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Targeting Metabolic Scavenging in Pancreatic Cancer

Costas A. Lyssiotis and Lewis C. Cantley

Pancreatic tumor metabolism is rewired to facilitate survival and growth in a nutrient-depleted environment. This leads to a unique dependence on metabolic recycling and scavenging pathways, including NAD salvage. Targeting this pathway in pancreatic cancer disrupts metabolic homeostasis and impairs tumor growth. *Clin Cancer Res; 20(1); 1–3. ©2013 AACR.*

In this issue of *Clinical Cancer Research*, Chini and colleagues demonstrate that targeting the NAD salvage pathway in pancreatic cancer cell lines and tumors impairs growth (1), suggesting that such a strategy could find application in humans. This work builds on a rapidly growing body of research and clinical data, which posit that targeting tumor metabolism in pancreatic cancer may bring new treatments for this devastating disease.

A pancreatic cancer diagnosis is a virtual death sentence. The 5-year survival rate is a staggeringly low 6% and median survival is only 6 months (2). These dismal statistics can be attributed in large part to the fact that effective treatment options and targeted agents are not available for this disease. Standard treatment modalities have been largely ineffective in pancreatic cancer due to several factors, among which is that pancreatic cancers exist in a unique metabolic environment. For example, such tumors are extremely dense with interstitial pressures that can exceed ten times those observed in normal organs like the liver or pancreas (3). Pancreatic tumors are also intensely fibrotic, where in many cases less than 10% of the total tumor mass is composed of cancer cells, the remainder being stromal fibroblasts, immune infiltrate, and deposited extracellular matrix. Collectively, these features act to impair vascularization, which makes pancreatic tumors extremely hypoxic and limits nutrient availability, not to mention drug delivery (4). Given this limited access to nutrients and oxygen, it is then no surprise that pancreatic tumor metabolism must adapt to facilitate survival and growth in this challenging metabolic environment.

The well-characterized metabolic adaptations of pancreatic cancer can be generally grouped together into a single category; features which are all underlined by the ability to scavenge and recycle metabolic substrates. For example, pancreatic cancers exhibit a high degree of basal autophagy and they are strictly dependent on this process for growth and survival (5, 6). In addition to the consumption of internal cargo, they also consume lipids (7) and protein (8) from the extracellular space. Such biomolecules are either used directly or broken down into component parts and then used for the maintenance of anabolic metabolism (9). Although these processes can also be observed in normal cells, it is important to note that pancreatic cancers depend on the continued activity of the aforementioned recycling and scavenging pathways. In fact, the dependence of pancreatic cancers on autophagy and extracellular protein eating (a process termed macropinocytosis) were both recently explored in clinical trials. In the case of the former, multiple clinical trials are ongoing in pancreatic cancer to test this approach given the availability of drugs such as hydroxychloroquine (an antirheumatologic drug that has been used safely in people for decades), which inhibits the last step of autophagy by blocking lysosomal function. Whether this will be an effective approach is not yet clear and will depend upon the ability of hydroxychloroquine to achieve therapeutic levels that inhibit autophagy in patients, not to mention that appropriate combination agents remain to be determined (10). In addition, the therapeutic application of a drug that exploits the dependence of pancreatic cancer on macropinocytosis was recently approved for metastatic disease (11). This agent is a protein–drug conjugate [albumin–paclitaxel; termed nab-paclitaxel or known by its trade name Abraxane (Celgene)]. That is presumably delivered to poorly vascularized pancreatic tumors through extracellular protein engulfment, thereby delivering the cytotoxic payload. Indeed, patients on standard of care plus Abraxane were afforded a 2-month increase in median survival, which is seen as major progress in a disease that has not seen significant clinical improvements in decades. Interestingly, these two approaches are also being combined in patients with pancreatic cancer through a Stand Up To Cancer initiative. In this study, patients will receive standard of care (gemcitibine) with Abraxane and hydroxychloroquine. Importantly, these results also demonstrate proof-of-principle that targeting metabolic scavenging pathways holds promise for pancreatic cancer.

