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MINIREVIEWS

Targeting pancreatic cancer immune evasion by inhibiting histone deacetylases

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Abstract

The immune system plays a vital role in maintaining the delicate balance between immune recognition and tumor development. Regardless, it is not uncommon that cancerous cells can intelligently acquire abilities to bypass the antitumor immune responses, thus allowing continuous tumor growth and development. Immune evasion has emerged as a significant factor contributing to the progression and immune resistance of pancreatic cancer. Compared with other cancers, pancreatic cancer has a tumor microenvironment that can resist most treatment modalities, including emerging immunotherapy. Sadly, the use of immunotherapy has yet to bring significant clinical breakthrough among pancreatic cancer patients, suggesting that pancreatic cancer has successfully evaded immunomodulation. In this review, we summarize the impact of genetic alteration and epigenetic modification (especially histone deacetylases, HDAC) on immune evasion in pancreatic cancer. HDAC overexpression significantly suppresses tumor suppressor genes, contributing to tumor growth and pro-

gression. We review the evidence on HDAC inhibitors in tumor eradication, improving T cells activation, restoring tumor immunogenicity, and modulating programmed death 1 interaction. We provide our perspective in targeting HDAC as a strategy to reverse immune evasion in pancreatic cancer.

Key Words: Histone acetylation; Histone deacetylases inhibitors; Immune evasion; Pancreatic cancers; Pancreatic ductal adenocarcinoma

Core Tip: There are several broad reviews covering histone deacetylases (HDAC) in cancer but none on its role in modulating immune evasion in pancreatic cancer. This is the first review to discuss the role of HDAC in the context of immune-evading pancreatic cancer. We also summarize the evidence of HDAC inhibitors in targeting immune-evading pancreatic cancer. This mini review also covers our perspective in the strategies to target overexpression of HDAC in pancreatic cancer.

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INTRODUCTION

Pancreatic cancer is the seventh most common cause of cancer-related deaths worldwide[1]. Pancreatic ductal adenocarcinoma (PDAC) is the most ubiquitous type of pancreatic cancer and remains incurable for 95% of patients. Pancreatic cancer is characterized by a devastating prognosis, with the lowest overall 5-year survival rate among all cancers[2]. The average survival time for pancreatic cancer is less than six months if left untreated[3]. Pancreatic cancer is thus estimated to be the second leading cause of death in the United States by 2030[3].

The dismal prognosis of PDAC is partly contributed by the lack of early clinical symptoms and poor sensitivity of PDAC diagnostic tests. Moreover, the treatment modalities available to date are generally ineffective for management of PDAC. Currently, the mainstay treatment for PDAC is surgery but only approximately 10% of PDAC patients qualify for surgical resection upon diagnosis[4]. Among the patients who undergo surgical resection, only < 25% could survive for more than five years. Besides, chemotherapeutic strategies have been exhausted in PDAC treatment, in which the use of chemotherapy has been limited by its well-established low efficacy, high toxicity and drastic decline in quality of life [5]. As a result, the search for an effective treatment regimen for PDAC remains a significant challenge.

Recently, immunotherapy has been hailed as a breakthrough in the realm of cancer therapy, which warrants further exploration for PDAC treatment. The use of immunotherapy in PDAC, however, is largely limited by its immune evasion barrier[6]. Thus, understanding the diverse mechanisms underlying the immune evasion in pancreatic cancer may empower the search for methods to tackle and prevent the bypass of immune surveillance[6,7].

GENETIC ALTERATION IN PDAC POTENTIATES ITS IMMUNE EVASION CAPABILITY

PDAC is an exocrine pancreatic cancer derived from pancreatic ductal cells. The progression to PDAC is characterized by its transition from normal pancreatic ductal cells to pancreatic intraepithelial neoplasia (PanIN) or its precursor lesions[8]. PanIN may be differentiated into three grades based on its histological or architectural changes[8]. PanIN1A and PanIN1B are characterized by the low-grade dysplasia while PanIN2 is characterized by the loss of polarity, nuclear crowding, enlargement of cell, and its typical papillary development. PanIN3 represents mature lesions with drastic nuclear aberrations, luminal necrosis, and show epithelial cell budding into the ductal lumen[8]. High-grade PanIN is almost uniquely found in invasive PDAC[8]. These precursor lesions develop into invasive PDAC following the accumulation of genetic mutations (Figure 1). Pertinent genetic alterations include *KRAS* oncogene mutation, the initiating genetic event in PDAC, followed by the loss of function in essential tumor suppressor genes such as *CDKN2a*, *TP53* and *SMAD4* (Figure 1).

