Cancer metabolism challenges genomic instability and clonal evolution as therapeutic targets

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Abstract
Although cancer precision medicine has improved diagnosis and therapy, refractory cancers such as pancreatic cancer remain to be challenging targets. Clinical sequencing has identified the significant alterations in driver genes and traced their clonal evolutions. Recent studies indicated that the tumor microenvironment elicits alterations in cancer metabolism, although its involvement in the cause and development of genomic alterations has not been established. Genomic abnormalities can contribute to the survival of selected subpopulations, recently recognized as clonal evolution, and dysfunction can lead to DNA mutations. Here, we present the most recent studies on the mechanisms of cancer metabolism involved in the maintenance of genomic stability to update current understanding of such processes. Sirtuins, which are NAD+-dependent protein deacetylases, appear to be involved in the control of genomic stability. Alterations of deleterious subpopulations would be exposed to selective pressure for cell survival. Recent studies indicated that a new type of cell death, ferroptosis, determines the survival of clones and exert cancer-restricting or -promoting effects to surrounding cells in the tumor microenvironment. Suppressing genomic instability and eliminating deleterious clones by cell death will contribute to the improvement of cancer medicine. Furthermore, the elucidation of the mechanisms involved is seen as a bridgehead to the pharmacologic suppression of such refractory cancers as pancreatic cancer.

KEYWORDS
ferroptosis, metabolism, oxidative stress, pancreatic cancer, sirtuins

Abbreviations: ACSL4, acyl-CoA synthetase long-chain family member 4; APN, aminopeptidase N; ATM, ataxia-telangiectasia mutated; BRG1, brahma-related gene 1; CD44v, CD44 variant; CHD4, chromodomain helicase DNA-binding protein 4; DDB2, damage-specific DNA-binding protein 2; DSB, DNA double-strand break; GLUD, glutamate dehydrogenase; GOT1, aspartate transaminase; GPX, glutathione peroxidase; GSH, glutathione; HIF1α, hypoxia-inducible factor 1 subunit alpha; HMGA2, high-mobility group AT-hook 2; HOXA13, homeobox A13; HR, homologous recombination; IGFBP1, insulin-like growth factor 2 mRNA-binding protein 1; LIN28B, Lin-28 homolog B; LOXPs, lipoxygenases; LPCAT3, lysophosphatidylcholine acyltransferase 3; PDAC, pancreatic ductal adenocarcinoma; PD-L1, programmed death-ligand 1; ROS, reactive oxygen species; RPA1, replication protein A1; SIRT1, sirtuin 1; SLC3A2, solute carrier 3A2; SLC7A11, solute carrier 7A11; YTHDC2, YTHDC2-B homology domain containing 2; α-KG, α-ketoglutarate; γH2AX, H2A.X variant histone.

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive and lethal malignancies with a poor 5-year survival rate of 5% due to a poor early diagnosis rate and limited response to treatments, despite the findings of recent extensive studies that stratified patients according to treatment to discover subtype-specific therapies. Clinical sequencing has elucidated three subtypes of PDAC, namely classical, quasi-mesenchymal, and exocrine-like ones, which correspond to their varying responses to therapy.

Clinical sequencing has shown that mutations of the oncogene KRAS occur in more than 90% of PDACs. Other major mutations observed include the SMAD family in the TGFβ pathway and tumor suppressor genes, including TP53 and P16INK4A. Recently, a study of metabolism in PDACs demonstrated that PDAC cells rely on the distinctive pathway in which glutamine supports PDAC growth through a KRAS-regulated metabolic pathway. Through this pathway, glutamine is converted to oxaloacetate by aspartate transaminase (GOT1), and oxaloacetate is converted further into malate and then pyruvate. The metabolic pathway is associated with an increased NADPH/NADP+ ratio that results in the maintenance of the cellular redox state. The KRAS pathway in PDAC is considered essential and indispensable, and the targeting oncogenes may provide novel therapeutic approaches to the treatment of PDACs. However, few studies have elucidated the mechanisms of cancer metabolism alterations involved in genetic alterations, that is, whether they are a result of genomic instability, as is characteristic of malignant tumors. Dysfunction in the maintenance of genomic stability will elicit the clonal evolution of cancers. The control of cancer metabolism, genomic instability, and cell death is expected to be useful in creating a new era of cancer medicines against refractory cancer cell clones, such as those of PDACs (Figure 1).

