IDDF2018-ABS-0085
PROSPECTIVE CROSS-SECTIONAL STUDY ON THE CLINICAL PROFILE AND MYOCARDIAL FUNCTION OF SEVERELY AND MODERATELY MALNOURISHED CHILDREN 2 MONTHS TO 18 YEARS OLD IN PHILIPPINE CHILDREN’S MEDICAL CENTRE (PCMC)

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10.1136/gutjnl-2018-IDDFabstracts.7

Background Malnutrition in children produces visceral protein loss and consequent cardiac atrophy. There are conflicting studies if this cardiac atrophy results in myocardial dysfunction.

This study aims to determine the prevalence of myocardial dysfunction and describe the demographic, clinical, electrolyte changes, electrocardiographic and structural and myocardial function in severely and moderately malnourished children.

Methods This is a prospective cross-sectional study conducted on severely and moderately malnourished children 2 months to 18 years old in Philippine Children’s Medical Centre. Serum potassium, magnesium, ionised calcium and phosphorus determination, 2D echocardiography and electrocardiogram (ECG) were done.

Results 73 subjects (43 moderately and 30 severely malnourished) were recruited. Majority had neurologic diseases (n=18, 25%), followed by tuberculosis (n=13, 18%). 2 had pneumonia, 2 had diarrhoea.

Hypokalemia was found in 5/30 or 16% severely malnourished (Potassium 2.21–2.96 mmol/L) and 4/42 or 9% moderately malnourished (Potassium 2.5–2.89 mmol/L) (p>0.05). Only one marasmic child had hypomagnesemia (0.5 mmol/L). Ionised calcium and phosphorus were normal. Both groups demonstrated prolonged QT interval, short and prolonged PR interval, prolonged QRS duration with no statistical significance. The most common ECG finding is short PR interval in moderately (n=29/42 or 69%) and severely malnourished (n=18/29 or 62%) subjects (p>0.05).

The systolic and diastolic functions were normal in both the severely and moderately malnourished. Although the left ventricular mass (LVM) was low with no statistical significance between the two groups, the LVM index remained to be normal. The presence of pericardial effusion in severely malnourished (Potassium 2.5–2.89 mmol/L) was not statistically significant.

Conclusion Hypokalemia, hypomagnesemia and shortened PR interval are common in malnutrition. Hence, vigilant monitoring of electrolytes and ECG should be done in all malnourished children.

IDDF2018-ABS-0096
MAJOR GENETIC ALTERATIONS IN SPORADIC COLORECTAL CANCER IN THE CHINESE POPULATION

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10.1136/gutjnl-2018-IDDFabstracts.9

Background Sporadic colorectal cancer accounts for 80% of all colorectal cancer. The 2 major mechanisms of genetic alteration are chromosomal instability (CIN) and microsatellite instability (MSI). The prevalence of KRAS, NRAS, BRAF and CTNNB1 mutations in western population was 42.4%, 5.1%, 15.2% and 1.1%, respectively. BRAF mutations in Chinese population were much lower (3.1%). RNF43 mutation was recently reported with a high prevalence of 18%. It was found mutually exclusive with APC inactivation and was associated with MSI-H tumours.

In this study, the prevalence of APC, KRAS, NRAS, BRAF, CTNNB1 and RNF43 mutations in Chinese sporadic colorectal cancer patients was confirmed by next generation sequencing (NGS). The association of RNF43 mutation with APC, BRAF mutations and MSI status of tumours, was analysed. Clinical-pathological correlation was evaluated.

Methods NGS was used to investigate the prevalence of major mutations in 55 subject samples. Data analysis was done by Statistical Package of the Social Sciences (SPSS) statistics. Clinical-pathological correlation was analysed by Cox regression and Kaplan-Meier estimate.
Results The frequency of APC, KRAS, NRAS, BRAF, CTNNB1 and RNF43 mutations were 76.4%, 61.8%, 9.1%, 3.6%, 1.8% and 9.1%. The most common RNF43 mutation was p. Gly659fs. RNF43 mutation was associated with MSI-H status (p<0.001) and BRAF V600E mutation (p<0.001). RNF43 and APC mutations were likely mutually exclusive. High pre-operative CEA level ≥10 (p=0.013), high grade (p=0.005), T4 tumours (p=0.006), Stage IV cancer (p<0.001) with distant metastasis (p<0.001) were poor predictors of disease-free survival. High grade (p<0.001), T4 tumours (p<0.001), Stage IV cancers (p<0.001) with distant metastasis (p<0.001) were poor predictors of overall survival.

Conclusions The frequency of major mutations in Chinese population was stable. RNF43 mutation is likely anti-EGFR therapy resistant and is an alternative to targeted therapy. The current clinical classification of colorectal cancer and blood tests for disease monitoring were the most effective way to predict clinical prognosis. More research of larger sample size on the pathogenicity of RNF43 mutation and clinical correlation of major mutations is required.

