

Exosomal miRNAs targeting NLRP3 inflammasome platform are associated with radiologic sequelae in survivors of COVID-19-associated acute respiratory distress syndrome

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Background: There is limited understanding of the pathophysiology of post-acute pulmonary sequelae in COVID-19-associated acute respiratory distress syndrome (ARDS). We aimed at investigating the association of circulating microRNAs (miRNAs) involved in post-transcriptional regulation of NLRP3-inflammasome pathways and lung radiological features among COVID-19-associated ARDS survivors.

Methods: We evaluated COVID-19-associated ARDS survivors at 4±2 months from clinical recovery. Patients were selected based on imaging pattern evolution according to chest high-resolution computerized tomography (HRCT) findings into “fully recovered” (FR), “pulmonary opacities” (PO) and “fibrosis-like lesions” (FL) according to radiological appearance. Plasma miRNA profiling was performed using real time quantitative polymerase chain reaction (RT-qPCR). The exosomal expression of NLRP3 inflammasome related miRNAs (miR-17-5p, miR-223-3p, miR-146a-5p) was evaluated.

Results: 31 patients (33% men, mean age 60±6 years, mean BMI 31.1±6.6 Kg/m²) were selected for the present study. No statistically significant differences between FR, PO and FL patterns were observed according to clinical features. NLRP3-inflammasome-related miRNAs such as miR-17-5p, miR-223-3p and miR-146a-5p were significantly up-regulated in patients with PO when compared to patients with FL. miR-146a-5p was also up-regulated in patients with FL than in FR.

Conclusions: In patients with long-term pulmonary radiological sequelae following COVID-19-associated ARDS, a down-regulation of miRNAs inhibiting NLRP3 (miR-17-5p, miR-146a-5p and miR-223-3p) correlated to fibrosis development in patients showing persistent hyper-reactivity to inflammatory stimulation. NLRP3-Inflammasome-related miRNAs could be a possible therapeutic target to prevent the fibrotic evolution of COVID-19-associated ARDS.

Exploring the role of FXR signaling in maintaining ileal mucosa integrity in subjects with altered glucose tolerance conditions

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Aim: Treatment with the FXR agonist obeticholic acid (OCA) has been found to improve glucose metabolism in type 2 diabetes (T2DM) subjects with mechanisms not completely elucidated. In the gut, FXR is mainly expressed in the ileum where promotes transcription of fibroblast growth factor-19 (FGF19) having positive effects on glucose homeostasis, and maintains gut barrier integrity by regulating tight-junction (TJ) proteins expression. Herein, we evaluate whether subjects with dysglycemic conditions exhibit a down-regulation of the intestinal FXR-FGF19-TJ axis and whether treatment with OCA may revert this aberration.

Methods: Levels of FXR, FGF19 and TJ proteins and pro-inflammatory cytokines were assessed in ileal mucosa specimens collected during colonoscopy from 53 subjects subdivided according to their glucose tolerance in: NGT (n=26), prediabetes (n=12) and T2DM (n=15). Effects of OCA treatment was assessed on ileal mucosa specimens of subjects with prediabetes or T2DM cultured in absence or presence of OCA for 6h.

Results: Ileal FXR protein and mRNA levels were progressively decreased in prediabetes (-26%) and T2DM (-34%) as compared to the NGT group (both P<0.05). Ileal FXR downregulation was paralleled by lower FGF19 expression and circulating levels (both P<0.05). Additionally, we observed a progressive decrease of proteins and mRNA levels of the TJ zonulin (ZO)-1, occludin and claudin-1 (P<0.05 for all) with an activation of pro-inflammatory pathways in the ileal mucosa of subjects with prediabetes and T2DM as compared to the NGT group. OCA treatment resulted in an up-regulation of FGF19 expression and release (both P<0.01), mRNA and protein levels of the TJ ZO-1, occludin and claudin-1 and in reduced pro-inflammatory cytokines synthesis and release (P<0.05 for all).

Conclusion: FXR stimulation by OCA treatment reverts the altered FGF19/TJ axis in subjects with prediabetes and T2DM, indicating intestinal FXR signaling as a novel target for prevention and/or treatment of T2DM.