SIRTUINS CONTROL GENOMIC STABILITY IN PDACs

Although metabolism and DNA repair are considered different processes, and the point of contact of their mechanisms has not been clarified, recent studies have reported that several NAD+-dependent signaling pathways regulate cell cycle progression and transcriptional regulation, as well as DNA repair, in response to genotoxic insult damages. NAD+-dependent protein deacetylases, such as sirtuins, are involved in DNA damage responses, such as repair and recombination, during replication. The sirtuin 1 (SIRT1) complex is involved in homologous recombination (HR) repair by reducing nucleosome density at DNA damage sites. The ATPase domain of brahma-related gene 1 (BRG1) and the zinc finger domain of SIRT1 interact with poly-ADP ribose in response to DNA damage and are responsible for repairing broken DNA.

FIGURE 1 Genomic and metabolic alterations in pancreatic ductal adenocarcinoma (PDAC) development. The schema represents the development of PDAC from pancreatic intraepithelial neoplasia (PanIN) 1, 2, and 3 in the precancer stages. Clinical sequencing results indicate the mutation frequencies of KRAS (99%), TP53 (85%), and SMAD4 (55%) and telomere shortening (91%), although numerous additional mutations occur during the metastatic process. Tissue abnormality has been associated with hypoxia and the Warburg effect at early and advanced stages of pancreatic carcinogenesis, but recent studies have shown that cancer metabolism alterations such as phosphatidylinositol-3 kinase (PI3K), AKT, mammalian target of rapamycin (mTOR), and sirtuins are supposed to be involved at least from PanIN 2 stages and can elicit oxidative stress and damage responses associated with genomic instability. Such alterations may induce further mutations in advanced stages of PDAC. Antitumorigenic adaptive immune response may be involved in early stages of pancreatic carcinogenesis, whereas protumorigenic innate immune response may be involved in advanced stages of PDAC. Oxidative stress controls the function of inflammatory cell types and mechanisms underlying genomic instability in PDAC. As the effect of genomic instability, numerous neoantigens can be targets of immune cells.
DNA ends. At the damage sites, SIRT1 deacetylates BRG1 at lysine residues 1029 and 1033, which stimulates ATPase activity to promote HR.6 SIRT2 and SIRT3 are reportedly involved in HR by utilizing I-SceI endonuclease-based green fluorescent protein reporter assays, which makes the precise introduction of DNA double-strand breaks (DSBs) possible. This study indicates that SIRT2 or SIRT3 is involved in the recruitment of RAD51 to DSB sites, an essential step for RAD51-dependent HR repair, as well as in the colocalization of the H2A.X variant histone (γH2AX) foci with replication protein A1 (RPA1).7 The deacetylase SIRT6 is reportedly involved in chromatin remodeling and DNA damage response. SIRT6 was found recruited to sites of UV-induced DNA damage and stimulated the repair of such damage by targeting damage-specific DNA-binding protein 2 (DDB2).8 Moreover, SIRT6 is responsible for more efficient DNA DSB repair. A panel study on rodent species with diverse lifespans indicated that DSB repair and SIRT6 were optimized during the evolution of longevity, which provides new targets for antiaging interventions.9 Furthermore, SIRT6 can coordinate with the chromatin remodeler chromodomain helicase DNA-binding protein 4 (CHD4) to promote chromatin relaxation in response to DNA damage.10 DNA damage can induce the activation of ataxia-telangiectasia mutated (ATM) protein by TIP60 acetylation and autophosphorylation, which trigger the cascade of DNA damage response and repair, whereas SIRT7 is essential to the dephosphorylation and deactivation of ATM, suggesting that SIRT7 regulates ATM activity and DNA damage repair.11 Given that DNA damage response defects are closely associated with genomic instability, an underlying hallmark of cancer, the appropriate functions of sirtuins are essential to the maintenance of DNA fidelity during replication and resultant genomic integrity.

