

## Gut – IDDF Young Investigator Award

## Basic gastroenterology

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**PROTEOMICS REVEALS THAT RECTAL CANCER PATIENTS WITH NEOADJUVANT RADIOCHEMOTHERAPY REACH PCR THROUGH IMMUNE ACTIVATION**

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**Background** Colorectal cancer (CRC) is the second leading cause of cancer death worldwide, and more than 1/3 of all cases are rectal cancer. The standard neoadjuvant radiochemotherapy for locally advanced rectal cancer fails to benefit all patients due to individualize sensitivity to radiotherapy. It's critical to understand the molecular mechanisms underlying pathological complete regression (pCR) in some patients.

**Methods** We collected 67 patients with rectal cancer who were treated with long-term radiotherapy and capecitabine chemotherapy from two hospitals. Among them, a total of 58 cases with both pre-treatment endoscopic biopsy specimens and surgical pathological sections available were picked procured and reassessed for Tumor Regression Grade (TRG) after treatment mentioned above. Formalin-fixed paraffin-embedded (FFPE) tissue samples from each individual were collected with two biological replicates. All the samples were processed by Pressure Cycling Technology coupled with Data-Independent Acquisition mass spectrometry for proteomic profiling. The abundances of immune infiltrates and their correlation with CDH11 were estimated by TIMER algorithm.

**Results** A total of 6483 proteins are quantified with high confidence with a high Pearson correlation ( $R^2=0.98$ ). Fifty-eight patients were divided into two groups according to the pCR condition after neoadjuvant radiochemotherapy. At the threshold of the adjusted p-value of 0.05 and fold change of > 1.5, we identified 127 up-regulated proteins and 205 down-regulated proteins in the pCR group. The former proteins were mainly involved in immune response and cell activation, while the latter mostly participated in metabolic processes. TIMER algorithm suggested a higher degree of immune cell infiltration in the pCR group, especially involving CD8+ T cell and Dendritic cells. The significantly up-regulated protein, Cadherin-11 (CDH11), was identified as a key factor contributing to various immune infiltrates, including T cells, Macrophage and Dendritic cells. Mutation of CDH11 gene has a high correlation between its copy number variation (CNV) and abundance of immune infiltrates. More details will be presented.

**Conclusions** Based on the proteomic analysis of biopsy specimens before neoadjuvant therapy, immune activation was identified as the potential mechanism via which some rectal cancer patients attained pCR.

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**LINC RNA MNX1-AS1 PROMOTES THE PROGRESSION OF COLORECTAL CANCER THROUGH STABILIZING YB1**

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**Background** Improving the prognosis of Colorectal Cancer (CRC) depends on the identification of the mechanisms of recurrence and metastasis, and developing new therapeutic targets. lncRNA has become an attractive potential therapeutic target because it is more precise and less toxic when compared with traditional protein targeted drugs. We aimed to identify novel lncRNAs that significantly affects the development of CRC, and investigate the potential associated therapeutic targets.

**Methods** Based on RNA-seq analysis, we screened out ten candidates and identified highly expressed lncRNAs in the 21 CRC tissue samples. An siRNA library was established to identify lncRNAs that significantly affected CRC cell proliferation and metastasis. RT-PCR and RNAi assays were performed to investigate the functional role of lncRNA MNX1-AS1 and clinical relevance. In vivo, cell-based and patient-derived xenograft (PDX) models were used to further explore roles of MNX1-AS1 in CRC tumorigenesis, metastasis and potential therapeutic target. RNA pull-down, mass spectrometry analyses, western blot and RNA-binding protein immunoprecipitation (RIP), DNA-binding protein immunoprecipitation (ChIP), and Double Luciferase Report experiment were performed to identify interaction proteins and related mechanisms.

**Results** MNX1-AS1 was upregulated in CRC tissues from patients with poor overall survival (OS), and MNX1-AS1 inhibition led to the impaired CRC cell line growth. Moreover, knockdown of MNX1-AS1 resulted in a decreased level of Y-box binding protein 1 (YB1), a multifunctional RNA/DNA binding protein. MNX1-AS1 blocked ubiquitination of YB1 and maintained its stability. This process prevented the degradation of YB1 through the MYC pathway. Therefore, knockdown of MNX1-AS1 attenuated the downstream effects of YB1. In addition, the transcription of MNX1-AS1 could be inhibited by MYC in CRC cells. In vivo experiments showed that the inhibition of MNX1-AS1 suppressed the proliferation of tumors in orthotopic models and patient-derived xenograft (PDX) models. **Conclusions** The newly identified MNX1-AS1, which is regulated by MYC, plays a pivotal role in CRC proliferation by enhancing YB1 stability, thus facilitating the development of CRC. Collectively, our study suggests that MYC- MNX1-AS1-YB1 axis might serve as potential biomarkers and therapeutic targets in CRC treatment.

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**LONG NON-CODING RNA LRTIS REGULATES MLL1-MEDIATED IMMUNOCHECKPOINT REMODELLING IN ESOPHAGEAL SQUAMOUS CELL CARCINOMA**

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