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## DISSECTING THE MOLECULAR MECHANISM AND CLINICAL SIGNIFICANCE FOR REGULATING THE MALIGNANT PROGRESSION OF GASTRIC CANCER BY HIPK3

Xiao-Jing Luo*, Qi-Nian Wu, Ze-Xian Liu, Rui-Hua Xu. *Sun Yat-Sen University Cancer Center, China*

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**Background** Gastric cancer (GC) is one of the most threatening malignant diseases in east Asia with largely unknown mechanisms. Protein kinases and their signaling pathways were closely related to cancer occurrence and progression. We decide to investigate the role of related protein kinases and their signaling pathways in GC.

**Methods** We analyze the protein kinases activity using the phosphorylated proteomic data of gastric cancer and find that the substrates of HIPK family with abnormal phosphorylated levels. HIPK3 with less known function and mechanisms is chosen for further research, and its low expression in GC is confirmed by qPCR and immunohistochemistry analysis in a large GC patient cohort. MTS assay, colony formation assay, transwell migration and invasion assays are performed after ectopic express or knockdown of HIPK3 in vitro. Additionally, subcutaneous xenograft and in situ xenograft models are built in vivo. We detect the HIPK3 mRNA and protein level in cisplatin-resistant GC cells by qPCR and western blotting and measure the tolerance of cisplatin after overexpression of HIPK3. Coimmunopreicipitation and mass spectrometry analysis identify the interaction between HIPK3 and MAP7. Immunofluorescence confirms their co-localization. Downstream mechanisms were examined by regular molecular biological methods.

**Results** We discovered the aberrant phosphorylation of substrates for HIPK family kinases based on the profiled gastric cancer phosphoproteome data and bioinformatical pipeline for kinase activity analysis. Then the low expression of HIPK3 in the gastric tumor was validated and correlated with patient overall survival. Cell line and mouse model experiments for gastric cancer showed that reducing the HIPK3 expression promoted the growth, proliferation, migration, invasion and metastasis, and high expression of HIPK3 could reverse the cisplatin resistance. Further molecular mechanism revealed that HIPK3 might regulate the progression of gastric cancer through phosphorylating MSH6 to regulate DNA mismatch repair and interaction with MAP7 to regulate cell morphology.

**Conclusions** Our study explicit the potential of HIPK3 as a key regulator for progression, an effective biomarker for prognosis and drug resistance, and a potential therapy to target gastric cancer.

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## THERAPEUTIC EFFECT OF DIETARY N-3 POLYUNSATURATED FATTY ACID IN CROHN'S DISEASE BY RESTORING TH17/TREG IMBALANCE THROUGH PPAR-R/AMPK/ACC MEDIATED PATHWAY

[1]Jiayin Yao*, [2]Bang Hu, [3]Jiachen Sun, [1]Min Zhi. *[1]Department of Gastroenterology, Guangdong Provincial Key Laboratory of Colorectal and Pelvic Floor Disease, The Sixth Affiliated Hospital of Sun Yat-Sen University, China; [2]Department of Colorectal Surgery, The Sixth Affiliated Hospital of Sun Yat-Sen University, China; [3]Department of Gastrointestinal Endoscopy, The Sixth Affiliated Hospital of Sun Yat-Sen University, China*

