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Novel pathological role and clinical usage of repetitive non-coding RNAs in pancreatic cancer

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Most satellite repeats in pericentmeric heterochromatin are epigenetically silenced and rarely transcribed into RNAs. However, in some pathological conditions, satellite RNA are transcribed and may deregulate cellular homeostasis. For example, human satellite repeat II (HSATII) RNA and mouse major satellite (MjSAT) RNA were reported to be highly and specifically detected in human and mouse pancreatic intraepithelial neoplasia (PanIN) tissues, which are precancerous lesions, and pancreatic ductal adenocarcinoma (Pdac) tissues.

To examine the biological roles of the satellite RNAs in the carcinogenesis steps, we constructed mouse PanIN-derived cells expressing major satellite (MajSAT) RNA, which showed increased frequencies of chromosomal instability and point mutations in genomic as well as mitochondrial DNA, affecting the cells transformation ability. We identified Y-box binding protein 1 (YBX1) as a protein that binds to MajSAT RNA. MajSAT RNA inhibits the nuclear translocation of YBX1 under stress conditions, which reduced its DNA damage repair function. The forced expression of YBX1 significantly decreases the aberrant phenotypes. These indicate that during the early stage of cancer development, satellite transcripts may act as “intrinsic mutagens” by inducing YBX-1 dysfunction, which may be crucial in oncogenic processes.

In addition, we developed a convenient and sensitive method for quantifying aberrantly expressed satellite repeat RNAs in sera, which can be used to efficiently detect patients with Pdac. That is, we introduced a Tandem Repeat Amplification by nuclease Protection (TRAP) method combined with droplet digital PCR (ddPCR) to detect human satellite II (HSATII) RNAs, which are difficult to measure due to their repetitive sequences and irregularities. HSATII RNA core sequence levels in sera were significantly higher in Pdac patients compared with non-cancer patients (median copy number: 14.75 and 3.17 per μl in the training set and 17.35 and 2.9 in the validation set, respectively). Further, patients with intraductal papillary mucinous neoplasm (IPMN), a precancerous lesion of Pdac, could also be efficiently detected. Thus, this method can be routinely applied to screen patients with Pdac and its high-risk patients.

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Although our study focused mainly on Pdac, I hope these knowledge and methods provide with some insights into the field of renal diseases as well.