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DIGESTIVE DISEASES



Principal Investigator

Professor Jun Yu

Team

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Research Progress Summary

A. Molecular pathogenesis

- Using a genome-wide shRNA screen in colorectal cancer (CRC) cells with mutations in APC and KRAS, the team identified a novel oncogenic candidate SLC25A22. SLC25A22 plays an important role in tumour metabolism in KRAS-mutant CRC by promoting biosynthesis of the nonessential amino acid aspartate. SLC25A22 protein and mRNA levels were independent prognostic markers associated with poor survival in KRAS-mutant CRC patients.
- Whole genome sequencing has identified solute carrier family 12 member 5 (SLC12A5) as a novel amplification gene in colorectal cancer. SLC12A5 possessed oncogenic properties by promoting tumour proliferation and metastasis, and inhibiting cell apoptosis. SLC12A5 protein overexpression was found to be an independent prognostic factor associated with shortened survival in colorectal cancer patients.
- Using methylated DNA immunoprecipitation array, the team identified Carbonic Anhydrase 4 (CA4) as a novel tumour suppressor gene silenced in colorectal cancer through promoter methylation. CA4 inhibited Wnt signalling pathway via WTAP-WT1-TBL1 axis, thereby suppressing colorectal cancer development. The team also found that methylation status of CA4 may serve as an independent biomarker for the recurrence of CRC.
- Sequencing of fimH gene of *Escherichia coli* (*E. coli*) leads to the identification of α -hemolysin-positive (hly+) type 1 *E. coli* that contributes to adenomagenesis and CRC in human females. Hly+ type 1-*E. coli* were more prevalent in stools from females with adenoma and CRC and their abundance was correlated with poor survival. Feeding hly+ type 1-*E. coli* to female, but not male mice, promotes colorectal tumourigenesis. Thus, hly+ type 1-*E. coli* are candidate causative factors of CRC in human females and a biomarker for diagnosis of CRC.
- Whole genome and transcriptome sequencing in a case of CRC leads to the discovery of a tumour-specific LACTB2-NCOA2 fusion originating from chromosomal rearrangement of chromosome 8. This fusion gene is present in 6.1% of CRC cases, and it disrupts tumour suppressive function of NCOA2, thereby leading to increased tumour growth.

B. Biomarkers and Cancer Screening

1. The team evaluated faecal microbial markers for clinical use in detecting CRC and advanced adenoma, including *Fusobacterium nucleatum* (*Fn*), *Peptostreptococcus anaerobius* (*Pa*) and *Parvimonas micra* (*Pm*). Among these bacteria, *Fn* emerged as a promising markers for CRC. The *Fn*, when combined with the faecal immunochemical test (FIT), showed superior sensitivity than FIT alone in detecting CRC in the same patient cohort.
2. MicroRNA microarray identified miR-20a as the one of the most up-regulated miRNA in CRC compared to adjacent normal tissues. The team analysed miR-20a in 595 faecal samples (198 CRCs, 199 adenomas, and 198 healthy controls) and found that miR-20a was significantly higher in faecal samples from CRC patients. Hence, miR-20a level in faeces is a non-invasive biomarker for diagnosis of CRC.
3. The team performed a systematic analysis of microRNA profiles from 1765 tumour samples from The Cancer Genome Atlas, including oesophageal, gastric, liver, pancreatic, colon and rectal cancers, and found that digestive cancers of different tissue origins could be differentiated according to their miRNA expression profiles. Moreover, the team identified novel microRNA signatures that are associated with patient outcome in digestive cancers.