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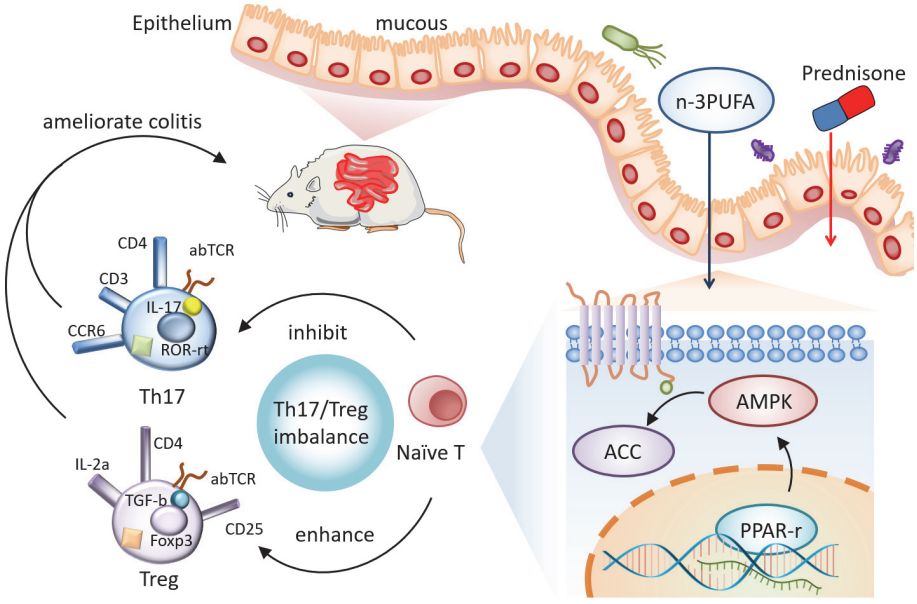
**Background** Effective treatments of Crohn's disease (CD) are limited. Diet is not only an environmental factor in the pathogenesis of CD but also an underlying therapeutic target. Our previous study confirmed the protective effect of dietary n-3 polyunsaturated fatty acid (n3-PUFA) in CD rats without mechanisms explored in-depth. In this study, we aimed to investigate and validate the mechanisms of n-3PUFA in CD in vivo and vitro focusing in T cell differentiation and immune disorder.

**Methods** Experimental CD-like colitis rats were induced by 2,4,6-trinitrobenzene sulfonic acid (TNBS) and naïve T cells were isolated from colonic mucosa lamina propria. Disease




**Abstract IDDF2020-ABS-0157 Figure 1** Hypothesis chart of this study

active index (DAI), Colon macroscopic damage index (CMDI), Tissue damage index (TDI) scores, weights, colon length and histologic manifestation were evaluated. Ratio of T helper cell type 17 (Th17)/regulatory T cells (Treg), expressions of differentiation-associated transducer and cytokines were detected. Relationship between Th17/Treg and peroxisome proliferator-activated receptor-r (PPAR-r)/adenosine monophosphate-activated protein kinase (AMPK)/acetyl CoA carboxylase (ACC) signal pathways were analyzed.

**Results** Dietary n-3PUFA attenuated CD rats by reducing DAI, CMDI, TDI scores and colon shortening, promoted weight gain, and ameliorated histologic manifestations. N-3PUFA shifted Th17 into Treg by activating PPAR-r and downstream AMPK, while inhibiting ACC. Effect of restoring imbalance of Th17/Treg could be enhanced by PPAR-r agonist rosiglitazone, AMPK agonist AICAR and ACC antagonist TOFA, inhibited by PPAR-r antagonist GW9662, AMPK antagonist compound C and ACC agonist citric acid.

**Conclusions** Dietary n-3PUFA effectively protected and ameliorated CD. The underlying mechanisms involved the restoration of Th17/Treg imbalance by regulating PPAR-r/AMPK/ACC signal pathways. (Figure 1).

## IDDF2020-ABS-0158 BRAF MUTATION INDUCES RAPID NEOPLASTIC TRANSFORMATION IN THE AGED AND EXTENSIVELY HYPERMETHYLATED INTESTINAL EPITHELIUM

[1]Lochlan Fennell*, [1]Alexandra Kane, [1]Cheng Liu, [1]Diane McKeone, [1]Gunter Hartel, [1]Catherine Bond, [2]Mark Bettington, [3]Barbara Leggett, [1]Vicki Whitehall. *[1]QIMR Berghofer Medical Research Institute, Australia; [2]Envoi Specialist Pathology, Australia; [3]The Royal Brisbane and Women's Hospital, Australia*

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**Background** Sessile serrated lesions (SSL) are common in both young and old individuals, but the BRAF mutant cancers arising occur predominantly the elderly. DNA Methylation is uncommon in SSL from young patients. Here we interrogate the role of aging and DNA methylation in SSL initiation and progression.

**Methods** We used an inducible model of Braf mutation to direct recombination of the oncogenic Braf V637E allele to the murine intestine. BRAF mutation was activated after periods of aging, and histological and DNA methylation analysis was performed thereafter. We investigated DNA methylation alterations in human SSLs.

