growth factor 19 (FGF19) in sera (Figure 1A-C. The association of clostridia rich microbiota with BA synthesis and excretion in IBS d patients a the histogram of the distribution of total fecal BA level in recruited subjects b c concentrations of C4). Their fecal metagenomes showed increased abundances of Clostridia and BA-transforming genomes (bdhA and baiA). The increase of Clostridia (e.g. Clostridium) was positively associated with the levels of fecal BAs and serum C4, while being negatively correlated with serum FGF19 (Figure 1D, E). However, there is no big difference in BA profile and BA-transforming microbiome found in other IBS-D patients with normal BA excretion (grouped as BA-I/BSD) relative to controls. Further, transplantation of Clostridia-rich microbiota from IBS-D donors and introduction of a BA-transforming Clostridium species both enhanced levels of serum C4 and hepatic conjugated BAs in mice and reduced ileal FGF19 expression. Inhibition of Clostridium species by vancomycin yielded opposite findings. Moreover, Clostridia-derived BAs, like conjugated and free ursodeoxycholic acid, were also found to be significantly suppressed intestinal FGF19 expression in vitro and in vivo.

Conclusions The Clostridia-rich microbiota contributes to excessive BA excretion in IBS-D patients. This study provided the basis for more precise clinical diagnosis and management for IBS-D.

**ROLE OF ADHESIVE-INVASIVE E. COLI IN INFLAMMATORY BOWEL DISEASE – EPIDEMIOLOGY, GENETICS AND THERAPEUTICS**

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**Background** Adherent-invasive Escherichia Coli (AIEC) colonizes mucosa of patients with Crohn’s disease (CD). Fecal microbiota transplantation (FMT) has been reported to be effective in treating CD but the response rates are variable. We investigated the prevalence of AIEC in Chinese population and explored the impact of AIEC on FMT efficacy.

**Methods** AIEC strains were isolated from ileal tissues of Chinese Crohn’s disease patients (n=64) and healthy subjects (n=53) by selection culture and protection assay in Intestine-407 cell lines and their genomes sequenced. Level of AIEC colonization was assessed by selective culture and Fluorescence in situ hybridization. Human ileal tissue and mice feces were collected for 16S rRNA sequencing.

**Results** Prevalence of AIEC was significantly higher in mucosa of CD subjects than healthy controls (p<0.05). Significant loss of Megamonas and Veillonella was observed in AIEC-positive ileal tissues, compared with AIEC-negative and healthy tissues. The majority of AIEC isolates belonged to B2 phylogroup. 43.9% of AIEC isolates were multi-drug-resistant. The Chinese AIEC isolates possessed a significantly higher prevalence of Quinolone-, Macrolide-, Sulphonamide-, Trimethoprim-, and Tetracycline-resistant genes, compared with previously reported strains. These anti-biotics resistant strains possessed significantly higher invasion properties than did non-resistant strains. In mice, FMT was not able to eradicate AIEC from the colon. After FMT, K12 (a non-invasive E. coli strain) colonised mice, but not AIEC-infected mice, showed ameliorated colitis with elongated colon, improved colonic histology and decreased fecal Lcn-2 levels. FMT increased microbial diversity in K12-colonised mice but not in AIEC-infected mice. The proportion of donor-derived microbes in K12-colonised mice was significantly higher than in AIEC-infected mice, where a lack of engraftment of Fecalibacterium prausnitzii, Akkermansia muciniphila and Allobaculum was seen in AIEC-infected mice.

**Conclusions** AIEC is a risk factor for CD in the Chinese population. The presence of AIEC was sufficient to compromise the efficacy of FMT by hindering the engraftment of beneficial bacteria, leading to incomplete recovery of inflammation.

**GUT MICROBIOTA MODULATES THE CHEMOPREVENTIVE EFFICACY OF ASPIRIN ON COLORECTAL CANCER THROUGH IMPACT ON ASPIRIN BIOAVAILABILITY**

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**Background** The gut microbiota, a pivotal regulator in colorectal cancer (CRC) development, is profoundly involved in drug metabolism. This study aims to decipher the role of the gut microbiota in aspirin-mediated chemoprevention of CRC in mice.

**Methods** Two models, azoxymethane (AOM, 10 mg/kg) and dextran sulfate sodium (DSS, 2.0%) induced CRC and APC<sup>min+/−</sup> induced CRC, were used in this study. Mice were orally administered aspirin (400 mg/L) with or without pre-antibiotics cocktail (0.1 g/L vancomycin, 0.2 g/L of ampicillin, metronidazole and neomycin). AOM/DSS-treated germ-free mice and conventionally reared germ-free mice (conventionalized mice) were used for validation. Aspirin concentration was estimated by ultra-high performance liquid chromatography (UHPLC). Aspirin-degrading microbes were identified by UHPLC and 16S rRNA gene sequencing.

