Background Tumour cells often exhibit altered energy metabolism for tumour progression, but whether long noncoding RNAs (lncRNAs) are involved in this process remains elusive. We aimed to identify novel lncRNAs significantly affecting the development of Esophageal Squamous Cell Carcinoma (ESCC) and investigate the metabolism-related mechanisms.

Methods A siRNA library was established using top 100 lncRNAs highly expressed in ESCC screened from TCGA database and transfected into ESCC cells to identify lncRNAs that significantly affected cell glucose metabolism and proliferation. RNAscope *in situ* hybridization, qRT-PCR and RNAi assays were performed to investigate the functional role of lncRNA AGPG (*Actin Gamma 1 Pseudogene*) and clinical relevance. *In vivo*, cell-based and patient-derived xenograft (PDX) models were used to further explore roles of AGPG in ESCC tumorigenesis. RNA pull-down, mass spectrometry analyses, western blot and RNA-binding protein immunoprecipitation (RIP) were performed to identify interaction proteins and related mechanisms.

Results We identified that lncRNA AGPG was markedly increased in ESCC and correlated with poor prognosis. AGPG depletion significantly repressed ESCC cell proliferation and glycolytic activity including decreased glucose uptake and increased lactate production. *In vivo* experiments further showed that silencing AGPG decreased tumours growth in cell-based xenografts and PDX models. Mechanistically, AGPG could interact with 6-phosphofructo-2-kinase/fructose-2, 6-biphosphatase 3 (PFKFB3) in the nucleus, thus enhancing PFKFB3 stability via preventing its ubiquitination and proteosomal degradation. Subsequently, AGPG-PFKFB3 promoted glycolysis and dysregulated cell cycle by suppressing p27 and over-activating cyclin-dependent kinase 1(CDK1), thereby leading to G1/S cell cycle progression. Additionally, TP53 could bind to the promoter of AGPG to negatively regulate its expression.

Conclusions We first identified that AGPG, which is regulated by TP53, is playing a pivotal role in glucose metabolism remodelling and cell proliferation through enhancing PFKFB3 stability, thus facilitating the development of ESCC. Collectively, our study suggests that TP53-AGPG-PFKFB3 axis might serve as potential biomarkers and therapeutic targets in ESCC.

10.1136/gutjnl-2018-IDDFAbstracts.25 IDDF2018-ABS-0191 ABERRANT GUT MUCOSAL MICROBIOME SIGNATURES OF MALAYSIAN COLORECTAL CANCER PATIENTS

¹Muhammad Afiq Osman*, ¹Hui-min Neoh, ¹Nurul Syakima Ab Mutalib, ¹Siok Fong Chin, ²Luqman Mazlan, ²Andee Dzulkarnaen Zakaria, ³Raja Affendi Raja Ali, ³Chai Soon Ngiu, ¹Mia Yang Ang, ¹Rahman Jamal. ¹UKM Medical Molecular Biology Institute, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia; ²Department of Surgery, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia; ³Department of Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

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Background The human gut holds the densest microbiome ecosystem essential in maintaining healthy host physiology, whereby disruption of this ecosystem has been linked to the development of colorectal cancer (CRC). Accordingly, 16S rRNA sequencing studies on CRC gut mucosal tissues have found bacteria such as *Fusobacterium nucleatum* and *Bacteroides fragilis* to be over-represented in CRC patients from various regions in the world. As CRC is one of the most

common malignancies in Malaysia, this study was carried out to profile the gut microbiome and identify over-represented bacteria in Malaysian CRC patients.

Methods This study was carried out from 2014 till 2017, where a total of 18 CRC patients and 18 healthy controls from UKM Medical Centre, Kuala Lumpur, Malaysia were included. 16S rRNA sequencing of gut mucosal tissue samples targeting the 16S rRNA V3/V4 regions was performed with an Illumina MiSeq(R) sequencer, while diversity analyses were carried out using QIIME to determine differences between gut mucosal microbiome profile of CRC patients compared to healthy controls.

Results We observed a significant difference in gut mucosal microbiome composition of CRC patients compared to healthy controls. Higher relative abundance of *Fusobacteria* and *Verrucomicrobia* phyla were detected. Further linear discriminant analysis (LDA) effect size analysis showed significant enrichment of *Fusobacterium*, *Parvimonas*, *Akkermansia* and *Peptostreptococcus* genera in CRC patients. Interestingly, these bacterial genera were found to be enriched in all CRC cases of this study, regardless of patient demographics and CRC staging.

