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INTERRUPT CANCERS IN PATIENTS WITH HEREDITARY GASTROINTESTINAL SYNDROMES AFTER ONE YEAR OF THE SARS-COV-2 PANDEMIC
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Background: Hereditary colorectal cancer syndromes require timely endoscopic surveillance.

Aims: This study evaluated the impact of Italian gastroenterologists to the surveillance of hereditary colorectal cancer syndromes in Italy. The worst repercussion reported up to five interval cancers.

Materials and methods: All members affiliated with the leading gastroenterology Italian societies (AIGO, SIED, and SIGE) received an online questionnaire. Data collection occurred between March 8, 2021, and May 3, 2021.

Results: One hundred and twenty-one clinicians from 96 Italian hospitals answered, not necessarily experts in the field (males: 73, 60.3%; average clinical experience: 20.1 ± 11.9 years). Many patients were enrolled in the surveillance of hereditary colorectal cancer syndromes. Almost half of the clinicians (45.3%) reported a delay in the surveillance (median: 4–12 months). Ultimately, 30.6% detected one interval colorectal cancer or more in at least one of their patients.

Conclusion: The SARS-CoV-2 pandemic directly affected the surveillance of hereditary colorectal cancer syndromes in Italy. The worst repercussion associated with COVID-19 and can persist long after the respiratory infection has cleared. We previously observed that ECs infection and/or infection of COVID-19 patients, 2) There is increased expression of vWF, PAI-1, VCAM-1, and ICAM-1 levels in the intestine. This is consistent with the recent report showing that cathepsin inhibition in ACE and an increase in CTSB and CTSL expression during active inflammation compared to healthy controls. Viral RNA expression did not correlate with ACE2 expression in cultured HMVECs. Treatment of HMVECs with S1 and S2 proteins upregulated VWF, PAI-1, VCAM-1, and E-selectin mRNA expression levels.

Tu1110
EXPRESSION OF EPITHELIAL PROTEASES PREDICTS SARS-COV-2 ENTRY IN HUMAN ENTEROIDS
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Introduction: Coronavirus Disease 2019 (COVID-19) is an ongoing public health crisis that has sickened or precipitated death in millions. The etiologic agent of COVID-19, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), infects the intestinal epithelium and can persist long after the respiratory infection has cleared. We previously observed that permissive SARS-CoV-2 levels varied by individual donors and did not correlate positively with ACE2, the cognate SARS-CoV-2 receptor. Therefore, we aimed to elucidate host factors that influence viral infection in the intestine.

Methods: Published dataset GSE75214 was downloaded and expression levels of select genes were queried. Primary human ileal enteroids (enteroids), derived from healthy donors and patients with Cronkh’s disease (CD), were grown on 2D transwells until confluent. Cells were differentiated for 3d and cultured for 0-24 hr. Studies: 1) cell viability and proliferation; 2) induction of HMVEC cell damage.

Results: Small intestine biopsy samples from CD patients demonstrated a reduction in ACE and an increase in CTSB and CTSL expression during active inflammation compared to healthy controls. Viral RNA expression did not correlate with ACE2 expression in cultured enteroids. A subset of CD enteroids exhibited enhanced protease expression (TMPRSS2, TMPRSS4, and CTSL), each of which correlated with higher viral RNA levels (P=0.04, P=0.002, respectively).

Expression of these proteases was higher in the pre-infection for the sample subset. Principle component analysis of uninfected expression data demonstrated these samples clustered separately from the others, with the difference driven by TMPRSS2, TMPRSS4, and CTSL. Modeling viral RNA levels based on gene expression revealed expression levels of these proteases as a predictive expression signature. Conclusions: Host protease expression can predict SARS-CoV-2 infection and represent potential therapeutic targets.
RNA data from dataset GSE75214 demonstrating reduced ACE2 and increased CTSB and CTSL in patients with Crohn’s disease during active inflammation compared to healthy controls.

|       | Pre-Infection | Post-Infection |
|-------|---------------|----------------|
| Gene  |               |                |
| ACE2  |               |                |
| TMPRSS2|               |                |
| CTSL  |               |                |
| CTSB  |               |                |

Enteroids from healthy control donors and patients with Crohn’s disease were grown in 2D transwells and expression of indicated genes was assessed in pre-infection (A) and after infection with VSV-SARS-CoV-2 (B).