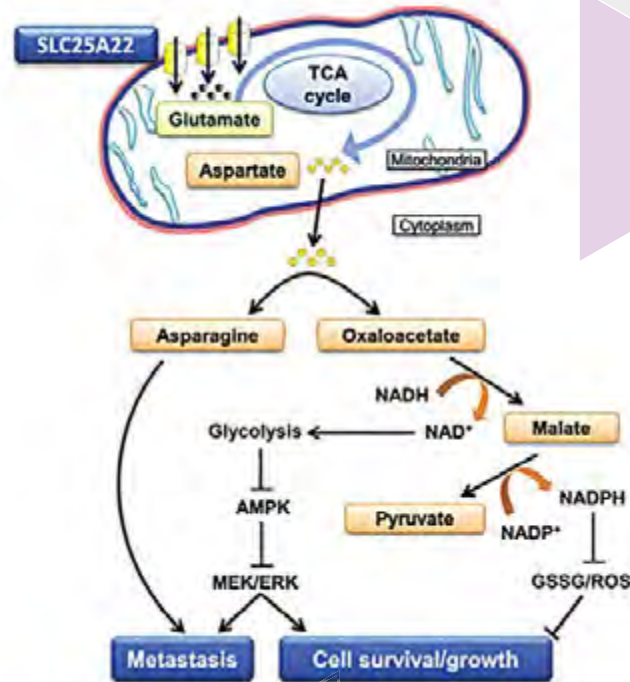
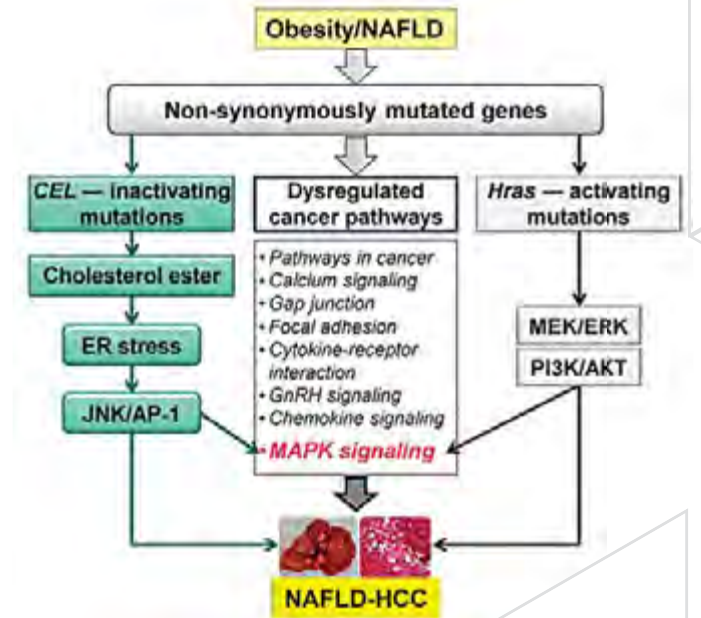


Figure 1. Gastroenterology, 151, 945-60
Cancer cells consume glutamine (Gln), which can be used in protein biosynthesis or biosynthetic pathways. In the paper by Wong et al., we discovered a novel oncogene, SLC25A22, which is critically important for glutamine metabolism in colon cancers with KRAS mutations. Targeting of SLC25A22 might be a novel strategy to inhibit the growth of KRAS-mutant colon cancers.

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Figure 2. Oncogene, 2016, 35, 6271-80.
Whole genome sequencing revealed novel genes harbouring mutations in NAFLD-HCC mice that affect eight cancer signalling pathways. Among all mutated genes, *Cel* and *Hras* are of particular interest. Mutations in these two genes both have oncogenic effects with different mechanisms.

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C. Gastric cancer

1. Using bioinformatics tools, the team integrated somatic mutational profiles and clinicopathologic information from 544 gastric cancers using previously published datasets, and redefined gastric cancer into regular (86.8%) and hypermutated (13.2%) subtypes. The team's analyses also uncovered 6 novel recurrently mutated genes (XIRP2, NBEA, COL14A1, CNBD1, ITGAV and AKAP6) in the regularly-mutated gastric cancer subtype. Finally, the team devised a novel mutational signature that predicts patient prognosis in regularly-mutated gastric cancer.
2. Methylated DNA immunoprecipitation array revealed that MDGA2 is hypermethylated in gastric cancer. MDGA2 exerted a potent tumour suppressive effect in gastric cancer by the induction of apoptosis and cell cycle arrest. Antitumour effect of MDGA2 was mediated through stabilising of DNA methyltransferase 1 associated protein 1, which activated p53/p21 signalling. MDGA2 methylation is an independent prognostic factor that predicts poor survival in with gastric cancer.
3. The team additionally identified novel tumour suppressor genes, RASSF10, RNF180 and GDF1 that are silenced in human gastric cancer by promoter methylation. Methylation status of these two genes was associated with poor survival of gastric cancer patients.
4. The team identified the miR-508-3p as a novel tumour suppressor microRNA in gastric cancer. miR-508-3p negatively regulates the expression NFKB1 and RELA, major components of NF- κ B oncogenic signalling, thereby inhibiting gastric cancer cell growth.
5. *Helicobacter pylori* (*H. pylori*) infection is associated with gastritis and gastric cancer. The team discovered that the antimicrobial peptide cathelicidin inhibit *H. pylori* growth, and cathelicidin knockout in mice resulted in stronger *H. pylori* colonization and inflammation. Bioengineered *Lactococcus lactis* with cathelicidin expression suppressed *H. pylori* infection and may be used as a therapeutic agent for treatment of gastritis.