IDDF2018-ABS-0104 MOLECULAR INSIGHTS INTO COLON MUCINOUS ADENOCARCINOMA
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Abstracts

Background It is well-known that tumour is caused by somatic mutations. However, great mutational heterogeneity is observed both across cancer types (3100 fold) and with a given cancer type, with a fraction of them harbour >10 mutations per Mb, thus termed hypermutation. Hypermutated patients are suitable for PD-1 blockade with favourable prognosis. Nevertheless, other omics such as transcriptome and methylome in hypermutated samples remain poorly understood. Here, we try to determine the genome-wide effects of high mutation loads on transcriptome and methylome across two cancer types, namely colorectal cancer (CRC) and stomach adenocarcinoma (STAD).

Methods All tumour mRNA expression datasets (RNASeqV2) and DNA methylation data (HumanMethylation450) were obtained from The Cancer Genome Atlas. Known batch effects were corrected using the ComBat function implemented in the Bioconductor sva package. Differentially expressed gene (DEGs, false discovery rate (FDR) adjusted P-value<0.05 and fold change ≥2 ) analysis between hypermutated and non-hypermutated was performed by DESeq package for R/Bioconductor. Significantly differentially methylated site (DMS, FDR adjusted P-value<1E-5 and beta value change >0.2) was performed by limma package for R/Bioconductor.

Results Results showed that MAC harbours 3366 frequent mutational gene sets (FMGSs, a priori method), in sharp contrast to only 94 in non-MAC. Three-fold higher BRAF mutation rate in MAC than non-MAC was observed, and this may account for a worse prognosis in MAC. Notably, we found ATM had the same high mutation rate as TP53 in MAC, thus rescue of ATM was rather important because ATM acts upstream of TP53. In addition, hundreds of DEGs such as AQP3, MUC2, and FCGBP and 4 differentially expressed miRNAs were determined between MAC and non-MAC. Additionally, 1,926 DMSs that were associated with inflammatory response, cell adhesion, neutrophil chemotaxis, and immune response were identified as well.

Conclusions The huge molecular difference exists between MAC and non-MAC inspires us treating CRC in a more careful manner because we are driving toward a new era of precision medicine. In other words, the medical decision making used in MAC cannot simply copy from strategy adopted in non-MAC.

Molecular Insights Into Colon Mucinous Adenocarcinoma

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Background Mucinous adenocarcinoma (MAC) is a histological subtype of colorectal cancer (CRC), in which account for 5%–15% of all primary CRC. MAC is characterised by the formation of a tumour comprised of >50% mucin. The prognostic value of MAC remains controversial; several studies report that MAC has a worse prognosis than nonmucinous adenocarcinoma (non-MAC), while others are not. Thus, it is important to decipher the molecular signature of MAC to better understand the unfamiliar subtype of the disease and improve the individualised management of patients with MAC.

Methods Here, we comprehensively characterised the somatic mutation, genome-wide transcriptional (mRNA and miRNA), and epigenetic (DNA methylation) profiles of the MAC, combined with correlation analyses of expression, methylation, and clinical data from the Cancer Genome Atlas. Differentially expressed gene (DEGs, false discovery rate (FDR) adjusted P-value<0.05 and fold change ≥2 ) analysis between MAC and non-MAC was performed by DESeq package for R/Bioconductor. Significantly differentially methylated site (DMS, FDR adjusted P-value<1E-5 and beta value change >0.2) was performed by limma package for R/Bioconductor.

Results Results showed that MAC harbours 3366 frequent mutational gene sets (FMGSs, a priori method), in sharp contrast to only 94 in non-MAC. Three-fold higher BRAF mutation rate in MAC than non-MAC was observed, and this may account for a worse prognosis in MAC. Notably, we found ATM had the same high mutation rate as TP53 in MAC, thus rescue of ATM was rather important because ATM acts upstream of TP53. In addition, hundreds of DEGs such as AQP3, MUC2, and FCGBP and 4 differentially expressed miRNAs were determined between MAC and non-MAC. Additionally, 1,926 DMSs that were associated with inflammatory response, cell adhesion, neutrophil chemotaxis, and immune response were identified as well.

Conclusions The huge molecular difference exists between MAC and non-MAC inspires us treating CRC in a more careful manner because we are driving toward a new era of precision medicine. In other words, the medical decision making used in MAC cannot simply copy from strategy adopted in non-MAC.

DECRYPTING MOLECULAR PROPERTIES OF HYPERMUTATED COLORECTAL AND GASTRIC CANCER
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Background The frequency of major mutations in Chinese population was stable. RNF43 mutation is likely anti-EGFR therapy resistant and is an alternative to targeted therapy. The current clinical classification of colorectal cancer and blood tests for disease monitoring were the most effective way to predict clinical prognosis. More research of larger sample size on the pathogenicity of RNF43 mutation and clinical correlation of major mutations is required.