In pancreatic cancer, SIRT1 regulates acinar-to-ductal metaplasia differentiation by deacetylating pancreatic transcription factor-1α and β-catenin, depending on its subcellular localization, and supports cancer cell viability, which can result in the sensitization of tumor cells to the SIRT1/2 inhibitor tenovin-6. Thus, SIRT1 may be an important regulator and potential therapeutic target in pancreatic carcinogenesis.12 Moreover, SIRT3 is involved in the hypoxia-inducible factor 1 subunit alpha (HIF1α) pathway, which is regulated by the tumor suppressor profilin 1. The mechanism to the HIF1α pathway is independent of its cytoskeleton-related activity, although profilin1 was originally identified as an actin-associated protein.13 Furthermore, a study on SIRT3 and SIRT7 as biomarkers for determining patient outcome indicated tumor-suppressing properties in the context of pancreatic cancer.14 In addition, a previous study demonstrated that the loss of SIRT6 resulted in histone hyperacetylation at the Lin-28 homolog B (LIN28B) promoter, MYC proto-oncogene recruitment, and pronounced induction of LIN28B and downstream let-7 target genes, high-mobility group AT-hook 2 (HMGA2), insulin-like growth factor 2 mRNA-binding protein 1 (IGF2BP1), and IGF2BP3.15 The overall significance of SIRT1, SIRT3, SIRT6, and SIRT7 in cancers has indicated their use as therapeutic targets against pancreatic cancer.5 Nevertheless, the involvement of sirtuins in the control of genomic stability at exact molecular levels needs further elucidation, which would be important in the development of novel drugs (Figure 2).

3 | LIPID-REACTIVE OXYGEN SPECIES CAN INDUCE FERROPTOSIS IN PDAC CELLS

Recent studies have indicated that the inevitable production of reactive oxygen species (ROS) during unlimited proliferation, a characteristic of tumors, is involved in the biological process of cells such as insults to DNA, repair of induced damage, and induction of cell death.16 Given that a hallmark of cancer is unregulated proliferation,1718 a detailed understanding of the mechanism of tumor survival against physiological stimuli and therapeutic inductions of cancer cell death is needed. A new form of regulated cell death, ferroptosis, was discovered in 2012,19 which involves the presence of intracellular iron and the accumulation of ROS. Recent studies have shown that such iron-regulated form of cell death can be caused by the accumulation of lipid-based ROS.16 Previous studies demonstrated that unique features of ferroptosis were frequently attributed to other cell death pathways, such as necrosis, apoptosis, autophagy, and programmed cell death, but ferroptosis appears to play a central role in multiple pathologies.16 These significant studies indicated that the following three factors can stimulate the ferroptoticy pathway: (1) long-chain polyunsaturated fatty acids contained in phospholipid membranes; (2) redox-activated iron; and (3) defects in the lipid peroxide repair system. Certain molecular substances can also target important proteins and related metabolic pathways to trigger these processes, which are associated with cancer-acquired drug resistance and immune evasion.20

Among those factors, the redox activation system is well characterized.20 The catalytic subunit of system Xc– has a critical role in dependent antioxidant function. A recent study indicated that the import of oxidized cysteine (cystine) by the deletion of a solute carrier 7A11 (SLC7A11), the catalytic subunit of system Xc–, induced PDAC-selective ferroptosis, a form of cell death that results from the catastrophic accumulation of lipid-based ROS, and resulted in the inhibition of PDAC growth; this molecule is involved in stemness of cancer cells.21 Antioxidant function can also contribute to tumorigenesis by suppressing cell death during chemotherapy and radiation therapy. Antioxidant function is activated by the transulfuration pathway of one-carbon metabolism, which is involved in various S-adenosyl methionine-induced methylation reactions.22

