessment of mitochondrial morphology in immune cells using transmission electron microscopy.
2. Measurement of growth differentiation factor (GDF15) and fibroblast growth factor 21 (FGF21) using a MAGPIX instrument (Luminex Corp., Austin, TX) in plasma of patients with AD cirrhosis and ACLF.
3. Assessment of the metabolic flux in peripheral mononuclear cells (PBMCs) of patients with AD cirrhosis and ACLF with MitoPlate S-1 and Mito-M1 plates for mitochondrial and cytosolic energy production.

RESULTS

Transmission electron microscopy: Mitochondrial morphology

Fig. 1 Transmission electron microscopic images of circulating leukocytes from a patient with ACLF grade 3, compared to a healthy subject. As compared to PBMCs from healthy individuals, PBMCs from patients with ACLF contained abnormally shaped mitochondria with cristae rarefication and less dense staining of the matrix. In the lower panel a zoom in of the upper images is shown.

Phenotype microarrays: Metabolic fluxes in PBMCs

Fig. 2 Patients with ACLF display elevated circulating biomarkers of mitochondrial dysfunction

FGF21 and GDF15 are regarded as circulating markers for inherited mitochondrial diseases (Lehtonen et al., 2016; Montero et al., 2016). For FGF21 measurement: Healthy n=20; AD n=87 (1 not detected); ACLF1 n=52; ACLF2 n=47; ACLF3 n=15. For GDF15 measurement: Healthy n=20; AD n=88; ACLF1 n=52; ACLF2 n=47; ACLF3 n=16. The values are displayed as median with range.

CONCLUSIONS

The current findings provide direct evidence of mitochondrial damage at the morphological and functional levels in immune cells from patients with AD cirrhosis. In these cells, a repurposed in energy production from mitochondrial to cytosolic pathways is seen to likely support the energetically expensive systemic hyperinflammatory state present in this condition.

REFERENCES


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CONTACT INFORMATION

Ingrid Wei Zhang IWZANG@clinic.at

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