



“RHAMM knockout” mice express a truncated RHAMM protein that promotes pancreatic cancer progression with dysfunctional p53

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Pancreatic cancer, which lacks effective treatment, has the highest mortality rate of all major cancers (1). A recent study by Lin *et al.* published in *Cancer Letters* (2) sought out to investigate whether RHAMM is a therapeutic target in pancreatic cancer using a *Rhamm*^{-/-} mouse strain. Surprisingly, a truncated HMMR^{Δexon8-16} protein expressed at higher levels than wild-type RHAMM protein was found in this “knockout” strain and HMMR^{Δexon8-16} accelerated pancreatic cancer progression in genetic engineered mouse models.

Pancreatic cancer is projected to become the second leading cause of cancer-related death by 2030 (3). The most common type of pancreatic cancer is pancreatic ductal adenocarcinoma (PDAC). Pancreatic neuroendocrine tumor (PNET) is the second common malignancy of pancreas and its incidence is increasing (4). Pancreatic cancer patients are often diagnosed at advanced stages. Despite intense efforts in improved diagnostic methods and development of targeted therapies, the overall survival for pancreatic cancer has changed little. It is critical to understand the biology of pancreatic cancer and identify novel therapeutic targets for this devastating disease.

Receptor for hyaluronan-mediated motility (RHAMM; gene name: HMMR) was identified as a protein that binds to hyaluronic acid (HA) (5). RHAMM promotes HA-induced motility, modulates cytoskeletal organization, and activates extracellular-regulated kinase (Erk) (6-8). RHAMM protein expression is limited in normal human tissues and not expressed in adult pancreas (9,10). In

contrast, RHAMM protein is overexpressed in pancreatic cancer and many other cancer types (9-13). *RHAMM* encodes 18 exons. *RHAMM*^B (known as *RHAMMv3*) is the most prominent alternative splicing *RHAMM* isoform found in pancreatic cancer patients (10). Human *RHAMM*^B overexpression promotes metastasis and knockdown of RHAMM by shRNA suppresses metastasis in mouse models of PNET (10,14). High *RHAMM*^B mRNA levels correlate with inferior survival of PDAC patients in TCGA cohort (10).

Lin *et al.* investigated whether genetic ablation of RHAMM is effective to impair pancreatic cancer progression using “RHAMM knockout” mice. The *Rhamm*^{-/-} mouse was previously generated by deleting exons 8~16 of the HMMR gene through homologous recombination in embryonic stem cells (15). However, the detailed molecular and histological characterization identified a truncated RHAMM (HMMR^{Δexon8-16}) of 239 amino acids with a molecular weight of ~27 kDa in the *Rhamm*^{-/-} mice and the HMMR^{Δexon8-16} protein was more abundant than the full-length protein in RHAMM wild-type mice. This *Rhamm*^{-/-} strain should be renamed as HMMR^{Δexon8-16/Δexon8-16}.

This study further demonstrated that while HMMR^{Δexon8-16} by itself did not promote the progression of pancreatic intraepithelial neoplasia (PanIN) to PDAC in the *p48-Cre; LSL-KRAS^{G12D}* mice, the combination of HMMR^{Δexon8-16} and heterozygous p53 loss significantly promoted earlier onset of invasive PDAC formation and shortened survival of *p48-Cre; LSL-KRAS^{G12D}; p53^{lox/+}*

mice. Moreover, HMMR^{Δ_{exon8-16}} decreased survival of *RIP-Tag* PNET mice, in which p53 was inhibited by SV40 T antigen. Importantly, pancreatic cancer patients with mutant *TP53* or loss of one copy of *TP53* had higher *RHAMM* expression, which, combined, predicted worse survival outcomes.

In summary, Lin *et al.* have shown that high levels of the N-terminal RHAMM protein, HMMR^{Δ_{exon8-16}} collaborated dysfunctional p53 to promote progression of PDAC and PNET in mouse models, and HMMR^{Δ_{exon8-16}}, possessed the oncogenic function. The unexpected discovery of a truncated RHAMM protein in the “*RHAMM* knockout” mouse provides critical insights for the re-evaluation of previous work using this mouse strain and cells derived from it (15-21). A true *RHAMM* knockout will be needed to assess the therapeutic value of targeting RHAMM for pancreatic cancer treatment in pre-clinical mouse models.

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