Interestingly, a recent study indicated that the m6A reader YT521-B homology domain containing 2 (YTHDC2), which can bind to methylated RNA and is frequently suppressed in lung adenocarcinoma, inhibits lung adenocarcinoma tumorigenesis by suppressing the catalytic subunit of system Xc–-dependent antioxidant function, indicating SLC7A11 is the direct target of YTHDC2.23 Furthermore, another subunit of system Xc–, solute carrier 3A2 (SLC3A2), was
found equally important for YTHDC2-induced ferroptosis. The same study showed that YTHDC2 is involved in the m⁶A-dependent destabilization of a transcription factor, homeobox A13 (HOXA13) mRNA, which plays a role in the promotion of SLC3A2 gene expression. YTHDC2 can be a powerful endogenous ferroptosis inducer that can suppress this solute carrier, such as TP53 and P16INK4A
essential for the ferroptosis, YTHDC2 upregulation can be an alternative ferroptosis-based cancer treatment.\textsuperscript{24}

In the downstream of system $X_C^−$, the glutathione peroxidase (GPX) family proteins reduce hydroperoxides at the expense of oxidizing two molecules of glutathione (reduced, GSH). Among the eight members of the GPX family proteins in mammals, four member proteins (GPX1, GPX2, GPX3, and GPX4) harbor a selenocysteine in their catalytic centers.\textsuperscript{25} Specifically, GPX4 has a broader substrate preference and can reduce directly complex hydroperoxides.\textsuperscript{20} Ferroptosis is mediated by GPX4 activity but also by acyl-CoA synthetase long-chain family member 4 (ACSL4), lysophosphatidylcholine acyltransferase 3 (LPCAT3), and lipoxygenases (LOXs).\textsuperscript{20} The dysfunction of those pathways can elicit the induction and activation of innate immune cells, such as neutrophils,\textsuperscript{26} and ferroptotic cells are efficiently engulfed by phagocytes,\textsuperscript{27} suggesting that ferroptotic cancer cells can modulate tumor immunity. In PDACs, various forms of regulated cell death, such as apoptosis, necroptosis, ferroptosis, pyroptosis, and alkaliptosis, are involved in the process, from pathogenesis to therapeutic response. However, the exact mechanisms involving mutation burdens, such as KRAS mutations and tumor suppressors TP53 and P16INK4A, stress responses to hypoxia, poor nutrition, and chemotherapeutic reagents, and radiation exposure, remain to be understood (Figure 3).\textsuperscript{28}