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Consistent with this framework, the study highlighted herein by Chini and colleagues now describes that pancreatic tumors are also dependent on the salvage of NAD for growth (1). NAD is a cofactor that performs two general functions in cells. It facilitates the shuttling of reducing equivalents generated from metabolic reactions (e.g., from glycolysis to the mitochondria) and can also be catabolized directly, where its metabolites are used to change the post-translational makeup of a cell. Following catabolism, NAD can be generated *de novo* or it can be recycled through its salvage pathway (Fig. 1). Like other metabolic scavenging pathways in pancreatic cancer, here, too, the salvage pathway is used. This was illustrated by pharmacologically or genetically inhibiting the first step in the NAD salvage pathway governed by nicotinamide phosphoribosyltransferase (NAMPT) and observing a drop in cellular NAD levels. Moreover, utilization of this salvage pathway seems to be another metabolic addiction in pancreatic cancer, as inhibition of NAMPT impairs tumor growth *in vitro* and in xenograft tumors. The authors go on to demonstrate that the dependence on NAD salvage is for the metabolic use of NAD in transferring reducing potential, rather than as a cofactor in SIRT1- or PARP1-mediated reactions. Pharmacologic inhibition of NAMPT results in attenuated glucose uptake, lactate release, oxygen consumption, and ATP production—features associated with impaired glucose metabolism through glycolysis and in the mitochondria (Fig. 1). Furthermore, NAMPT inhibition also led to the phosphorylation of AMP-dependent protein kinase, a readout for cells under energy stress. In contrast, pharmacologic or genetic inhibition of SIRT1 or PARP1 had negligible effects on pancreatic cancer growth. Perhaps more convincingly, the authors also demonstrate that the impairment of pancreatic cancer growth following NAMPT inhibition can be rescued by using metabolites downstream of NAMPT that bypass pharmacologic inhibition [e.g., nicotinamide mononucleotide (NMN)]. Collectively, these results illustrate that inhibition of NAD salvage results in a metabolic collapse in pancreatic cancer that impairs growth.

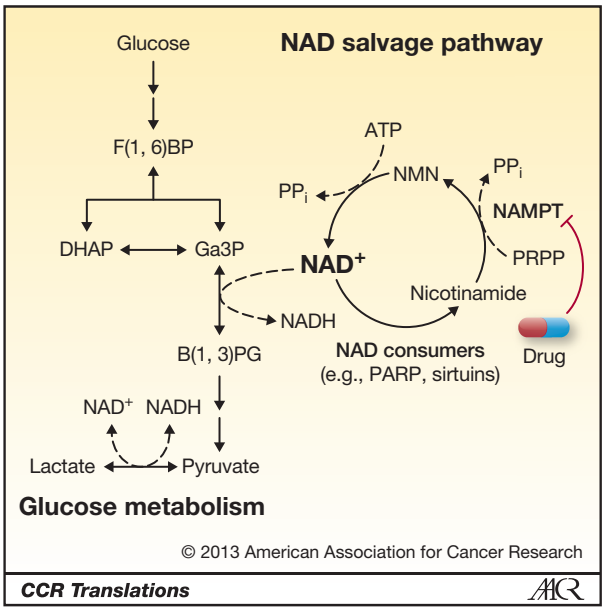

Figure 1. The intersection of glucose metabolism and NAD salvage. Glycolysis, depicted on the left, reduces two units of NAD^+ per unit glucose metabolized. The reducing equivalent stored in NADH can be transferred to the mitochondria to facilitate oxidative phosphorylation or can be oxidized back to NAD^+ concurrent with the generation of lactate. In both cases, regeneration of NAD^+ facilities continued glucose metabolism in glycolysis. The NAD salvage pathway is depicted on the right and recycles nicotinamide back into NAD^+ after its metabolism by NAD^+ consumers (e.g., SIRT1 or PARP1). Small molecule–mediated inhibition of NAMPT, the rate limiting enzyme in NAD salvage, impairs pancreatic tumor growth. ATP, adenosine-triphosphate; B(1,3)PG, 1,3-bisphosphoglycerate; DHAP, dihydroxyacetone-phosphate; F(1,6)BP, fructose 1,6-bisphosphate; Ga3P, glyceraldehyde 3-phosphate; PPi, pyrophosphate; PPRP, phosphoribosyl pyrophosphate.