**Results** The tumor number and load were significantly reduced after aspirin treatment in antibiotics-treated mice in both AOM/DSS-treated and APC<sup>min+/−</sup> models, but not significantly changed in non-antibiotics-treated mice. Consistently, aspirin-treated germ-free mice exhibited significantly less tumor number and load compared to those not receiving aspirin, which was not seen in conventionalized mice, suggesting that gut microbiota impairs the chemopreventive efficacy of aspirin on CRC. UHPLC analysis revealed that plasma levels of aspirin were significantly higher in microbiota-depleted mice compared to microbiota-intact mice, indicating that gut microbiota limits aspirin bioavailability. Co-incubation of aspirin-containing medium and bacteria showed that aspirin levels in medium were significantly reduced when incubated with the fecal commensal bacteria from microbiota-intact mice compared to those from microbiota-depleted mice. Screening 1,093 bacterial colonies isolated from the feces of microbiota-intact mice.
revealed that *Lysinibacillus sphaericus* significantly reduced the aspirin levels in aspirin-containing medium. Moreover, the germ-free mice monocolonized with *Lysinibacillus sphaericus* showed significantly lower plasma aspirin levels post aspirin administration relative to the intact germ-free mice, confirming a role of this bacterium in reducing aspirin bioavailability.

**Conclusions** Gut microbiota modulates the chemopreventive efficacy of aspirin on CRC through impact on aspirin bioavailability in mice. *Lysinibacillus sphaericus* may play a critical role in aspirin degradation in the gut.

**Background** Rapid proliferation and glucose metabolism remodeling are hallmarks of cancers. Long non-coding RNAs (lncRNAs) are potentially involved in Warburg effect. We aimed to identify oncogenic lncRNAs that significantly affect the development of esophageal squamous cell carcinoma (ESCC) and investigate the metabolism-related mechanisms.

**Methods** Bioinformatics analysis and siRNA library screening were used to pinpoint lncRNAs that significantly affected cell glycolysis and proliferation. RNAscope(R) in situ hybridization and qRT-PCR assays were performed in clinical samples to investigate expression levels and clinical relevance of the lncRNA. RNA interference and CRISPR-Cas9 were used to explore the functional roles of the lncRNA. *In vivo*, cell-based and patient-derived xenograft (PDX) models were used. Extracellular acidification rate and 13C-labeled intracellular metabolites were determined. RNA pull-down, MS2-Tagged RNA affinity purification, RNA-binding protein immunoprecipitation and cross-linking immunoprecipitation were performed to identify lncRNA associated proteins and related mechanisms.

**Results** The lncRNA LOC148709 was identified as a metabolism-related lncRNA. Increased expression of LOC148709 was observed in ESCC and was correlated with poor prognosis. LOC148709 knockdown significantly decreased cell proliferation and glycolysis. Mechanistically, LOC148709 was directly associated with PFKFB3 and significantly affected PFKFB3 stability. LOC148709 interacted mainly with the C-terminal fragment of PFKFB3 and the T5 (2031–2321) fragment of LOC148709 mediated the interaction with PFKFB3. Through inhibiting K302 ubiquitination, LOC148709 protected PFKFB3 from proteasomal degradation, which subsequently activated glycolytic flux and promoted cell cycle progression by regulating p27 and CDK1. P53 could bind to the LOC148709 promoter and repress its transcription, p53 loss or mutation triggered striking LOC148709 upregulation. Multiple micro-environmental factors, including hypoxia and oncogenic stress, were also involved in the LOC148709 regulatory network via affecting the status of p53. Notably, our patient-derived xenograft (PDX) model studies demonstrated that LOC148709 knockdown dramatically impaired tumor growth.

**Conclusions** The lncRNA LOC148709 plays an essential role in glycolytic reprogramming by binding to and stabilizing PFKFB3. This study identified a novel metabolism-related lncRNA and revealed a novel mechanism underlying lncRNA-mediated cancer metabolism remodeling. Translational studies further implicated that LOC148709 is a promising biomarker for cancer diagnosis and therapy.

**Background** The incidence of colorectal cancer (CRC) is rapidly rising worldwide. Understanding the molecular mechanism underlying CRC pathogenesis is critical to uncover novel drug targets and diagnostics for this disease. Our preliminary work identified SCNN1B as an outlier down-regulated in CRC. SCNN1B mRNA and protein expression were down-regulated in primary CRC and CRC cell lines, suggesting that it might function as a tumor suppressor in CRC.

**Methods** Clinical significance of SCNN1B in evaluated using tissue microarray cohort of CRC (N=153). Biological function of SCNN1B was investigated in CRC cells lines using cell proliferation, apoptosis, cell cycle, cell migration and subcutaneous xenograft assays. Molecular mechanism of SCNN1B was evaluated by Gene Set Enrichment Analysis (GSEA), and assessment of Ras-Raf-MEK-ERK pathways.

**Results** In a pilot tissue microarray cohort of CRC (N=153), SCNN1B protein expression was an independent prognostic factor predicting favorable patient survival. Ecotopic expression of SCNN1B in two CRC cell lines inhibited cell proliferation, induced apoptosis and cell cycle arrest, and suppressed cell migration. Gene Set Enrichment Analysis (GSEA) revealed that SCNN1B expression was associated with KRAS signaling pathway. SCNN1B inhibited p-MEK/p-ERK and SRE luciferase activity, confirming blockade of Ras-Raf-MEK-ERK oncogenic signaling. Mechanistically, SCNN1B suppressed the activation of c-Raf by inducing its inhibitory phosphorylation. Ecotopic expression of c-Raf rescued cell proliferation and colony formation in SCNN1B-overexpressed CRC cells, confirming c-Raf as a molecular target of SCNN1B.

**Conclusions** SCNN1B inhibits colorectal tumorigenesis via inhibition of RAS-MEK-ERK signalling. SCNN1B expression may serve as an independent prognostic biomarker for CRC patients.