SHORT COMMUNICATION

Potential Roles of Renalase in Pancreatic Cancer

Yasheen Gao[1], Melinda Wang[2], Marie Robert[3], Fred Gorelick[4], Gary Desir[1*]

[1,2]Department of Medicine, Yale University School of Medicine, New Haven, Connecticut, United States of America

[3]Department of Pathology, Yale University School of Medicine, New Haven, Connecticut, United States of America

[4]Department of Internal Medicine and Cell Biology, VA CT Healthcare System and Yale University School of Medicine, 950 Campbell Ave, West Haven, CT 06516, United States of America

DESCRIPTION

Renalase is a multi-functional secretory protein made by the kidney and other tissues. It was discovered as a renal secretory protein that mediates select disease features in chronic kidney disease. Renalase was subsequently found in other tissues and to possess prosurvival and anti-inflammatory effects demonstrated in murine models of acute pancreatitis1 and acute renal and heart injury. These injury studies determined the function of renalase by administering both a recombinant full-length protein and a whole-body renalase knockout in mice. By expressing different peptide domains of full-length renalase, we subsequently found that renalase's anti-inflammatory and prosurvival activity was contained in a 20 aa renalase peptide (aa 220-239 from human renalase isoform) conserved in all known isoforms and termed RP220 [1]. When added extracellularly, this renalase peptide binds its effector, the Plasma Membrane Calcium ATPase (PMCA4b) [2,3]. In all cell types reported to date, including healthy and cancer cells, extracellular renalase PMCA4b for its biological effects. PMAC4b has an intracellular site that can bind intracellular proteins with a PDZ domain. This gives PMCA4b the potential to interact with the PDZ domain-containing proteins linked to multiple signaling pathways.

In this context, renalase stimulation of PMCA4b activates ERK, AKT, and STAT3 signals and can also enhance calcium efflux from pancreatic acinar and HEK cells [4]. These studies suggest a critical role for extracellular renalase acting as a cytokine that might signal through multiple potential pathways depending on which are available to couple to PMAC4b. Renalase likely has an additional intracellular role that depends on the molecule's enzymatic domain. Renalase has potential metabolic effects related to a region of the molecule separate from the RP220 site. When discovered, potential NAD/NAPDH-binding and separate FAD binding sites were identified in renalase. In tissues from a renalase knockout mouse, the ratio of NAD+/NADH levels and NADH oxidase levels were significantly decreased [5]. Such renalase-dependent changes, if persistent, could lead to increased reactive oxygenspecies and reduced mitochondrial function, as summarized (see Figure 1 and [6]). Unpublished work from our laboratory suggests that deficient intracellular renalase may cause mitochondrial dysfunction with direct and indirect effects on mitochondrial function. Renalase's potential to enhance the survival of neoplastic cells was explored in pancreatic cancer using cellular and animal models. It drives pancreatic cancer growth in cellular and *in vivo* systems [7]. Further, renalase levels were found to be increased in select cancers [7]. Since the hypoxia-inducible factor-1 can induce renalase expression, its elevation in cancers was not surprising [8].

When tissue levels of renalase were quantified by immunohistochemistry or mRNA expression, we found an inverse relationship between the levels of pancreatic cancer and patient survival. Inhibition of renalase with a monoclonal antibody directed to the RP220 site reduced the growth of cultured human pancreatic cancer cells and tumor growth in an *in vivo* murine model of pancreatic cancer [7]. Renalase had similar effects in human melanoma, a murine melanoma model, and colon cancer [9]. These studies suggested that increased production of renalase by some cancers could drive their growth and shorten patient survival. It also raised the possibility that inhibiting renalase activity might be an attractive

Received 29-Dec-2023 Manuscript No. IPP-23-18661
Accepted 05-Jan-2024 Manuscript No. IPP-23-18661
Published 19-Jan-2024 DOI: 10.51268/1590-8577-23.S9.1-3

Correspondence Gary Desir
Department of Medicine, Yale University School of Medicine, New Haven, Connecticut, United States of America
E-mail gary.desir@yale.edu

approach for treating select cancers.

Our most recent study of renalase in pancreatic cancer has made two additional critical observations [10]. First, tissue renalase levels appear to be increased in the pancreatic tissues of premalignant diseases. These included chronic pancreatitis, PanIN, IPMN, and mucinous cystic neoplasms. Of note, tissue renalase increases in chronic pancreatitis unassociated with pancreatic cancer appeared to be much less than when not cancer-associated. These findings suggest that increased tissue renalase levels may have a role in promoting precancerous pancreatic lesions.

Second, plasma levels of a distinct form of renalase were found to be a biomarker for the cancer stage and correlated inversely with patient survival. Plasma renalase levels had significant predictive value for survival; plasma CA19-9 levels did not predict survival. Plasma renalase levels also predicted who will undergo resection for those with locally advanced pancreatic cancer. These observations suggest that plasma renalase levels could help predict pancreatic cancer survival or resectability but need confirmation in a large prospective cohort. Further, whether the plasma renalase comes from the cancer tissues or represents a systemic reaction to the cancer is unknown.

How renalase might drive the growth of pancreatic cancer and other neoplasms is unknown, but our experimental studies suggest that more than one mechanism may be active. Figure 2 summarizes some of the mechanisms that could drive cancer growth, including:

a) Direct effects on cancer cells of renalase from local sources (e.g., cancer cells, macrophages) or by renalase delivered from circulation [9],

b) Indirectly by suppressing CD8-T-cell mediated local cancer immunity [11,12],

c) Changing cancer cell metabolism.

