Metabolic Subtyping for Novel Personalized Therapies Against Pancreatic Cancer

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SUMMARY

Through metabolic subtyping, metabolic vulnerabilities can be exploited for developing efficacious treatments. A glycolytic subtype indicates poor survival in patients with pancreatic cancer, whereas a cholesterogenic subtype correlates with better outcomes potentially due to more energy expenditure. Personalized medicine holds great promise for improving therapy outcomes by optimally targeting metabolic pathways.

See related article by Karasinska et al., p. 135

In this issue of *Clinical Cancer Research*, Karasinska and colleagues report that metabolic subtypes of pancreatic ductal adenocarcinoma (PDAC) correlate with patient survival outcomes (1)

Patients with pancreatic cancer suffer from poor survival outcomes. Despite developments in therapeutic strategies, it remains unclear which patients respond, and which ones do not. Hence, there is an urgent need for personalized medicine approaches that require a detailed understanding of the genetic features of the tumor. Recent advances in molecular subtyping have presented opportunities to predict which patients may respond to therapy. However, at a mechanistic level, it remains a challenge to identify novel agents that may further sensitize patients to existing therapies.

Metabolic alterations represent a key hallmark feature of cancer cells that regulate aggressiveness and therapy response in tumors including pancreatic cancer. All cancer cells need biomass production to proliferate. Even the nonproliferating/slow-growing cancer stem cells undergo metabolic reprogramming that causes dependency on certain metabolic pathways (2). The metabolic reprogramming in tumor cells presents novel opportunities to target PDAC tumors. However, not all the tumors have similar dependencies on the underlying metabolic features. By performing bioinformatics analysis of genomic, transcriptomic, and clinical data in an integrated cohort of 325 resectable and nonresectable PDAC, Karasinska and colleagues identified four subgroups, that is, quiescent, glycolytic, cholesterogenic, and mixed (1). These studies demonstrate that the metabolic subtypes can be identified by transcriptomic signature–based subtyping. The glycolytic subtype had the worst survival outcomes, while the cholesterogenic subtype had the longest patient survival in patients with PDAC.

What drives the metabolic subtypes? Karasinska and colleagues demonstrated that tumors with *KRAS* mutations and *MYC* copy gain were more glycolytic. However, *MYC* amplification alone had a rather weak correlation with the glycolytic genes. Of note, a previous study demonstrated that stabilization of hypoxia-inducible factor 1-alpha by MUC1, an oncogene with increased expression and aberrant signaling in pancreatic cancer, enhanced the glycolytic phenotype and worsened the overall survival on gemcitabine and FOLFIRINOX therapies (3). The studies by Karasinska and colleagues demonstrate that increased expression of *HIF1A*-regulated genes is predominant in tumors of the glycolytic subtype, whereas the cholesterogenic subtype shows the increased expression of *SREBF2* transcriptional regulator. Furthermore, components of the PI3K/AMPK and glutamine metabolism pathways are uniquely dysregulated in glycolytic and cholesterogenic tumors, with reduced expression of PRKAA1, which encodes one of the catalytic subunits of AMP-activated protein kinase (AMPK) in glycolytic tumors. This has implications for AMPK-based and PI3K-based inhibitors that are currently in preclinical and clinical studies as while some patients may respond, others may have no efficacy.

How do tumors differentially route the metabolic flux? HIF1A-driven increases in the expression of LDHA may facilitate conversion of pyruvate into lactate that can be secreted outside the cells (**Fig. 1**) in glycolytic tumors. However, in cholesterogenic tumors, increased expression of mitochondrial pyruvate carriers (MPC) may facilitate entry of pyruvate into mitochondria. MPCs that regulate mitochondrial pyruvate flux showed a differential expression in different subtypes in studies by Karasinska and colleagues. While MPC1 was frequently deleted in PDAC, MPC2 was often amplified and induced in expression in the cholesterogenic subtype to facilitate entry of pyruvate into the mitochondria for generating acetyl CoA for cholesterol biosynthesis. However, because MPC is known to be functional as a heterodimer of MPC1 and MPC2 in mammalian cells, it raises the question if MPC can be functional as a homodimer of MPC1 in tumor cells with the loss of MPC2. Only functional assays with MPC2-null cancer cells can address this question.

One of the caveats of the study is that the expression profiles of metabolic genes may not necessarily correlate with the metabolite profiles. Nonetheless, previous studies have demonstrated that increased glycolytic phenotype, as observed with increased 18F-FDG-PET signal, and the downstream increased nucleotide pools correlate with poor survival outcomes in patients with PDAC on fluoropyrimidine analogue–based therapies, including gemcitabine and 5-fluorouracil that is a component of FOLFIRINOX (3). These studies established the utility of targeting glucose metabolism and downstream nucleotide metabolism in sensitizing cells to chemotherapy. The COMPASS trial demonstrated that the basal-like subtype that had the highest expression of GLUT1 transporter, had overall poor

