

P095 The genetic risk in ER stress and autophagy translates into quantifiable epithelial ER stress levels in IBD patients

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Background

The crucial role of the intestinal epithelium in IBD is underscored by association of epithelial homeostasis pathways such as bacterial sensing, autophagy and ER stress signaling. Reducing ER stress has therefore gained attention as a novel therapeutic approach. Nevertheless, molecular tools for patient stratification and therapeutic decision making are lacking.

Therefore, we wanted to study whether ER stress profiles could be quantified in patient-derived (ex vivo) intestinal epithelial cell (IEC) cultures.

Methods

IBD patients (n=35) undergoing endoscopic evaluation were selected based on the number of IBD-associated ER stress risk alleles in XBP1 (rs35873774) and ORMDL3 (rs2872507). In addition, autophagy risk alleles in ATG16L1 (rs2241880), IRGM (rs10065172 and rs4958847), MTMR3 (rs2412973), LRRK2(rs11175593) and ULK1 (rs12303764) were also investigated since autophagy is a compensatory ER stress resolving mechanism. For this second analysis, patients were grouped into genetic risk quartiles based on the combined ER stress and autophagy risk allele (RA) distribution (Q1: ≤4 RA, Q2: 5 RA, Q3: 6 RA, Q4: ≥7 RA). As described previously, we were able to culture IECs derived from mucosal biopsies. These cultures were subjected to ER stress using thapsigargin (Tg, 0.4 μM) and the ER stress response was measured in cell lysates with a binding immunoglobulin protein (BiP)-ELISA. Statistical analyses were performed with Mann-Whitney U tests (α=0.05).

Results

Median [IQR] Tg-mediated BiP-induction (vs. untreated) read-outs were 2.67 [1.01–6.07], 1.87 [1.50–3.16], 1.70 [1.32–2.41] and 4.48 [3.76–4.64] in IECs from patients carrying 0 (n=4), 1 (n=17), 2 (n=11) or 3 (n=3) ER stress risk alleles, respectively. Patients with 3 ER-stress-related risk alleles had significantly more epithelial ER stress (BiP) induction rates when compared to patients with 1 or 2 risk alleles (p=0.026 and 0.043, respectively). When risk alleles in autophagy genes were added, median [IQR] Tg-mediated BiP-induction read-outs were 1.34 [1.08–1.91], 2.16 [1.68–4.05], 3.60 [1.39–4.48] and 2.41 [1.61–3.27] in IECs from patients belonging to Q1 to Q4, respectively. Patients in Q2 (n=10), Q3 (n=7) and Q4 (n=10) had significantly higher ER stress induction rates when compared to Q1 (n=8) (p=0.034, 0.040 and 0.034, respectively).

Conclusion

IBD patients with an increased genetic risk for ER stress and autophagy have more ER stress as measured in patient-derived IECs. These patients would benefit most from ER stress reducing therapies such as tauroursodeoxycholic acid (TUDCA), which has already shown to reduce inflammation in murine IBD models. We thus present a novel tool for molecular characterization of IBD patients for which pilot studies should be considered.