mixed-iCCA and abolished the capacity of both iCCA-subtypes to form colonies.

FPRX is down-regulated in iCCA cells, but its activation by OCA results in in vitro anti-cancerogenic effects against both mucin and mixed-iCCA human primary cell cultures. The effects of OCA predominate against mixed-iCCA, consistent with the lower aggressiveness and the higher FPRX expression in this CCA subtype.

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T-05
Adherence to EASL antibiotic treatment recommendations improves the outcomes of patients with cirrhosis and bacterial infections. Results from the ICA “Global Study”


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Introduction: Bacterial infections are a common cause of decompensation in patients with cirrhosis. On 2014, EASL recommendations for antibiotic treatment in patients with cirrhosis and bacterial infections were published. The effects of adherence to these recommendations have never been investigated so far.

Aim: To assess the clinical impact of the adherence to EASL recommendations in patients with cirrhosis and bacterial infections.

Methods: In the “Global Study”, 1302 patients with cirrhosis and bacterial infection were enrolled. Demographic, clinical, microbiological and treatment data were collected at the diagnosis of infection and during the hospitalization. Patients were followed up until death, liver transplantation or discharge. The empirical antibiotic treatment was considered adherent to EASL recommendations if at least one of the antibiotic/combination recommended was administered.

Results: The antibiotic treatment was adherent to EASL recommendations in 61% of patients, while was broader in 14% and weaker in 25%. Northern American centers prescribed more frequently broader antibiotics (31vs13%; \( p < 0.001 \)) while Northern European and Asian centers administered more frequently weaker ones (30vs21%; \( p < 0.001 \)). Adherence to EASL recommendations was poorer in pneumonia (27vs71%; \( p < 0.001 \)) and nosocomial infections (54vs64%; \( p = 0.002 \)). In patients with positive cultures (57%), the administration of antibiotics weaker than those suggested by EASL recommendations resulted in lower antimicrobial
susceptibility (50 vs 75%; p < 0.001). However, bacteria isolated in Asian centers had a lower antimicrobial susceptibility to antibiotics suggested by EASL recommendations (58 vs 80%; p > 0.001), mainly due to a high prevalence of multi drug resistant bacteria (51 vs 28%; p < 0.001).

After adjusting for confounders (age, ACLF, quick SOFA and MELD-Na score), the administration of antibiotics weaker than EASL recommendations was associated with a higher risk to develop new organ failures (OR = 1.50; p = 0.010), septic shock (OR = 1.51; p = 0.044) and in-hospital mortality (OR = 1.47; p = 0.034).

Conclusions: The adherence to EASL recommendations was associated with better outcomes in patients with cirrhosis and bacterial infections and should be promoted. However, different empirical antibiotic strategies should be developed in certain countries due to the high prevalence of MDR bacteria.

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T-06

The inhibitory effect of ADM on hepatic NF-κB activation in 2D and 3D hepatic cell cultures

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The neuropeptide adrenomedullin (ADM) shows anti-inflammatory activity but its role has not been investigated in liver diseases. We assessed the hepatic ADM expression in different inflammatory liver diseases (HCV, AIH, NASH) and the mechanism(s) by which ADM affects NF-κB activation in classical 2D and a new 3D model.

Immunofluorescence analysis was performed on liver tissue to assess ADM expression and α-smooth muscle actin colocalization. HepG2 and LX2 were exposed to LPS (1 ng/mL) for 24 h, or ADM (10−7) for 4 h followed by LPS. ICC for p65 nuclear translocation and QRT-PCR was performed. Human liver 3D scaffolds were obtained by decellularization of healthy and cirrhotic livers, hHSCs were cultured on scaffolds for 10 days. Primary hHSC in healthy scaffolds were treated as above, or with LPS for 1–3 h, PDGF-BB (1–10 ng/mL), or TGFbeta1 (2–5 ng/mL) for 24 h. hHSCs in cirrhotic scaffolds were exposed to ADM for 4 h. QRT-PCR was performed.

HSCs ADM-related fluorescence intensity in NASH patients (n = 5) was less than in HCV (n = 5) and AIH (n = 5) patients, but the degree of colocalization was similar. ADM pretreatment of LX2 and HepG2 in 2D reduced p65 nuclear translocation and increased IkBα gene expression. ADM gene expression decreased in TGFbeta1 and LPS-treated hHSCs cultured in 2D and was upregulated in 3D. In contrast, TGFbeta1 and PDGF-BB-treated hHSCs in 3D showed a reduced ADM expression. ADM pretreatment in hHSCs in healthy scaffolds increased ADM expression, reduced NFKB1 and completely abrogated the effect of subsequent exposure to all stimuli. ADM expression was upregulated in hHSCs in cirrhotic vs healthy scaffolds and exogenous ADM treatment favoured hHSCs deactivation in cirrhotic scaffolds.

ADM expression changes with respect to the aetiology of liver inflammation and leads to a reduction in activation of the canonical NF-κB pathway in hepatic cells. Therefore, the ADM system might be a possible pharmacological target for the management of inflammatory liver diseases.

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T-07

Hepatic ischemic injury decreases using negative allosteric modulators of metabotropic glutamate receptor subtype 5

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The selective blockade of metabotropic glutamate receptor subtype 5 (mGluR5) with 2-methyl-6-[(phenylethynyl) pyridine (MPEP), a negative allosteric modulator (NAM), improves the viability of anoxic hepatocytes. However, in microglia and astrocytes, MPEP reduced ATP production. Since ATP depletion is involved in the ischemic injury, we investigated the mechanism of MPEP-mediated ATP depletion, the protection mediated by other NAMs against ischemia and the liver functionality in an ex-vivo model of ischemia/reperfusion (I/R) injury.

Male Wistar rat hepatocytes were exposed to 90 min anoxia at 37°C with MPEP and 3-((2-methyl-4-thiazolyl) ethynyl) pyridine (MTEP) at 3–30 μM, Fenobam (Fen) at 1–10–50–100 μM. Hepatocytes viability was evaluated by trypan blue exclusion and LDH release. Rat liver mitochondria were treated with MPEP, MTEP, Fen at 0.3–3–30 μM. Mitochondrial respiratory control ratio, membrane potential, ROS production and F1FO-ATPase activity were assessed. ATP was assessed in hepatocytes, mitochondria and in acellular buffers containing ATP and MPEP, MTEP, Fen. Wildtype and mGluR5 knockout livers from Balb-c mice were isolated, subjected to I/R and treated with MPEP 0.3 μM; LDH, AST and TNF-alpha release were evaluated.

MPEP 30 μM, MTEP 3 μM and Fen 50 μM improved significantly anoxic hepatocytes viability respect to anoxic controls. ATP was monitored before and after N2 insufflation. MPEP significantly lowered ATP respect to oxygenated controls; MPEP-treated cells showed a slower decline in ATP after N2 insufflation. The same trend was observed for MTEP but not for Fen. In mitochondria, MPEP induced a dose-dependent ATP depletion, without affecting mitochondrial functionality. In acellular solutions only MPEP and MTEP reduced ATP content. MPEP addition during I/R significantly reduced LDH, AST and TNF-alpha release respect to ischemic controls.

MPEP, MTEP and Fen protected hepatocytes against ischemic injury. Although an MPEP-dependent ATP depletion occurred in isolated hepatocytes, mitochondria and acellular solutions, mitochondrial functionality was not affected and, in an ex-vivo model, MPEP was able to reduce the hepatic I/R injury.

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