Gut-IDDF 2018 Best Abstracts

Basic Gastroenterology

IDDF2018-ABS-0123 NOVEL MODALITY OF NON-INVASIVE COLORECTAL CANCER SCREENING: COMBINATION OF FAECAL CYCLOOXYGENASE 2 (COX-2) MRNA, CARCINOEMBRYONIC ANTIGEN (CEA), AND FAECAL IMMUNOCHEMICAL TEST (FIT)

¹Murdani Abdullah*, ²Yusra Yusra, ¹Saskia Aziza, ³Utami Susilowati, ¹Arlyando Saragih, ²Latifah Anandari, ²Cynthia Ariani, ²Tammy Nurhardini, ²Dwi Novianingtyas. ¹Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia/Cipto Mangunkusumo Hospital, Jakarta, Indonesia; ²Department of Clinical Pathology, Faculty of Medicine Universitas Indonesia/Cipto Mangunkusumo Hospital, Jakarta, Indonesia; ³Clinical Epidemiology Unit, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia/Cipto Mangunkusumo Hospital, Jakarta, Indonesia

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Background Colorectal is the third most commonly occurring cancer in men and the second most commonly occurring cancer in women. Screening modalities and guidelines directed at prevention and early detection have progressed and resulted in a significant decrease in the prevalence and mortality of colorectal cancer via direct visualisation or using specific markers. Noninvasive screening modalities are continuously being studied. Identification of specific genetic alterations and biomarkers in the adenoma-cancer sequence allow for the study and development of noninvasive screening modalities beyond guaiac-based faecal occult blood testing. The purpose of this study is to highlight some of the new candidate predictive and prognostic colorectal cancer molecular markers for stool samples.

Methods A cross-sectional study was conducted at Ciptomangunkusumo Hospital patients underwent colonoscopy and biopsy for advanced precancerous lesion and colorectal cancer; stool samples were also obtained from the patients. We compared noninvasive test from stool sample using faecal immunochemical test (FIT), KRAS, Carcinoembryonic Antigen (CEA), Cyclooxygenase 2 (COX-2) mRNA, M2-Pyruvate Kinase (M2-PK), calprotectin and its combination in persons at average risk for colorectal cancer.

Results 97 patients with mean age 56 years old (deviation standard ± 11.9). The proportion of female 47.4% (n=46), and male 52.6% (n=51). The proportion of colorectal cancer patients were 15.5%, advanced precancerous lesions were 24.7%. Combination of faecal COX2-CEA-FIT yields the highest sensitivity score. The sensitivity for detecting colorectal cancer was 93.3% with combination of faecal COX2-CEA-FIT. The sensitivity for detecting advanced precancerous lesions was 75% with combination of faecal COX2-CEA-FIT. Specificities with combination of COX2-CEA-FIT for detecting colorectal cancer was 61.3%. Specificities with combination of COX2-CEA-FIT for detecting advanced precancerous lesions was 62%. AUC score for discriminating colorectal cancer was 77.3% (CI 66.4%–88.2%), while AUC score for discriminating advanced precancerous lesions was 68.5% (CI 56.4%–80.6%). PPV 31.1%, NPV 98% LR+2.41, LR- 0.11 for discriminating colorectal cancer; while PPV 40%, NPV 88%, LR+1.97, LR- 0.4 for discriminating advanced precancerous lesions.

Conclusions Faecal COX2-CEA-FIT yields a high sensitivity rate for screening colorectal cancer.

IDDF2018-ABS-0163 PANCREATIC JUICE MUTATION CONCENTRATIONS CAN HELP PREDICT THE GRADE OF DYSPLASIA IN PATIENTS UNDERGOING PANCREATIC SURVEILLANCE

¹Masaya Suenaga*, ¹Yasuhiro Kodera, ²Michael Goggins. ¹Department of Gastroenterological Surgery (Surgery II), Nagoya University Graduate School of Medicine, Japan; ²Department of Pathology, Johns Hopkins Medical Institutions, USA

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Background The measurement of mutations in pancreatic juice samples collected from the duodenum during endoscopic ultrasound (EUS) may improve the diagnostic evaluation of patients undergoing pancreatic surveillance. Our aim was to evaluate the accuracy of using pancreatic juice mutation concentrations to predict the presence and histologic grade of neoplasia in the pancreas.