4 | SIRTUINS REGULATE FERROPTOSIS IN DAMAGED CELLS

A recent study has described the significant role of SIRT1 in the induction of ferroptosis in liver damage in mice.\textsuperscript{29} A deficiency in intestinal SIRT1 mitigates ferroptosis, which protected mice from ethanol-induced liver damage. This finding indicates that targeting SIRT1-dependent ferroptosis signaling in the intestine and liver may be therapeutic against liver damage,\textsuperscript{29} although the detailed mechanism remains to be elucidated. SIRT3 is reportedly involved in the induction of autophagy-dependent ferroptosis via the activation of the activated protein kinase–mTOR pathway and GPX4 suppression, indicating that SIRT3 deficiency provides resistance against the inductions of high-glucose–induced autophagy and its resulting ferroptosis.\textsuperscript{30} Interestingly, a study on gallbladder cancer indicated that SIRT3 plays a role in the inhibition of AKT serine/threonine kinase 1–dependent mitochondrial metabolism, as well as in the blockade of epithelial-mesenchymal transition, which thus can lead to tumor suppression by ferroptosis.\textsuperscript{31} On the contrary, a study on traumatic brain injury indicated that SIRT2 can exert a suppressive function against TPS3-mediated ferroptosis.\textsuperscript{32} A study using an experimental traumatic brain injury model suggests that the deacetylase function of SIRT2 is associated with the deacetylation of TPS3, which inhibits TPS3 expression and thus suppresses TPS3-mediated ferroptosis. Interestingly, TPS3 deficiency alleviated the SIRT2 inhibition–induced exacerbation of ferroptosis.\textsuperscript{32} Considering that TPS3 is inactivated in many cancers, whether SIRT2 may induce ferroptosis independently of TPS3 expression remains to be further investigated. A recent study on pancreatic cancer in mice indicated that K147 of KRAS is a SIRT2-specific deacetylation target site which was identified by mass spectrometry, and its acetylation status is associated with KRAS activity and tumor growth, suggesting that SIRT2 regulates the oncogene at the post-translational modification level.\textsuperscript{33} Moreover, a study on a PDAC model indicated that SIRT2 deficiency increases and prolongs a caerulein-induced pancreatitis-permissive phenotype, which is closely associated with the development of PDAC.\textsuperscript{34} Notably, SIRT2 loss resulted in the induction of spontaneous KRAS mutations in mice. Furthermore, the pancreas in Sirt2–/– mice exhibited a proinflammatory genomic signature. The loss of SIRT2 possibly enhanced the immune response to pancreatic injury by inflammation and induced an inflammatory phenotype permissive of the accumulation of cell clones carrying oncogenic KRAS mutations.\textsuperscript{34} Taken together, these data suggest that sirtuins control the cell death process and are involved in the elimination of damaged cells and in the survival of abnormal cell clones with deleterious mutations in refractory cancers such as PDAC.

5 | FERROPTOSIS DETERMINES CLONE SURVIVAL IN TUMOR MICROENVIRONMENT

As mentioned previously, the oxidative stress–dependent apoptotic pathway is critical in determining cell fate and cell death in the tumor microenvironment. Ferroptosis is possibly involved in the cellular response of surviving cell populations (ie, cancer stem cells)\textsuperscript{35} after therapeutic exposure to chemotherapy and radiation, the pharmacological mechanism of action of which is mainly ROS induction in cancer cells.\textsuperscript{36}

Previous studies indicated that targeting SLC7A11 increased the ROS level and reduced cysteine and GSH levels, which subsequently attenuated the viability of cancer stem cells. This phenomenon was characterized by the induction of ferroptosis. Erastin, an inhibitor of SLC7A11, was found to hold a remarkably stronger cytotoxic effect on cancer stem cells.\textsuperscript{37} SLC7A11 interacts with CD44 variant (CD44v), an adhesion molecule expressed in cancer stem-like cells.\textsuperscript{38} CD44 ablation resulted in the loss of SLC7A11 from the cell surface, thereby suppressing tumor growth in a gastric cancer mouse model with the activation of p38 (MAPK), a downstream target of ROS, and p21 (CIP1/WAF1) expression, indicating that CD44v functions as a regulator of ROS defense\textsuperscript{38} and that ROS-dependent ferroptosis may be involved in the selection of surviving clones after therapeutic interventions. Moreover, a study on head and neck squamous cell carcinoma indicated that the high expression of SLC7A11 and glutamine transporter SLC1A5 (ASCT2) is correlated with poor differentiation.\textsuperscript{39} The administration of sulfasalazine, an SLC7A11 inhibitor, exhibited cytotoxicity to cancer cells via the induction of ASCT2-dependent glutamine uptake and glutamate dehydrogenase (GLUD)-mediated α-ketoglutarate (α-KG) production. This process consequently impaired GSH synthesis and enhanced oxidative phosphorylation in
mitochondria, indicating oxidative damage.\textsuperscript{39} In addition, another study on cell membrane–bound aminopeptidase N (APN) indicated that APN plays a role in the reduction of ROS levels in cancer stem cell clones.\textsuperscript{40} The inhibition of APN resulted in the induction of cell death due to oxidative stress after exposure to chemotherapeutic agents.\textsuperscript{41} Although multiple cell death pathways are suggested in therapeutic resistance in PDAC,\textsuperscript{42} ROS-dependent cellular responses possibly play a critical role in determining which cells survive. Monitoring by measurement or sequencing will help obtain an exact diagnosis and determine further therapeutic targets.

