anterior tibialis muscle, $p < 0.05$), cross section area of muscle fiber ($3,944 \pm 536$ vs. $3,066 \pm 211\ \mu m^2$, $p < 0.05$) and muscular protein content (211 ± 10 mg/g vs. 151 ± 9 mg/g, $p < 0.05$), inhibited myotropic markers expression (MuRF1 and MAFbx, $p < 0.05$), M1 macrophage infiltration ($p < 0.05$), muscular nitrotyrosine concentration (229.4 ± 11 vs. 320 ± 43 pmol/mg, $p < 0.05$) and normalized myogenic markers expression (MyoD1 and MHC, $p < 0.05$). Moreover, acute thalidomide incubation in TNF-α pretreated C2C12 myoblasts normalized the abnormal expressions of NFκBp65/iNOS, myotropic and myogenic markers ($p < 0.05$). However, the *in vitro* beneficial effects of thalidomide were reduced by concomitant pre-incubation of amioguanidine.

Conclusions: By down-regulating of NFκBp65-iNOS pathway, chronic thalidomide treatment decreased circulating $CD16^+$ (inflammatory) monocytes, inhibited muscular macrophage infiltration, suppressed myotropic signals and normalized myogenic signals expression. Taken together, thalidomide is a potential agent for treatment of cirrhotic muscle wasting.

FRI-064

Considerable aquaretic effects in experimental ascitic cirrhosis achieved through blunting of adrenergic function with α2A adrenergic receptor agonists

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Background and Aims: Catecholamines trigger proximal tubular fluid retention and decrease Na^+ and water delivery to the diluting segment of the Henle's loop, thereby reducing renal excretion of solute-free water. In advanced cirrhosis, non-osmotic hypersecretion of vasopressin (ADH) has a role in causing dilutional hyponatremia, but the advantage of ADH V_2 receptor antagonists is still controversial in the treatment of ascites. We meant to test the hypothesis that adrenergic hyperfunction might greatly contribute to water retention in experimental ascitic cirrhosis.

Methods: Hormonal status, renal function and tubular free-water reabsorption (TFWR) were assessed in six groups of rats with ascitic cirrhosis: rats with cirrhosis due to 13-week CCl_4 administration (group G1); cirrhotic rats receiving, from 11^{th} to 13^{th} weeks of CCl_4, daily diuretics alone (0.5 mg/kg furosemide plus 2 mg/kg K^+-canrenoate) (G2), or diuretics associated with guanfacine oral prodrug ($\alpha 2_A$ adrenergic receptor agonist and sympatholytic agent) 2 (G3), 7 (G4), or 10 mg/kg (G5), or diuretics plus SSP-004240F1 (V_2 receptor antagonist) 1 mg/kg (G6).

Results: Natriuresis was lower in G1 than in G2, G4 and G6 (all $P < 0.05$). Low-dose guanfacine, added to diuretics in G3, reduced serum norepinephrine from 423 ± 22 (in G2) to 211 ± 41 ng/L (in G3) ($P < 0.05$), plasma renin activity from 35 ± 8 to 9 ± 2 ng/mL/h (G2 vs. G3) ($P < 0.05$), and TFWR from 45 ± 8 to 20 ± 6 microL/min (G2 vs. G3) ($P < 0.01$). Compared to G1 (untreated ascitic cirrhosis) or G2 (ascitic cirrhosis treated with sole diuretics), TFWR was reduced to the same extent in groups G3 (low-dose guanfacine plus diuretics) and G6 (V_2 antagonist plus diuretics). TFWR correlated only with plasma aldosterone ($r = 0.51$, $P < 0.01$) and urinary potassium excretion ($r = 0.90$, $P < 0.001$).

Conclusions: In ascitic cirrhosis, reduced volaemia with secondary aldosteronism and adrenergic hyperfunction, especially when exacerbated by potassium-depleting diuretics (furosemide), contributes to tubular retention of water and dilutional hyponatremia. In this case, suitable doses of sympatholytic agents are as effective as V_2 antagonists when the aquaretic effect is needed.

FRI-065

Activation of proinflammatory citokines is involved in muscle wasting in mice model of carbon tetrachloride induced liver cirrhosis

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Background and Aims: Muscle wasting is a common feature in cirrhosis. Our aim was to investigated main molecular pathways contributing to muscle wasting in an experimental model of carbon tetrachloride induced liver cirrhosis (CCl4).

Methods: 12-week old male wild-type (FVB) mice were used. Cirrhosis was induced by intraperitoneal injection, twice a week, of CCl4 for 12 weeks according to a well-established model. Control animals received intraperitoneal injections of vehicle only (CTR). Twelve weeks after body weight was recorded and mice were sacrificed. Liver histological analysis was performed to confirm cirrhosis. Peripheral muscles were rapidly dissected at the sacrifice and weighed. Contractile properties of extensor digitorum longus (EDL) was studied in vitro in both isometric and isotonic conditions. Muscle samples were then rapidly stored for histological and biological analysis. mRNA and proteins were quantified using real time qRT-PCR and immunoblots.

Results: Results refer to fourteen mice, 7 CCl4 and 7 CTR. At the end of 12 weeks, cirrhosis was histological confirmed in all the CCl4 treated mice. Compared with CTR, CCl4 mice had a reduction in skeletal muscle weights, mainly in quadriceps and gastrocnemius. The average cross sectional area (CSA) and The total myofiber number of the quadriceps were significantly reduced in CCl_4 vs CTR. The frequency distribution of muscle fibers' revealed a shift toward a smaller size in CCl_4 treated mice. Muscle atrophy was not associated with a significant modification in muscles' contractile properties. Main molecular pathways involved in muscles atrophy were subsequently investigated. Neither myostatin, AKT and mTOR expressions was modified in CCL4 vs CTR. Upregulation of proinflammatory citochines TNFα and IL6, mRNA and protein expressions, were observed in CCl4 mice. Since TNF-alfa mediates its effect on muscle by activation of NF-kB, we have also investigated the expression of NFkB which was found to be significantly increased in CCL4 mice. An upregulation of MuRF-1 expression was also observed confirming activation of NF-κB-mediated gene transcription.

Conclusions: Muscle atrophy is a characteristic complication in experimental models of CCl4 induced cirrhosis. NF-κB overexpression in skeletal muscle is activated by inflammatory cytokines, particularly tumor necrosis factor α (TNFα), suggesting that inflammation is an important trigger of muscle atrophy in this model of liver cirrhosis.

FRI-066

Vascular morphology alterations during liver cirrhogenesis in rats

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