IDDF2020-ABS-0177 ERBB4 HIGH EXPRESSION AND MUTATIONS IN GASTRIC CANCER PRESENT OPPORTUNITIES FOR CLINICAL LANDSCAPE AND THERAPEUTIC DEVELOPMENT

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Background The human ERBB receptor tyrosine kinase family is deregulated in multiple cancer types either through amplification or mutations. The ERBB4 mutation of gastric cancer (GC) is listed as the top 2 alteration frequency, which was around 10%.

Methods In order to understand the biological functions of ERBB4 wild-type (WT) and mutants, ERBB4 WT and its several hot spot mutants including R106H, R393W, S774G, and L798R were constructed into adenovirus with red fluorescent protein. We examined the ERBB4 WT and mutants for their roles in cell proliferation and metastasis and validated their sensitivity to tyrosine kinase inhibitors (TKIs) in vitro and in vivo.

Results We found that the ERBB4 amplification and mutations played the oncogenic roles in GC, in which the ERBB4 mutations had more significant effects. ERBB4 overexpression and mutants increased the sensitivity of GC cells to TKIs in vitro and in vivo, especially the ERBB4 mutants had stronger effects. The mechanisms of ERBB4 oncogenic activities were dependent or independent on kinase active ERBB2.

Conclusions This finding broadened the clinical application of TKIs targeted to ERBB2 or pan-ERBB, suggesting that they may provide therapeutic benefits to GC patients with ERBB4 overexpression or mutations. Moreover, ERBB4 is supposed to be a significant biomarker for GC treatment.

IDDF2020-ABS-0179 CHOLESTEROL-RORα/Γ AXIS PROMOTES COLORECTAL CANCER PROGRESSION THROUGH C-MYC STABILIZATION

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Background Cholesterol is essential for colorectal cancer (CRC) cells. Cholesterol and its derivates are ligands for different nuclear receptors (NRs). However, which NR plays a key role in the downstream of cholesterol in CRC is unknown. This study aimed to elucidate the cholesterol-NRs axis in CRC.

Methods We detected the levels of putative nuclear receptors of cholesterol metabolism in CRC cells treated with cholesterol deprivation. Then we built the RORα/γ knockdown and overexpression cell lines and examined the roles of RORα/γ in cell proliferation and migration of CRC in vitro and in vivo. Subsequently, we explored the downstream mechanisms and investigated the efficacy of the combination of Atorvastatin and RORα/γ agonists in mice.

Results We found that the retinoic acid receptor-related orphan receptors RORα/γ levels increased most obviously in CRC cells after treated with cholesterol deprivation. RORα/γ can promote CRC cell proliferation and migration in vitro and in vivo. Mechanically, RORα/γ promotes c-myc degradation through activating ubiquitinase NEDD4 transcription. The combination of Atorvastatin and RORα/γ agonist SR1078 synergistically inhibited CRC cell growth and metastasis.

Conclusions These findings demonstrate that cholesterol is essential for sustaining c-myc levels in CRC cells. The inhibition of RORα/γ by cholesterol and its derivatives is important for c-myc protein levels. And the combination of Atorvastatin and RORα/γ agonist might represent a therapeutic strategy in CRC.

IDDF2020-ABS-0225 MODULATION OF LEUCINE-RICH-ALPHA-2-GLYCOPROTEIN 1 (LRG1) PROMOTES THE SURVIVAL OF LOW-GRADE COLORECTAL CANCER VIA SUPPRESSION OF AUTOPHAGY BUT NOT IN HIGH-GRADE CANCER

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Background Previous quantitative proteomic study from our laboratory had identified leucine-rich-alpha-2-glycoprotein 1 (LRG1) as the most prominent marker for colorectal cancer (CRC). This marker was significantly up-regulated in the serum of late-stage CRC patients and present in a stage-dependent manner in the CRC cells. Many studies have linked autophagy to cancer, but none had explored the relationship between LRG1 and autophagy in CRC. This study (FRGS/1/2018/SKK08/UKM/03/3) is aimed to investigate the effect of LRG1 modulation on the autophagy mechanism in colorectal cancer.

Methods Colorectal adenocarcinoma cells, HT29 (low-grade CRC) with the lowest endogenous level of LRG1 were chosen for the over-expression of human LRG1 gene, whereas colorectal carcinoma cells, HCT116 (high-grade CRC) with the highest endogenous level of LRG1 were used for the LRG1 knockdown experiment. The cells were stably transduced with lentivirus containing LRG1 open reading frame (ORFs) and short hairpin RNA (shRNA), respectively. The selection was carried out with Blasticidin S and Puromycin, respectively prior to RNA extraction and gene expression assessment via RT-qPCR. Statistical analysis of Independent T-test was performed using GraphPad Prism 8.0.1.

Results Over-expression of LRG1 in HT29 increased cell proliferation by activation of Ki67 mRNA ($p<0.01$). Similarly, the over-expression increased cell migration and invasion via ZEB1 ($p<0.05$). LRG1 over-expression also reduced the mRNA levels of autophagy markers, including Beclin-1, ATG3, and ATG5 ($p<0.05$). Conversely, knockdown of LRG1 in HCT116 slightly reduced the cell proliferation ($p>0.05$), but several autophagy markers (Beclin-1, ATG4D, ATG5, LC3 and GABARAP, except ATG3) were in a decreasing trend.

Conclusions In summary, LRG1 enhanced the survival of low-grade colorectal cancer and tumour progression by suppression of autophagy but failed to reverse the mechanism in the knockdown model of high-grade cancer. More related works are currently on-going.