Conclusions In summary, we successfully characterised the gut mucosa-associated microbiome of Malaysian CRC patients. Significant abundance of *Fusobacterium*, *Parvimonas*, *Akkermansia*, and *Peptostreptococcus* in these patients indicates the importance of these genera towards colorectal carcinogenesis. Nevertheless, a larger study to test the reproducibility of these results will be crucial before these bacteria could be utilised as screening biomarkers for CRC in Malaysians.

10.1136/gutjnl-2018-IDDFAbstracts.25 IDDF2018-ABS-0193 CYTOKINE IL9 MEDIATES THE PATHOGENESIS OF CROHN'S DISEASE THROUGH THE MIR21-CLDN8 PATHWAY

Shenghong Zhang*, Li Li, Shanshan Huang, Ting Feng, Gaoshi Zhou, Minhu Chen. Department of Gastroenterology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

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Background Cytokine interleukin-9 (IL9) plays an essential role in the pathogenesis of inflammatory bowel disease. However, the molecular mechanism underlying the IL9 pathway remains unknown. Here, we initiate a series of studies to characterise the essential components of this pathway.

Methods The expression of IL9 in colon biopsies from Crohn's disease (CD) and controls were examined by Western blot and immunohistochemistry. The trinitrobenzene sulfonic acid (TNBS)-induced colitis model was used to verify the therapeutic efficiency of anti-IL9 mAb. Bioinformatics analysis was performed to predict putative candidate microRNAs that mediate the crosstalk between the IL9 proinflammatory signal and the downstream target gene in intestinal barrier function. Caco-2, NCM460 and SW480 cells were used to assess the specific pathway *in vitro*.

Results We demonstrated the proinflammatory role of IL9 in colonic mucosa of patients with Crohn's disease (CD). Animals treated with anti-IL9 exhibited significant recovery of many cardinal signs of colitis. The junction complex protein Claudin 8 (CLDN8) was identified as a critical downstream component of the IL9 inflammatory cascade. Anti-IL9 treatment alleviated TNBS-induced colitis by restoring CLDN8 levels in colonic

Abstract IDDF2018-ABS-0193 Figure 1

mucosa (figure 1). Notably, we characterised microRNA miR21 as a critical player that mediates the crosstalk between the proinflammatory IL9 and the downstream CLDN8 in both *in vitro* and *in vivo* models.

Conclusions Our results, for the first time, uncover a critical role of miR21 and CLDN8 in the complex network that IL9 regulates the intestinal epithelium barrier in the pathogenesis of CD. Interventional blockade of the IL9-miR21-CLDN8 pathway could be a novel therapeutic approach for the management of CD.

IDDF2018-ABS-0196 EXOSOMES DERIVED FROM HUMAN IPSC-MSCS PROTECTED AGAINST TNBS-INDUCED COLITIS

Ting Feng*, Yun Qiu, Shenghong Zhang, Rui Feng, Hongsheng Yang, Ren Mao, Baili Chen, Yao He, Zhirong Zeng, Minhu Chen. The First Affiliated Hospital of Sun Yat-sen University, China

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Background Growing evidence indicates that exosomes derived from human MSCs (MSCs-Exo) have a favourable efficacy on several immune disease models. Thus, we assessed their efficacy on a chemically induced colitis mouse model.

Methods hiPSC-MSCs were characterised by microscopy and flow cytometry. hiPSC-MSCs-Exo were isolated by ultracentrifugation and identified by transmission electron microscopy and Western blot. The trinitrobenzenesulfonic acid (TNBS)-induced colitis mouse model was used. Different doses of hiPSC-MSCs-Exo or iPSC-MSCs were injected into BALB/C mice. Survival rates, colitis symptoms, and macroscopic and histologic scores were evaluated. CD4⁺T helper (Th) cell subgroups in lymphocytes were quantitated by flow cytometry. Furthermore, stem cell markers Lgr5 and Bmi1 and proliferation index ki67 were analysed by immunofluorescence staining in colonic tissues.

Results Intraperitoneally injected hiPSC-MSCs-Exo alleviated TNBS-induced colitis by increasing survival rates, relieving symptoms, and improving macroscopic and histologic scores compared with mice treated with hiPSC-MSCs in a dose-dependent manner. Increases in regulatory T cells (Tregs) and decreases in Th1 cells, Th17 cells, and several pro-inflammatory cytokines were observed with hiPSC-MSCs-Exo treatment. It was also shown that the high dose-hiPSC-MSCs-Exo could increase the numbers of Lgr5⁺ and Bmi1⁺ cells and promote cell proliferation in colon.

Conclusions hiPSC-MSCs-Exo protected against experimental colitis by correcting Treg/Th17/Th1 imbalances, thus providing a more favouring condition for colonic stem cell.