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Chromofungin ameliorates colitis and reduces endoplasmic reticulum stress/p53-apopotitic pathways

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Background:

Chromofungin (CHR), a chromogranin-A derived peptide, is produced by epithelial enterochromaffin cells and implicated in the development of ulcerative colitis (UC). In UC and macrophages, the transcription factor X-linked binding protein (XBP1) is a key component of the endoplasmic reticulum (ER) stress response, which induces intestinal mucosal injury and epithelial apoptosis. Intestinal epithelial apoptosis is mediated by p53-apoptotic pathway through the activation of p53-upregulated modulator of apoptosis (PUMA), Bcl-2-associated-X protein (BAX), Bcl-2 associated death promoter (BAD) and Bcl-2 antagonist/killer-1 (BAK1) proteins.

Objective:

to investigate whether CHR suppress inflammation-induced epithelial apoptosis through ER stress/p53-apoptotosis in colitis.

Methods:

mRNA expression of CHGA Exon-IV expressing CHR, XBP1, and p53-apoptotic pathways were quantified in healthy individuals and patients with active UC using q-RT-PCR. UC-related colitis was induced in C57BL/6 mice (7 weeks) by administrating DSS (5%, 5 days). Preventive CHR (2.5 mg/kg/day) or vehicle treatment started 1-day before colitis induction and lasted for 5-days. Disease activity index, histologic scores, exon-IV, XBP1, and p53-apoptotic pathways were assessed. Naïve peritoneal macrophages were exposed to CHR (200 ng/ml, 2h) and then to LPS (100 ng/ml, 6h) to promote classically activated macrophages (M1) and markers were studied

Results:

Exon-IV expression was decreased in active UC when compared to healthy and associated with an increase in XBP1, and PUMA, BAD, BAX and BAK. Moreover, CHR demonstrated a significant negative correlation with XBP1 and PUMA, BAD, BAX and BAK. Experimentally, CHR ameliorated the onset and severity of colitis, which associated was associated with a dramatic reduction in ER stress/p53-dependent apoptosis as reflected by *Xbp1, Puma, Bad, Bax and Bak1*. To gain mechanistic insights, compared to untreated group, LPS-stimulated macrophages treated with CHR demonstrated a significant decrease of ER stress and p53-apoptotic markers

Conclusion:

CHR decreases the severity of colitis and the inflammatory process via the suppression of mucosal and macrophages-related ER stress/p53-dependent apoptosis.