D. Non-Alcoholic Fatty Liver Disease (NAFLD)

1. Epidemiological data showed that obesity and NAFLD are associated with hepatocellular carcinoma (HCC) development. Whole-exome sequencing of chemically-induced HCC in genetically obese mice and wild-type lean mice liver identified mutations in Carboxyl ester lipase (Cel) gene and Harvey rat sarcoma virus oncogene 1 (Hras) genes. Mutations in Cel gene cause cholesteryl ester accumulation, leading to endoplasmic reticulum stress that consequently activated IRE1 α /c-Jun N-terminal kinase (JNK)/c-Jun/activating protein-1 (AP-1) signalling cascade to promote liver cell growth. On the other hand, gain of function mutations in Hras promoted cell growth via activating MAPK and PI3K/Akt pathways. Thus, Cel and Hras have important functional roles in the development of NAFLD-HCC.
2. The team elucidated underlying role of CXC chemokine receptor 3 (CXCR3) in non-alcoholic steatohepatitis (NASH) development using CXCR3 knockout mice. CXCR3 knockout mice were remarkably resistant to both methionine-and-choline-deficient (MCD) diet and high-fat high-carbohydrate high-cholesterol (HFHC) diet-induced NASH. CXCR3 was found to be involved in mediating pro-inflammatory response, autophagosome-lysosome impairment and endoplasmic reticulum stress, which contributed to NASH development.
3. The team identified Ying Yang 1 (YY1) as an oncogenic factor in HCC. YY1 is a transcription factor whose binding motif was enriched in H3K27me3-occupied genes, including genes for fifteen tumour-suppressive miRNAs. H3K27me3 is a repressive marker and YY1 over-expression suppressed expression of these tumour suppressive miRNA, thereby activating NF- κ B signalling in hepatocarcinogenesis.
4. The team unraveled RASSF10 as a tumour suppressor silenced in HCC by promoter methylation. Adhesion genes PCR array revealed that the Matrix Metalloproteinase 2 (MMP2) was a downstream effector of RASSF10. Down-regulation of MMP2 by RASSF10 contributed to reduced cell invasion and migration in HCC cell lines.

E. Inflammatory Bowel Disease (IBD)

1. IBD is an emerging GI disease in Asia, but little is known about disease progression. In a prospective population-based study, the team enrolled 413 patients with IBD from 8 countries in Asia. The team found that disease progression in Asian patients was comparable with that of the West, and patients with Crohn's disease have a more severe disease progression and accelerated use of immunosuppressants.
2. Targeted expression profiling of patients with Crohn's disease (CD), ulcerative colitis (UC) and healthy controls identified KAT2B as the most significantly down-regulated epigenetic regulator in IBD. KAT2B drives the expression of anti-inflammatory cytokine IL-10 via histone H4K5 acetylation. Thus, decreased KAT2B expression led to repression of IL-10, resulting in unchecked innate and adaptive inflammatory responses in IBD.
3. The team investigated the interaction between miRNAs and IL-23/Th-17 pathway in IBD using a mice model of chemically-induced colitis. RNA microarray profiling identified CLDN8 as a novel target gene in IBD that was down-regulated in both human IBD and induced IBD in mice. The team further showed that miR-223 mediates crosstalk between IL-23/Th-17 pathway and CLDN8 expression by directly targeting CLDN8 3'UTR region. Targeting of the IL23/miR-233/CLDN8 axis may provide therapeutic strategies for IBD management.