**Results** Inducing Braf mutation in aged mice was associated with a 10-fold relative risk of serrated lesions compared with young mice. Methylation analysis revealed extensive differences in age-associated DNA methylation between animals induced at 9 months versus wean; with relatively little differential Braf-specific methylation, implicating age-associated DNA methylation rather than Braf-specific DNA methylation in the heightened risk. DNA methylation at WNT pathway genes scales with age and Braf mutation accelerated age-associated DNA methylation. In human SSLs, increased epigenetic age was associated with high-risk serrated colorectal neoplasia.

**Conclusions** SSLs arising in the aged intestine are at a significantly higher risk of spontaneous neoplastic progression. These findings support a new conceptual model for serrated neoplasia whereby the risk of progression is related to the milieu of epigenetic alterations in the intestinal epithelium at the time of BRAF mutation, rather than the length of time since polyp initiation. This has implications for surveillance and chemopreventive strategies targeting the epigenome.

## IDDF2020-ABS-0174 ONSET OF HYPERTRIGLYCERIDEMIA IN RELATION TO DIETARY INTAKE, GUT MICROBIOME AND METABOLOMICS SIGNATURES AMONG HOME DWELLING ELDERLY

[1]Hajar Fauzan Ahmad*, [2]Josue Leonardo Castro Mejia, [2]Lukasz Krych, [2]Bekzod Khakimov, [3]Witold Kot, [4]Rasmus Leidesdorff Bechshøft, [4]Søren Reitelseder, [2]Søren Balling Engelsen, [5]Lars Holm, [6]Karoline Faust. *[1]Faculty of Industrial Sciences and Technology, Department of Industrial Biotechnology, Universiti Malaysia Pahang, Malaysia; [2]Department of Food Science, Faculty of Science, University of Copenhagen, Denmark; [3]Department of Environmental Science, Aarhus University, Denmark; [4]Institute of Sports Medicine Copenhagen, Department of Orthopedic Surgery M, Bispebjerg Hospital, Denmark; [5]School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, UK; [6]Department of Microbiology and Immunology, Rega Institute, KU Leuven, Belgium*

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**Background** The human gut is home for plethora of microbes including prokaryotic, eukaryotic and other microorganisms. During ageing, imbalances in the gut microbiota are associated with significant phenotypic effects for the host such as the development of metabolic disorders like changes in serum lipids levels, including general physiological decline. However, the presence of fungal communities and their possible association with host health are poorly understood. Therefore, we aim to elucidate trajectory for the progression of atherogenic dyslipidemia during ageing.

**Methods** The interplay between dietary intake, gut microbiota composition, plasma and fecal metabolome and clinical measurements were investigated. The gut bacterial and fungal compositions were determined by high-throughput sequencing of V3 region of 16S rRNA and internal transcribed spacer (ITS2) gene amplicons, respectively. The plasma and fecal metabolomes were determined by GC-TOF-MS. Finally, the dietary intake records and the anthropometric/body-composition measurements at baseline were taken from 75 senior citizens aged 65 years old and above (69.57 ± 3.64).

**Results** At phyla, the gut is home to three main eukaryotic, namely Ascomycota, Basidiomycota and Zygomycota, with genera Penicillium, Candida, and Aspergillus being particularly common. Hypertriglyceridemia group (HG) was associated with low species richness as compared to Normotryglyceridemia group (NG), indicate by α-diversity - Observed species, PD whole tree and Chao1 indices; $p$ <0.05, and Bray-Curtis dissimilarity matrix-based analysis showed significant ($p$ <0.05) clustering according to fasting levels of circulating plasma triglycerides (Tg). Inversely, the hypertriglyceridemia clustering based on the prokaryotic component was not observed among both groups. Higher levels of Tg significantly associates with increased relative abundance of genus Penicillium, possibly mediated by a higher dietary fat intake (ANOVA,$p$ <0.05), and Aspergillus and Guehomyces were positively associated with short-chain fatty acids (SCFAs) groups.

**Conclusions** Collectively, these findings suggest that the gut mycobiome dysbiosis is associated with hypertriglyceridemia, a known risk factor for the development of cardiovascular disease among the elders.