博士論文（要約）

The function of nuclear RNA decay in the regulation of immune response gene expression and cancer cell survival

(免疫応答遺伝子発現と癌細胞増殖制御における核内 RNA 分解制御機構)

タンジナ タヌ

TANZINA TANU

Background

Knowledge of RNA degradation regulation is necessary to understand decay-mediated gene expression regulation. In the past few years, major advances in understanding RNA degradation reveals numerous protein factors, enzyme, and mechanistic pathway. Although RNA degradation pathways of many RNA species and underlying mechanism of RNA degradation mediated regulatory functions are largely unknown especially in disease conditions. This study is aimed to focus on nuclear RNA degradation mediated gene regulation. Firstly, we introduce a novel degradation pathway of nuclear lncRNA NEAT1v2 and its impact on target gene expression. Secondly, we explore how overexpressed RNA decay factor EXOSC4 impacts gene expression regulation and pancreatic cancer cell proliferation.

HNRNPH1-MTR4 complex-mediated regulation of NEAT1v2 stability is critical for IL8 expression

A large share of transcripts is retained in the nucleus and some of which play important roles in regulating gene expression [1]. The functional role of these RNA molecules is largely determined by their stability which is regulated by nuclear RNA exosome. The nuclear RNA exosome, which tightly binds MTR4, is an essential co-factor for most nuclear RNA decay. However, the interaction of MTR4 and the RNA exosome with RNA is largely non-specific [2, 3] where associated RNA binding proteins provide the target specificity. This study was aimed to find the protein factor that can recruit RNA exosome onto NEAT1v2. Therefore, we searched for overlapped proteins between published MTR4 interacting proteins and known paraspeckle proteins, reveals 4-factor proteins namely, HNRNPH1, HNRNPF, AKAP8L, and RBM7 [4, 5]. Although only HNRNPH1 knockdown induces NEAT1v2 expression level indicates a possible target for NEAT1v2 degradation regulation. Here we found HNRNPH1 depletion stabilizes NEATv2 and induces paraspeckle formation. Furthermore, we found HNRNPH1 interacts with MTR4 in an RNA independently. Taken together, our results suggest that HNRNPH1 plays an

important role in NEAT1v2 degradation by recruiting the MTR4-RNA exosome complex, and this in turn control IL8 expression. Although further research is needed to define whether HNRNPH1 conducts this activity as part of a larger exosome adaptor complex.

Exploring the regulatory function of the exosome component EXOSC4 in Pancreatic cancer

This present study reported the regulatory function of EXOSC4 in controlling pancreatic cancer cell survival for the first time. EXOSC4 is transcribed from chromosome 8q24.3 regions. Chromosome 8 is one of the most frequently amplified in different cancer causes overexpression of corresponding genes. Here we found that EXOSC4 overexpression is necessary for PAAD cancer cell survival. From RNA sequencing data, we observed that genome-wide transcriptional change under EXOSC4 knock-down revealed differential expression of cell growth regulatory genes. We showed that BCL-2 interacting killer (BIK) upregulation and stabilization of Sestrin-2 (SESN2) which are function as apoptosis inducer and tumor-suppressive genes respectively [6]. Here we showed that nuclear decay factors RRP6 and DIS3 are regulated by overexpressed EXOSC4 and cause SESN2 stabilization. Based on these findings we think overexpression of EXOSC4 in pancreatic cancer might have a regulatory function in nuclear RNA decay by affecting other RNA degradation factors.

References

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