**Recognitions****Awards and Fellowships**

Member's Full Name	Details
Jun Yu	Croucher Senior Research Fellowship for 2016-2017
Jun Yu	Council Member, American Gastroenterology Association (AGA) Oncology, USA
Jun Yu	Chairman of Hong Kong Immunology Association
Jun Yu	Pao Yue-Kong Scholar Chair Professor, Ningbo University
Henry LY Chan	Fellowship of American Association for the Study of Liver Disease
Simon SM Ng	The Royal College of Surgeons of Edinburgh China Medal
Simon SM Ng	The Best Original Paper Award in 2015 by Surgical Practice
Siew C Ng	Young Investigator Award by American Gastroenterology Association Digestive Disease Week, San Diego, USA
Siew C Ng	Exemplary Teaching Award, Faculty of Medicine, CUHK
Siew C Ng	Top Reviewer Award, Alimentary Pharmacology and Therapeutics (APT) from Editors of APT
Siew C Ng	Distinguished Research Paper Award for Young Investigators, Hong Kong College of Physicians
Siew C Ng	Research Excellence Award, Chinese University of Hong Kong

Grants and Consultancy

Full Name of PI	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK\$)
Joseph Sung / Jun Yu / Francis Chan	Partner State Key Laboratory of Digestive Diseases	Innovation and Technology Commission – Innovation and Technology Fund	01/04/2016	31/03/2018	10,000,000
Jun Yu	Characterization of WNT2 in the Oesophageal Cancer Microenvironment: Prognostic and Therapeutic Implications	Research Grants Council – General Research Fund	01/01/2014	31/12/2016	736,128
Jun Yu	Functional Characterization of Squalene Epoxidase in Promoting Fatty Liver Disease-associated Liver Cancer	Research Grants Council – General Research Fund	01/01/2016	31/12/2018	1,141,432
Jun Yu	Elucidation of a Novel Tumour Suppressor Gene MAP9 in Regulating Chromosome Instability in Colon Cancer	Food and Health Bureau – Health and Medical Research Fund	01/01/2016	31/12/2018	1,195,728
Jun Yu	Elucidation of a Novel Tumour Suppressor Gene Tripartite Motif 67 (TRIM67) in Colorectal Cancer	Research Grants Council – General Research Fund	01/01/2017	31/12/2019	1,154,550
Jun Yu (Co-PI), Henry LY Chan (Co-PI)	The Liver Cancer Genome Project: Translating Genetic Discoveries to Clinical Benefits	Research Grants Council – Theme-based Research Scheme	2011	2016	45,000,000
Jun Yu	State Key Laboratory of Cancer Biology (CUHK Joint Research Base in Shenzhen)	Shenzhen Virtual University Park Support Scheme	2012	2017	RMB 500,000
Jun Yu	Microbe, Colorectal Cancer and Obesity	SH Ho Foundation	2012	2018	5,000,000
Jun Yu	MicroRNA-based Detection of Colorectal Cancer: Key Technology Development Project Investigators	Technology and Innovation Project Fund, Shenzhen	2013	2016	RMB 4,000,000

Full Name of PI	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK\$)
Jun Yu (Co-PI)	腸道微生物生態與感染及代謝的研究	National Basic Research Program	2013	2017	RMB 22,000,000
Jun Yu (Co-PI)	Macrophage-Myofibroblast-Transition in Organ Fibrosis: Molecular Mechanisms and Clinical Implications	Research Grants Council – Collaborative Research Fund	01/01/2013	31/12/2016	8,800,000
Henry LY Chan (Co-PI)	Massively Parallel Sequencing of Plasma Nucleic Acids for the Molecular Diagnostics of Cancers	Research Grants Council – Theme-based Research Scheme	2011	2016	31,999,000
James YW Lau	Urgent Versus Early Endoscopy in High Risk Patients with Acute Upper Gastrointestinal Bleeding	Food and Health Bureau – Health and Medical Research Fund	01/01/2014	31/12/2016	829,400
James YW Lau	Endoscopy Photodynamic Therapy*(PDT) for Inoperable Bile Duct Cancers in Hong Kong Chinese Patients	SK Yee Medical Foundation	2014	2016	1,639,924
Siew C Ng	Fecal Microbiota Transplantation (FMT) for Severe Clostridium Difficile Infection (CDI): A Randomised Study with Concurrent Stool Microbiota Assessment	Hong Kong Society of Gastroenterology	01/06/2014	31/05/2016	300,000
Siew C Ng	A Prospective Study of Serial Interferon-gamma Release Assays (IGRA) for the Diagnosis of Tuberculosis (TB) Infection in Patients with Immune-mediated Inflammatory diseases (IMID) Treated with Biologics	Food and Health Bureau – Research Fund for the Control of Infectious Diseases	01/01/2015	31/12/2017	750,000
Siew C Ng	Health economic research in IBD	Abbvie Pharmaceutical	2015	2017	250,000