In addition to providing further evidence supporting the notion that targeting the disrupted metabolic state in pancreatic cancer may prove efficacious, this study also pinpoints a specific target, NAMPT, for which first-generation clinical grade inhibitors are currently available and have been examined in several tumor contexts. This study also raises the question of whether NAMPT inhibition may synergize with other methods that target metabolic dependencies in pancreatic cancer that are being examined or deployed in the clinical setting (10, 11). Specifically, it has been previously demonstrated that NAD salvage inhibition induces autophagy (12). Given the critical role of autophagy in PDAC survival, it is conceivable that the combination of autophagy suppression and inhibition of NAD salvage may act synergistically. In summary, the observation that NAD salvage is required by pancreatic cancer cells to maintain energy homeostasis provides yet another piece to this interesting metabolic puzzle. Together with the recent clinical assessment of Abraxane and hydroxychloroquine, these results suggest that through targeting the disrupted metabolic state in pancreatic cancer, promising therapies may be in reach for this dreaded disease.

Disclosure of Potential Conflicts of Interest

L.C. Cantley is a member of the board of directors and a consultant/advisory board member for Agios Pharmaceuticals, for which he also has ownership interests (including patents). Celgene is an investor in and collaborator with Agios Pharmaceuticals. No potential conflicts of interest were disclosed by the other author.

Authors' Contributions

Conception and design: C.A. Lyssiotis, L.C. Cantley
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References

1. Chini CCS, Gonzalez Guerrico AM, Nin V, Camacho-Pereira J, Escande C, Barbosa MT, et al. Targeting of NAD metabolism in pancreatic cancer cells: potential novel therapy for pancreatic tumors. Clin Cancer Res 2014;20:XXXX–XX.
2. Hidalgo M. Pancreatic cancer. N Engl J Med 2010;362:1605–17.
3. Provenzano PP, Cuevas C, Chang AE, Goel VK, Von Hoff DD, Hingorani SR. Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma. Cancer Cell 2012;21:418–29.
4. Olive KP, Davidson CJ, Jacobetz MA, Honess D, McIntyre D, Madhu B, et al. Inhibition of hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer. Science 2009;324:1457–61.
5. Yang S, Wang X, Contino G, Liesa M, Sahin E, Ying H, et al. Pancreatic cancers require autophagy for tumor growth. Genes Dev 2011;25:717–29.
6. Guo JY, Chen HY, Mathew R, Fan J, Strohecker AM, Karsli-Uzunbas G, et al. Activated Ras requires autophagy to maintain oxidative metabolism and tumorigenesis. Genes Dev 2011;25:460–70.
7. Kamphorst JJ, Cross JR, Fan J, de Stanchina E, Mathew R, White EP, et al. Hypoxic and Ras-transformed cells support growth by scavenging unsaturated fatty acids from lysophospholipids. Proc Natl Acad Sci U S A 2013;110:8882–7.
8. Commisso C, Davidson SM, Soydaner-Azeloglu RG, Parker SJ, Kamphorst JJ, Hackett S, et al. Macropinocytosis of protein is an amino acid supply route in Ras-transformed cells. Nature 2013;497:633–7.
9. Son J, Lyssiotis CA, Ying H, Wang X, Hua S, Ligorio M, et al. Glutamine supports pancreatic cancer growth through a KRAS-regulated metabolic pathway. Nature 2013;496:101–5.
10. Mancias JD, Kimmelman AC. Targeting autophagy addiction in cancer. Oncotarget 2011;2:1302–6.
11. Von Hoff D. Gemcitabine plus albumin-bound paclitaxel in patients with advanced metastatic pancreatic cancer. Bethesda (MD): National Library of Medicine (US). 2000–2013. Available from: http://clinicaltrials.gov/ct2/show/NCT00398086. Date accessed: November 8, 2013.
12. Cea M, Cagnetta A, Fulciniti M, Tai YT, Hideshima T, Chauhan D, et al. Targeting NAD^+ salvage pathway induces autophagy in multiple myeloma cells via mTORC1 and extracellular signal-regulated kinase (ERK1/2) inhibition. Blood 2012;120:3519–29.

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