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AUTOPHAGY, BUT NOT THE UNFOLDED PROTEIN RESPONSE, REGULATES THE EXPRESSION OF IL-23 IN THE GUT OF PATIENTS WITH ANKYLOSING SPONDYLITIS AND SUBCLINICAL GUT INFLAMMATION

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Background: IL-23 is a heterodimeric cytokine that has been implicated in the pathogenesis of Ankylosing Spondylitis (AS). High serum and tissue levels for this cytokine have been demonstrated in AS and correlated with entheseal inflammation but the mechanisms responsible for its over-expression are currently not clear.
Objectives: The aim of the study was to clarify the immunological mechanisms underlying the increased IL-23 expression in the gut of AS patients.
Methods: Consecutive gut biopsies from 20 HLA-B27+ AS patients and 10 normal subjects were considered for the present study. The occurrence of HLA-B27 misfolding was studied by assessing the co-localization of HLA-B heavy chains (HCs) with the E3 ubiquitin ligase synovial apoptosis inhibitor 1 (SYVN1) . Unfolded protein response (UPR) and autophagy were studied by rt-PCR and immunohistochemistry. In order to evaluate the role of UPR and autophagy in regulating the production of IL-23p19 by lamina propria macrophages and dendritic cells, isolated lamina propria mononuclear cells were stimulated with LPS with or without pre-incubation with thapsigargin (1 μM) (to activate UPR) and/or 3-methyl-adenine (100ug/ml, to inhibit autophagy).
Results: Two monoclonal antibodies (W6/32 and HC10), specific for β2m-free HLA-B and C HCs (FHCs), including misfolded forms of HLA-B27, were used. Both SYVN1 and free and conformational heavy chains were significantly up-regulated in the gut of AS patients. A strong intracellular co-localization of SYVN1 and FHCs but not a significant over-expression of UPR genes (HSPA5, PDIA4, GADD34, PERK, ATF6, XBP-1) was observed only in the gut of AS patients. Conversely, a strong up-regulation of the genes involved in the autophagy pathway (ATG5, ATG12, ATG16L1, IRGM and MAP1LC3) was observed only in the gut of AS patients and was correlated with the levels of IL-23p19. Immunohistochemical analysis showed an increased expression of LC3II, ATG5 and ATG12 in the ileum of AS patients. LC3 expression was observed in particular among infiltrating mononuclear cells and epithelial cells resembling Paneth cells. The occurrence of active autophagy was also confirmed, by the confocal microscopy demonstration of intense co-localization of ATG5 and LC3II in the gut of AS patients. Finally, in vitro studies demonstrated that inhibition of autophagy but not induction of UPR increases the expression of IL-23 on isolated lamina propria mononuclear cells.
Conclusions: Our data strongly suggest that HLA-B27 misfolding occurs in the gut of AS patients but appears to be accompanied by intense activation of autophagy rather than an unfolded protein response. Activation of autophagy appears to be associated with up-regulation of IL-23 in the gut of AS patients. Since the important role of autophagy in the defense against microorganisms, our results could provide an intriguing link between gut microbiome and IL-23 over-expression observed in AS patients.

Disclosure of Interest: None Declared