P41 – **BLF501 A synthetic compound as intestinal barrier protector and immunomodulator in inflammatory animal model of IBD**

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Background: The mucosal surfaces of the gastrointestinal tract is one of the main interfaces between the environment and the host. Its integrity loss predispose to infection. Moreover, intestinal epithelial cells are in continuous interplay with immune cells that are present in the gut lamina propria and the gut homeostasis results from an equilibrium of these components. The epithelial surfaces also provide absorptive functions for the intake of food. SGLT-1 is a Na^+/Glucose co-transporter. Accumulating data support the notion that SGLT1 orchestrates a number of fundamental cellular processes besides its absorptive function. Presented results show a novel role of SGLT-1: this protein modulates the immune response and protect barrier functions.
Objective: Recent findings indicate that the activation of SGLT-1 inhibits bacteria-induced inflammatory processes, assuming a role as an immunological player. This protective effect can be achieved with high dose oral glucose administration of 2.5 g/kg, with inevitable drawbacks. Our goal was to achieve the same result with a synthetic compound we developed BLF501.
Methodology: Chronic colitis model: Mice were treated with 2% dextran sodium salt ad libitum, then orally with BLF501 or glucose 2,5 g/kg. Intestinal mucosal epithelium integrity was assessed by histological analysis, cellular proliferation assays, real-time PCR gene expression assays and Western blot assays. Student's t-test and $\chi 2$ analyses were used for comparisons between groups.
Cellular assays: Caco2 monolayers were incubated with DSS 5% or with DSS 5% and BLF501 5 µg/l. Same treatments were performed in Caco-2 grown in coverslips on 24 well so to detect TJ protein with immunofluorescence methods. Intestinal lamina propria mononuclear cells (LPMC), isolated from biopsies taken from IBD patients, were stimulated with LPS with or without BLF-501. Transcripts for IFN-g and TNF-a were evaluated by Real-Time PCR.
SGLT-1 was silenced by small interfering RNA transfection using HT-29 cells.
Results: Oral administration of BLF-501 in a model of acute and chronic intestinal inflammation leads to inhibition of inflammatory response and restores intestinal epithelial barrier function. In IBD, the hyper-permeable properties of the intestinal epithelium appear to have interwined early roles in the initiation of this disease. In vitro we evaluated that BLF501 5 µg/l protects paracellular pathway against INF-γ and TNF-α damage, and that SGLT-1 activation by BLF501 stabilizes TJ-protein localization. In LPMCs from patients with IBD, incubation with BLF-501 cuts down RNA levels of IFN-g and TNF-a induced by LPS.
Conclusions: BLF501, acting on SGLT-1 at pharmacological dosages, represents a new pharmacological drug that can improve acute and chronic inflammation, given the cytoprotective and anti-inflammatory effects linked to SGLT-1 activation

References:

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-La Ferla et al., ChemMedChem (2010) 5, 1677–1680.