Given that intratumor heterogeneity is one of the causes of the intractability of cancers, the sustained survival of cancer stem cells and their derivative clones may be involved in the generation of tumor heterogeneity.\textsuperscript{43} A super-computational analysis of colorectal cancer revealed that driver gene aberrations were observed in patients with early-stage cancer, whereas parental clones branched into numerous subclones in advanced-stage cancer, with minor mutations such as neutral evolution.\textsuperscript{43} A previous sequence analysis of PDAC demonstrated that clonal populations that give rise to distant metastasis are represented within the primary tumor tissues. The clonal populations are genetically evolved from nonmetastatic clones, suggesting that at least five more years are required for the acquisition of metastatic ability,\textsuperscript{44} presumably via the accumulation of spatial and genetic divergences of mutations over time.\textsuperscript{45} A deep sequence analysis indicated that epithelial remodeling via the expansion of clones with driver mutations is an inevitable consequence of normal aging and depends on lifestyle risks, such as tobacco or alcohol use.\textsuperscript{46} A study on long-term survivors of pancreatic cancer indicate the involvement of MUC16/CA125 neoantigens, which were lost during metastatic progression, suggesting neoantigen immunoediting.\textsuperscript{47} Although many studies have suggested that oxidative stress response is involved in immunological monitoring mechanisms\textsuperscript{48} and that ROS play an important role in T-cell function,\textsuperscript{49} further research is needed on the mechanism involving ferroptosis in the processes of these immunological surveillance mechanisms.

### 6 | THERAPEUTIC TARGETING IN PDAC METABOLISM

Previous studies have indicated that targeting the metabolic differences between tumor and normal cells holds promise as a novel anticancer strategy.\textsuperscript{50} Although evidence of the usefulness of therapeutic targeting in PDAC is accumulating, the previous studies actually identified several sirtuin modulators that functioned as activators or inhibitors that may be useful against several types of cancers. Resveratrol functions as an activator of SIRT1, SIRT3, and SIRT5.\textsuperscript{51,52} Resveratrol and piceatannol (both activators of SIRT1, SIRT3, and SIRT5) upregulated programmed death-ligand 1 (PD-L1) expression in breast and colorectal cancer cells via histone acetylase 3/p300–mediated nuclear factor kappa-light-chain-enhancer of activated B-cells signaling,
suggesting the usefulness of a combination of immune checkpoint therapy. In contrast, nicotinamide inhibits SIRT2 and SIRT6 and is considered beneficial in the prevention of breast cancer recurrence. In the sirtuin-targeting strategy, family-specific reagents will be necessary to be innovated, given that the standard therapeutic approaches are still not effective enough. For resectable PDAC cases, surgery followed by adjuvant chemotherapy with gemcitabine plus capcitabine is the standard of care. For borderline resectable and locally advanced unresectable PDACs, neoadjuvant protocols are utilized, whereas for metastatic PDACs, FOLFIRINOX (fluorouracil, irinotecan, and oxaliplatin) and nab-paclitaxel–gemcitabine are standard treatment options in patients with good performance status. We therefore emphasize that understanding the underlying mechanisms that allow sirtuins to show apparently two opposite anticancer roles should be one of our main challenges in developing effective PDAC treatment (Figure 4).

Improving the treatment results of pancreatic cancer has been a longstanding goal in the oncological field. The genetic changes in pancreatic cancer are relatively simple, centered on KRAS drivers; however, their biological malignancy is extremely high. As analyzed in this paper, the metabolic characteristics of pancreatic cancer are closely related to genomic changes. Clarifying the mechanism for the selection and creation of dangerous clones is a major challenge in the medical treatment of pancreatic cancer. If the dangerous clones resulting from the oxidative stress response can be eradicated, current standard treatments can be combined to improve the outcome of pancreatic cancer.

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