Methods Digital next-generation sequencing (NGS) of pancreatic juice DNA using a targeted 12-gene panel was performed on 67 patients undergoing pancreatic evaluation during EUS at Johns Hopkins Hospital including patients with pancreatic ductal adenocarcinoma, patients who subsequently underwent pancreatic resection for precursor lesions, patients undergoing surveillance for their familial/inheritable susceptibility to pancreatic cancer, and normal pancreas disease controls.

Results One hundred fifty-five unique somatic mutations were detected after filtering based on the in-house developed algorithm. The most commonly mutated genes after KRAS and GNAS were in descending order of prevalence in TP53, RNF43, SMAD4, ARID1A, CDKN2A, FDXB7 and TGFBR2. Pancreatic juice mutations were detected in all 14 cases with pancreatic cancer, 12 of 13 (92.3%) cases with suspected precancerous lesions, 23 of the 31 high-risk individuals (74.2%) and 4 of 9 disease controls with a normal pancreas. Patients with pancreatic cancer or high-grade dysplasia as their highest grade lesion had significantly higher pancreatic juice mutation concentrations than all other subjects (mean/s.d. digital NGS score; 46.6 $\pm$ 69.7 vs. 6.2 $\pm$ 11.6, p=0.02). Pancreatic juice mutation concentrations distinguished patients with pancreatic cancer or high-grade dysplasia in their resection specimen from all other subjects with a sensitivity, 72.2%, specificity, 89.4% (area under the curve, AUC 0.872). Mutant TP53/SMAD4 concentrations could distinguish patients with pancreatic cancer or high-grade dysplasia in their resection specimen, from all other subjects with 61.1% sensitivity, 95.7% specificity (AUC 0.819). Among 31 high-risk individuals under surveillance, 2 of the 3 individuals with most abnormal pancreatic juice mutation profiles also had the most abnormalities on pancreatic imaging.

Conclusions Pancreatic juice mutation analysis using digital NGS has potential diagnostic utility in the evaluation of patients undergoing pancreatic surveillance.

IDDF2018-ABS-0178 CONSTRUCTION OF COLORECTAL CANCER SUBTYPES BASED ON STROMA-SPECIFIC GENE EXPRESSION AND PREDICTION OF DRUG RESPONSE

Xiaoqiang Zhu*, Xianglong Tian, Jing-Yuan Fang, Jie Hong, Haoyan Chen. State Key Laboratory for Oncogenes and Related Genes; Division of Gastroenterology and Hepatology; Key Laboratory of Gastroenterology and Hepatology, Ministry of Health; Renji Hospital, School of Medicine, Shanghai Jiao Tong University; Shanghai Institute of Digestive Disease, China

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Abstract IDDF2018-ABS-0178 Table 1 Characteristics of each crss subtype of colorectal cancer

	CRSS-A	CRSS-B	CRSS-C	CRSS-D	CRSS-E	CRSS-F
Incidence	23%	23%	12%	8%	25%	10%
Precursor lesions	non-serrated adenoma	non-serrated adenoma	serrated adenoma	non-serrated adenoma	serrated adenoma	serrated adenoma
Colon cell derivation	crypt top, epithelial	crypt base, epithelial	crypt top, epithelial	crypt top, EMT	crypt base, EMT, stem-like	crypt base, EMT, stem-like
Transcriptomic pathways	glycolytic process activation	DNA replication activation	IL-6 pathway activation	IL-2 pathway activation	Immune pathways activation	IGF1 pathway activation
Associated mutations	KRAS	TP53	hypermutation, BRAF	TP53	KRAS, TP53	hypermutation, KRAS
Stroma-immune cells population	NK cells	very few stroma and immune cells enriches	cytotoxic lymphocytes and monocytic lineage	many stroma and immune cells enriched	endothelial cells and fibroblasts	endothelial cells, fibroblasts and monocytic lineage
Epigenomic associations	CIN(-), CIMP(-), MSS	CIN(-), CIMP(-), MSS	CIN(+), CIMP(+), MSI	CIN(-), CIMP(-), MSS	CIN(-), CIMP(-), MSS	CIN(-), CIMP(-), MSS
Location	distal	Distal	proximal	distal	distal	Mixed
Prognosis	intermediate	Intermediate	good	intermediate	poor	Poor
Treatment strategies	EGFR inhibitors (Cetuximab), 5-FU	EGFR inhibitors (Cetuximab), 5-FU	tyrosine kinase inhibitor (Genifitnib)	FOLFIRI or FOLFOX chemotherapy regimen	FOLFIRI or FOLFOX chemotherapy regimen	FOLFIRI or FOLFOX chemotherapy regimen

Background Gene expression profiling has been used to classify molecular subtypes in colorectal cancer (CRC). Given that tumour transcriptome signals not only derive from cancer cells but also from tumour microenvironment. Recent studies have shown that noncancerous components might affect the classification of CRC subtypes. We hypothesised that using stroma-specific gene signature would be more effective to identify CRC subtypes with clinical relevance.