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Clin Cancer Res 2020;26:6–8

doi: 10.1158/1078-0432.CCR-19-2926

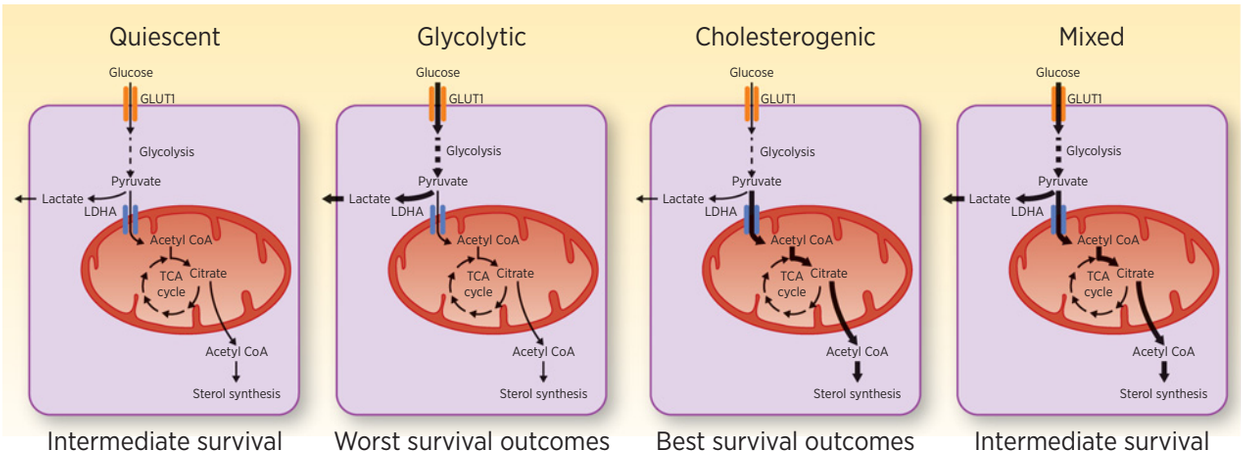

Figure 1.

Metabolic subtypes and patient survival outcomes in PDAC. The illustration depicts different metabolic subtypes characterized on the basis of the mRNA expression profiles of genes involved in glycolysis or cholesterogenesis. Patients with high tumoral expression of genes in the glycolysis pathway fall in the glycolytic cohort that shows the worst patient outcomes. Patients with increased tumoral expression of genes in the cholesterogenesis or sterol biosynthesis have the best survival outcomes. Patients with low gene expression for both the pathways and high expression of both the pathways show trends for intermediate survival.

survival on gemcitabine/nab-paclitaxel or modified FOLFIRINOX therapies (4). These studies further confirmed that majority of the glycolytic tumor subtypes belonged to the basal-like molecular cohort. Thus, high glucose uptake in PDAC corresponds to poor response to chemotherapy.

Another important limitation of the studies by Karasinska and colleagues is that the studies are primarily based on the RNA signature in primary tumors. Studies have indicated that the metabolic gene expression profiles, although generally induced in PDAC, may vary in primary tumor and metastatic lesions at different sites (5). Hence, it remains to be identified whether the glycolytic subtype would respond poorly to chemotherapy at both primary as well as the metastatic sites. The differences in the stromal components at the primary and metastatic lesion may alter response to therapy. Hence, it remains to be identified whether the primary tumors and metastatic lesions at distant sites in a given patient fall into the same molecular/metabolic subtype and whether they would respond similarly to molecularly designed therapies.

The studies by Karasinska and colleagues also suggest novel potential therapeutic opportunities. Cholesterol is critical for membrane integrity and cell growth. However, the source of cholesterol is not clear for PDAC cells. The work by Karasinska and colleagues suggests that perhaps the tumors with the glycolytic phenotype are reliant on the exogenous cholesterol and the cholesterogenic tumors rather synthesize their own cholesterol. The glycolytic tumor subtype being the one with the poor patient survival outcomes, these studies raise the possibility that statins that decrease cholesterol systemically may diminish the availability of cholesterol availability to the tumors. Thus, cholesterol availability may represent a metabolic vulnerability for the glycolytic subtype. However, it is not clear whether the tumor cells or the surrounding stroma may have sufficient metabolic plasticity to produce sufficient cholesterol in the tumor itself under the state of cholesterol depletion. Even then, it is expected that the biosynthesis may be an energy drain and thus, may diminish the aggressiveness of the tumors. Lacking such plasticity, the glycolytic subtype may efficiently be targeted by combining inhibition of glycolysis with statins. On the other hand, the cholesterogenic subtype can be efficiently targeted by targeting the cholesterogenesis directly or via MPC-1/2. However, should the tumors be plastic, targeting cholesterogenesis in the cholesterogenic subtype may also switch them to the more aggressive subtype. Thus, the metabolic subtyping will likely play a significant role in devising personalized therapeutic approaches for the patients.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

This work was supported in part by funding from the NIH grant (R01 CA163649, NCI) to K. Mehla and (R01 CA163649, R01 CA210439, and R01 CA216853, NCI) to P.K. Singh; the Specialized Programs for Research Excellence (SPORE, 2P50 CA127297, NCI) to K. Mehla and P.K. Singh; and P01 (P01 CA217798, NCI) to P.K. Singh.

Received September 24, 2019; revised October 4, 2019; accepted October 15, 2019; published first October 18, 2019.

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