Tu111

REGULATION OF INTESTINAL ACE2 EXPRESSION BY THE BILE ACID RECEPTOR GPBAR1 IS MEDIATED BY A GBPBAR1/GLP-1/GLP-1R AXIS

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Background: ACE2 is a carboxypeptidase homolog to the dipeptidase ACE but with different substrate specificity, while ACE2, a principal activator of ACE, catalyzes the hydrolysis of angiotensin I to angiotensin II. This study aimed to analyze the role of the bile acid receptor GPBAR1, mainly expressed in the liver, in the regulation of intestinal ACE2 expression.

Methods: Enteroids from healthy control donors and patients with Crohn’s disease were grown in 2D transwells and expression of indicated genes was assessed in pre-infection (A) and after infection with VSV-SARS-CoV-2 (B).

Results: The inflammatory stimulus increased the expression of Ace2 in HT29 cells and in colonic mucosa of mice according to the data obtained in human samples from patients with IBD. GPBAR1 agonism by BAR501 relieved inflammation both in vitro and in vivo but depleted of intestinal macrophages via administration of clodronate liposomes, suggesting that macrophages play a pivotal role in inhibition of bacterial translocation to the liver.

Conclusions: GPBAR1/GLP-1/GLP-1R axis plays a crucial role in the regulation of Ace2 by GPBAR1/GLP-1/GLP-1R axis.

Tu1112

THE MOLECULAR REASON WHY THE GUT COMMENSAL PATHOBIONT KLEBSIELLA PNEUMONIAE DISRUPTS THE EPITHELIAL BARRIER AND TRANSLATES TO THE LIVER

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Introduction: Although Klebsiella pneumoniae is a gut commensal bacterium, it disrupts the epithelial barrier to translate and cause liver inflammatory responses (Nature Microbiol. 6:492, 2019). However, it is uncertain why K. pneumoniae can disrupt the epithelial barrier and translocate to the liver. We detected translocated K. pneumoniae in the mice of mice depleted of intestinal macrophages via administration of clodronate liposomes, suggesting that macrophages play a pivotal role in inhibition of bacterial translocation to the liver.

The present study sought to elucidate the mechanisms by which macrophages inhibit bacterial translocation. Methods: Klebsiella pneumoniae ATCC43816 was used for infection experiments. In vitro K. pneumoniae infection models were constructed using transwell co-culture systems with Caco-2 epithelial cells and RAW264.7 macrophages. Young (15-week-old) and aging (17-week-old) mice were given drinking water containing antibiotics for 4 weeks prior to K. pneumoniae infection. Cytokine array analysis was performed using an ELISA-based quantitative array platform.

Results: In macrophage-depleted specific pathogen-free young mice administered clodronate liposomes, liver injury with bleeding was detected by hematoxylin and eosin staining, and translocated K. pneumoniae was detected by culture of liver tissue. Additionally, K. pneumoniae invading cecal epithelial cells was detected in these mice by immunostaining analysis. In vivo K. pneumoniae infection models, the invading number of bacteria in Caco-2 cells was significantly decreased in the presence of RAW264.7 cells. Growth arrest-specific 6 (Gas6) was released by RAW264.7 cells that recognized K. pneumoniae infection. Releasing Gas6 co-localized with the TAM receptor tyrosine kinase Axl and increased the expression levels of tight junction proteins, ZO-1 and Occludin, in Caco-2 cells.

Conclusions: Gas6 expression determined by the aging-related decline in intestinal macrophages allows K. pneumoniae to invade gut epithelial cells and facilitates its translocation to the liver.

Tu1113

BIFIDOBACTERIUM BIFIDUM CAUSES AN ENHANCEMENT OF INTESTINAL EPITHELIAL TIGHT JUNCTION BARRIER BY A NOVEL MECHANISM INVOLVING PEROXISOME PROLIFERATION-ACTIVATED RECEPTOR GAMMA (PPAR-γ)

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Background: Bifidobacteria are the most commonly utilized probiotics that have been shown to protect against intestinal inflammation, in part, by enhancing the intestinal epithelial tight junction (TJ) barrier function. However, the association between BB and PPAR-γ is uncertain. The aim of this study was to examine the involvement of PPAR-γ in mediating the enhancement of the intestinal epithelial TJ barrier by BB.

Methods: BiP and PPAR-γ pathway in Caco-2 cells was significantly increased in the presence of RAW264.7 cells. Gas6 expression determined by the aging-related decline in intestinal macrophages allows K. pneumoniae to invade gut epithelial cells and facilitates its translocation to the liver.