Methods To this end, we analysed gene expression profiles from 1821 CRCs. We firstly constructed a signature where genes were both stroma-specifically expressed and associated with drug response. Further, we identified CRC stroma-specific subtypes (CRSS) using K-means clustering based on the signature and verified the classification in two datasets. We also used the nearest template prediction algorithm to predict drug response.

Results The CRSS subtypes were associated with distinct clinicopathological, molecular and phenotypic characteristics and specific enrichments of gene signatures and signalling pathways (table 1): (i) CRSS-A: non-serrated adenomas, colon crypt top derived, glycolytic, epithelial, KRAS-mutant, sensitive to Cetuximab, enriched with NK cells; (ii) CRSS-B: non-serrated adenomas, colon crypt base derived, DNA replication activity, epithelial, BRAF wild-type, TP53 mutant, chromosomal stability, distal CRC, sensitive to Cetuximab; (iii) CRSS-C: serrated adenomas, colon crypt top derived, interleukin-6 pathway activity, epithelial, microsatellite instability (MSI), BRAF mutant, hypermutation, chromosomal instability, CpG island methylator phenotype, proximal CRC, sensitive to Gefitinib, good prognosis, enriched with cytotoxic lymphocytes and monocytic lineage; (iv) CRSS-D: non-serrated adenomas, colon crypt top derived, interleukin-2 pathway activity, epithelial-mesenchymal transition (EMT), chromosomal stability, sensitive to FOLFIRI and FOLFOX chemotherapy regimens; (v) CRSS-E: serrated adenomas, colon crypt base derived, EMT, immune pathways activation, poor prognosis, sensitive to FOLFIRI and FOLFOX, enriched with endothelial cells and fibroblasts; (vi) CRSS-F: serrated adenomas, colon crypt base derived, EMT, IGF1 pathway activity, poor prognosis, sensitive to FOLFIRI and FOLFOX, enriched with endothelial cells, fibroblasts and monocytic lineage.

Conclusions We classified CRC into six molecular subtypes (CRSS). The identification of CRSS subtypes is critical, as it provides possibilities to identify robust prognostic models and provide more precise therapeutic options for each CRC subtype.

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ADIPOSE-DERIVED MESENCHYMAL STEM CELLS PROMOTE HEALING OF NSAID-RELATED GASTRIC ULCER THROUGH THE PARACRINE EFFECTS IN PIGS

¹Xianfeng Xia*, ²Kai Fung Chan, ³Gerald Tsz Yau Wong, ⁴Baldwin Po Man Yeung, ⁵Liu Liu, ⁴Enders Kwok Wai Ng, ⁴James Yun Wong Lau, ⁴Philip Wai Yan Chiu. ¹Chow Yuk Ho Technology Center for Innovative Medicine, The Chinese University of Hong Kong, Hong Kong; ²Department of Biomedical Engineering, The Chinese University of Hong Kong, Hong Kong; ³Chow Tai Fook-Cheng Yu Tung Surgical Stem Cell Research Centre, The Chinese University of Hong Kong, Hong Kong; ⁴Department of Surgery, Institute of Digestive Disease, State Key Laboratory of Digestive Disease, The Chinese University of Hong Kong, Hong Kong; ⁵Department of General Surgery, The First Affiliated Hospital of University of Science and Technology of China, China

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Background Long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) will induce severe gastrointestinal toxicity. Stem cell therapy is proposed to facilitate tissue repair and regeneration. This study aimed to investigate whether endoscopic submucosal injection of adipose-derived mesenchymal stem cells (ADMSCs) could accelerate healing of NSAID-related gastric ulcer.

Methods Porcine model of NSAID-related gastric ulcer was induced by indomethacin and endoscopic submucosal dissection (ESD)(Fig 1A). Indomethacin was given in all porcine models 10 days prior to ESD. We performed ESD at body and antrum of the stomach in each pig under general anaesthesia to create the ulcer model. After ESD, one of the ulcers was treated by endoscopic submucosal injection of ADMSCs, while the other ulcer was injected with saline as control. Further endoscopic injections were performed at respective ulcer on day 7 and 14. Indomethacin was continued after ESD until