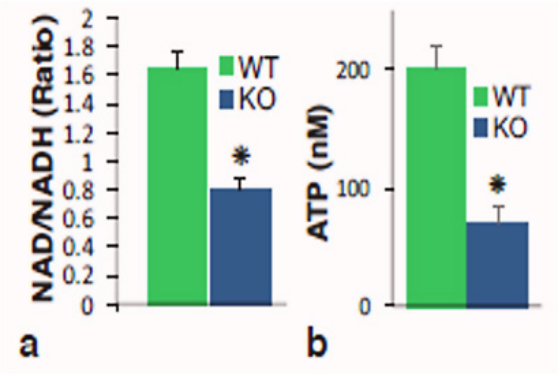

Figure 1. Renalase-dependent energy metabolism. Wild-type (WT) mice were compared to a global renalase Knockout (KO). a) Relative levels of NAD to NADH; b) ATP content (nM) in cardiac tissue homoge-nates (normalized to protein content). **Note:** (■): WT; (■): KO; (*) Indicates $p<0.05$.

Though important questions remain, these observations support the notion that inhibition of renalase might be an attractive therapeutic option [Figure 2]. Successful treatment of unresected cancer with an inhibitory antibody or another renalase inhibitor would be complex because of the cancer's dense extracellular matrix. However, such approaches might be effective as adjuvant therapy after resection or for the early treatment of a recurrence.

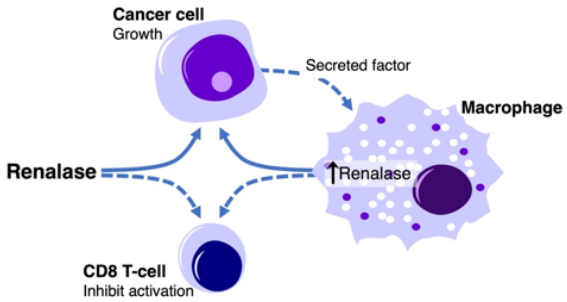

Figure 2. Renalase from multiple sources, including macrophages and cancer cells themselves, can increase cancer growth. Though the mechanisms are unknown, cancer cells increase tumor macrophage renalase production and renalase can suppress anti-tumor CD8 T-cells activation.

ACKNOWLEDGMENTS

For research support, Department of the Army, W81XWH-22 and W81XWH1910439 to FSG and GVD, and VA Merit Award BX003250 to FSG.

REFERENCES

1. Kolodecik TR, Reed AM, Date K, shugrue CA, Patel V, Chung SL, et al. The serum protein renalase reduces injury in experimental pancreatitis. J Biol Chem. 2017; 292(51): 21047-21059. [PMID: 29631305]

2. Wang L, Velazquez H, Moeckel G, John C, Ahorm H, Thomas LH, et al. Renalase prevents aki independent of amine oxidase activity. J Am Soc Nephrol. 2014; 25(6): 1226-1235. [PMID: 24511138]

3. Wang L, Velazquez H, Chang J, Safirstein R, Desir GV. Identification of a receptor for extracellular renalase. PLoS One. 2015; 10(4): e0122932. [PMID: 25906147]

4. Pointer TC, Gorelick FS, Desir GV. Renalase: A multi-functional signaling molecule with roles in gastrointestinal disease. Cells. 2021; 10(8): 409e418. [PMID: 34440775]

5. Wu Y, Xu J, Velazquez H, Wang P, Li G, Liu D, Benedita Sampaio-Maia, et al. Renalase deficiency aggravates ischemic myocardial damage. Kidney Int. 2011; 79(8): 853-860. [PMID: 21178975]

6. Stojanovic D, Stojanovic M, Milenkovic J, Velickov A,

Citation: Gao Y, Wang M, Robert M, Gorelick F, Desir G. Potential Roles of Renalase in Pancreatic Cancer. JOP. J Pancreas. (2024) 23:1-3.

Ignjatovic A, Milojkovic M. The multi-faceted nature of renalase for mitochondrial dysfunction improvement in cardiac disease. Cells. 2023; 12(12):1607. [PMID: 37371077]

7. Guo X, Hollander L, MacPherson D, et al. Inhibition of renalase expression and signaling has antitumor activity in pancreatic cancer. Sci Rep 2016;6():22996. [PMID: 1802271]

8. Du M, Huang K, Huang D, Yang L, Gao L, Wang X, et al. Renalase is a novel target gene of hypoxia-inducible factor-1 in Protection against cardiac ischaemia-reperfusion injury. Cardiovasc Res. 2015;105(2):182-191. [PMID: 25497549]

9. Hollander L, Guo X, Velazquez H, Chang J, Safirstein R, Kluger H, et al. Renalase expression by melanoma and tumor-associated macrophages promotes tumor growth through a STAT3-mediated mechanism. Cancer Res. 2016;76(13):3884-3894. [PMID: 27197188]

10. Gao Y, Wang M, Guo X, Joanna Hu, Chen TM, Finn SMB, et al. Renalase is a novel tissue and serological biomarker in pancreatic ductal adenocarcinoma. PLoS One 2021;16(9):e0250539. [PMID: 34587190]

11. Guo X, Jessel S, Qu R, Kluger Y, Chen TM, Hollander L, et al. Inhibition of renalase drives tumour rejection by promoting T Cell activation. Eur J Cancer 2022;165:81-96. [PMID: 35219026]

12. Nakahodo J, Kikuyama M, Fukumura Y, Horiguchi S, Chiba K, Tabata H, et al. Focal pancreatic parenchyma atrophy is a harbinger of pancreatic cancer and a clue to the intraductal spreading subtype. Pancreatology. 2022:22(8);1148-1158. [PMID: 36273992]

Citation: Gao Y, Wang M, Robert M, Gorelick F, Desir G. Potential Roles of Renalase in Pancreatic Cancer. JOP. J Pancreas. (2024) 23:1-3.