Effect of pancrestatin inhibition on colonic epithelial cells in an experimental model of ulcerative colitis

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Ulcerative colitis (UC), an inflammatory disorder of the colon, is characterized by impaired mucosal repair. Pancreastatin (PST), an intestinal epithelial cells-derived peptide highly expressed in colonic tissues of UC patients, binds to the glucose-regulated protein (GRP)78, which regulates ER signaling and survival pathways. Moreover, PST correlates with colitis severity a mucosal barrier dysfunction. However, the effect of PST on the colon mucosal healing process remains unknown. We investigated the impact of PST inhibition with pancreastatin inhibitor 8 (PSTI8) on colonic epithelial regeneration in an experimental model of UC induced by dextran sulfate sodium (DSS). C57BL/6 mice treated intrarectally with PSTi8 (2.5mg/mL/kg) or PBS for six-days received 5% DSS or water (control) for five-days. The disease activity index was assessed daily. Colonic tissues were tested for inflammatory and regenerative cytokines interleukin (IL)-6, IL-18, and IL-22. Genetic markers associated with microbial infiltration (resistin-like molecule, RELMβ), stem cells (fast-cycling Lgr5, and fetal-like Ly6a cells) and GRP78-mediated ER activation (ATF6), apoptosis (CHOP), cell survival and proliferation (Gsk3b and mTOR) were evaluated using qRT-PCR. In acute colitis, PST inhibition reduced disease activity with higher stool consistency ($p<0.01$), delayed bleeding onset (2-4 days,) lower macroscopic score (3.75-3, $p=0.05$), and lower RELMβ expression (1.7-0.38, $p<0.16$). DSS-mediated colitis was associated with elevated IL-6 and reduced IL-22 in PSTi8 and PBS-treated mice. No changes were noted between both groups. Contrastingly, PSTi8 treatment in basal conditions resulted in markedly elevated IL-22 concentration. Inflammation down-regulated Lgr5 expression and increased Ly6a in PBS-treated mice ($p<0.0001$). However, Ly6a expression was reduced in PSTi8-treated mice in colitis. Moreover, PST inhibition led to elevated ATF6, CHOP, Gsk3b, and mTOR expression in colitic PSTi8-treated compared to PSTi8-control mice. Yet no changes were noted between PBS-treated colitic mice and control mice. PST inhibition reduced disease severity and lowered inflammation while increasing ER stress, cell survival, and proliferation.