Full Name of PI	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK\$)
Siew C Ng	A Combined Phase 2/3, Double-Blind, Randomized, Placebo-Controlled, Induction and Maintenance Study Evaluating the Safety and Efficacy of GS-5745 in Subjects with Moderately to Severely Active Ulcerative Colitis	Gilead Pharmaceutical	2015	2017	1,000,000
Siew C Ng	A Prospective Study on the Risk of Colorectal Neoplasms in Individuals with a Family History of Advanced Adenomas	Research Grants Council – General Research Fund	01/01/2014	31/12/2016	1,039,239
Simon SM Ng (Co-PI)	Plasma DNA as a Platform Technology for Cancer Detection	Research Grants Council – Theme-based Research Scheme	01/01/2017	31/12/2021	40,000,000
Vincent WS Wong	Prevalence and Clinical Significance of Nonalcoholic Fatty Liver Disease in Patients with Type 2 Diabetes: A Prospective Cohort Study Using Controlled Attenuation Parameter and Liver Stiffness Measurements	Research Grants Council – General Research Fund	01/01/2014	31/12/2016	560,756
Vincent WS Wong	Incidence of Non-alcoholic Fatty Liver Disease and Advanced Fibrosis in Patients with Type 2 Diabetes: A Prospective Cohort Study Using Paired Controlled Attenuation Parameter and Liver Stiffness Measurements	Research Grants Council – General Research Fund	01/01/2017	31/12/2019	658,050
Vincent WS Wong (Co-PI)	Functional Liver Cancer Epigenomics: Exploiting Epigenetic Vulnerabilities for Therapeutics	Research Grants Council – Collaborative Research Fund	01/01/2015	31/12/2017	7,418,375

Full Name of PI	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK\$)
Dennis CC Wong	PGE2-induced DNA Methylation in Gastric Cancer: Mechanisms and Therapeutic Implications	Research Grants Council – General Research Fund	01/10/2015	30/09/2018	852,552
Dennis CC Wong	新抑癌基因SCNN1B在胃癌中的功能機制和臨床應用價值研究	The National Natural Science Foundation of China	01/01/2016	31/12/2018	RMB 170,000

Publications

A. Journal Papers

- Bai AH, Wu WK, Xu LL, Wong SH, Go MY, Chan AW, Harbord M, Zhang SH, Chen MH, Wu JC, Chan MW, Chan MT, Chan FK, Sung JJ, Yu J, Cheng AS, Ng SC. Dysregulated lysine acetyltransferase 2B promotes inflammatory bowel disease pathogenesis through transcriptional repression of interleukin-10. *Journal of Crohns & Colitis*. 2016; 10(6):726-34.
- Chan AW, Yu SN, Yu YH, Tong JH, Wang L, Tin EK, Chong CC, Chan SL, Wong GL, Wong VW, Chan HL, Lai PB, To KF. Steatotic hepatocellular carcinoma: a variant associated with metabolic factors and late tumour relapse. *Histopathology*. 2016; 69(6):971-84.
- Chan HC, Wong VW, Wong GL, Tang W, Wu JC, Ng SC. Prevalence of hepatitis B and clinical outcomes in inflammatory bowel disease patients in a viral-endemic region. *Bmc Gastroenterology*. 2016; 16:100.
- Jin Y, Tang SW, Li WL, Ng SC, Chan MW, Sung JJ, Yu J. Hemolytic *E. coli* promotes colonic tumorigenesis in females. *Cancer Research*. 2016; 76(10):2891-900.
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- Li XC, Wu WK, Xing R, Wong SH, Liu YX, Fang XD, Zhang YL, Wang MY, Wang JQ, Li L, Zhou Y, Tang SW, Peng SL, Qiu KL, Chen LY, Chen KX, Yang HM, Zhang W, Chan MT, Lu YY, Sung JJ, Yu J. Distinct subtypes of gastric cancer defined by molecular characterization include novel mutational signatures with prognostic capability. *Cancer Research*. 2016; 76(7):1724-32.
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38. Wu RN, Nakatsu G, Zhang X, Yu J. Pathophysiological mechanisms and therapeutic potentials of macrophages in non-alcoholic steatohepatitis. *Expert Opinion on Therapeutic Targets*. 2016; 20(5):615-26. (Review)
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