KRAS oncogene mutation is found in nearly all PDACs[9]. High expression of the mutated *KRAS* is also associated with poor prognosis[9]. The *KRAS* GTPase switches between being bound to guanosine

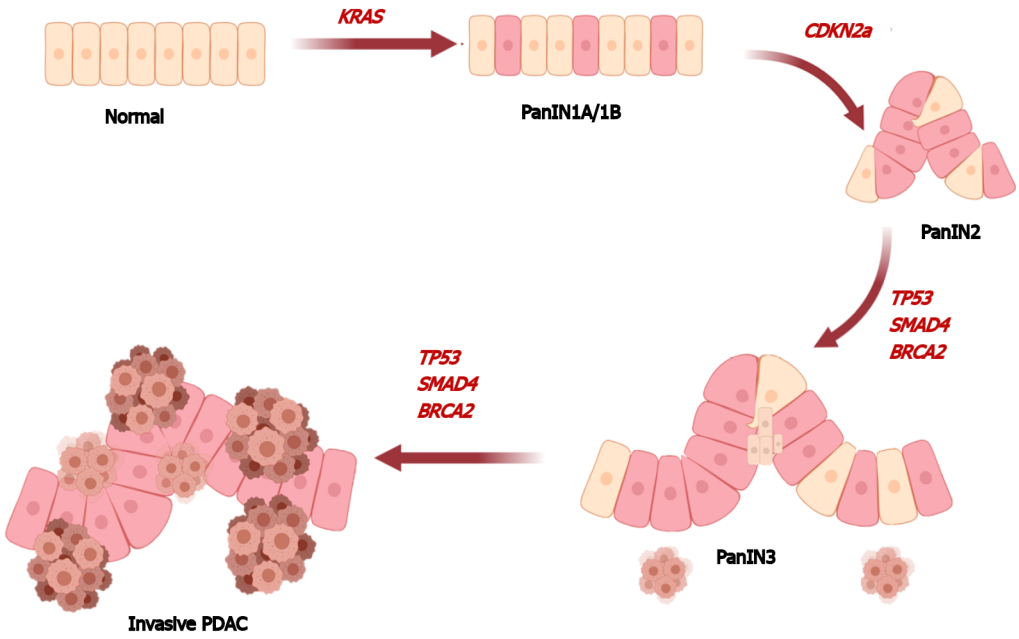

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Figure 1 Association of common genetic alterations and pancreatic ductal adenocarcinoma pathogenesis. The progression from the early to invasive stage of pancreatic ductal adenocarcinoma (PDAC) is supported by different genes alteration at different stages. *KRAS* mutation transforms the normal pancreatic ductal cells to pancreatic intraepithelial neoplasia (PanIN). The PanIN1A, PanIN1B and PanIN2 are low grade PanIN. Additional mutation such as *CDKN2A* is required to develop PanIN2. As the disease deteriorates, additional genes mutation such as *TP53*, *SMAD4* and *BRCA2* are involved to develop high grade PanIN3 and eventually invasive PDAC. PDAC: Pancreatic ductal adenocarcinoma. The figure in this review paper is created by using BioRender.com by the authors.

diphosphate, GDP (inactive state) and being bound to guanosine triphosphate, GTP (active state)[10]. In cancer development, missense mutations cause RAS to be persistently bound to GTP allowing an unlimited cellular proliferation. The alteration of *CDKN2a* results in unimpeded G1/S transformation and unrestrained cell division, facilitating tumor to evade host immunomodulation[11]. As expected, PDAC patients with *CDKN2a* inactivation are associated with poor overall survival and prognosis[11].

The metastasized tumors also exhibit several genetic alterations, namely *TP53*, *BRCA2* and *SMAD4*, indicating that these tumors have successfully evaded host immunosurveillance by leveraging on these genetic alterations[12-14]. *TP53* tumor suppressor gene on chromosome 17p is often mutated in cancer [15]. Up to 75% of PDACs present with loss or mutation of *TP53* expression[15]. The loss of *TP53* gene expression decreases cell cycle arrest and apoptosis, allowing for damaged DNA to replicate and aggregate genetic alterations. Accumulation of *TP53* mutants significantly increases the incidence of cancer metastasis[12]. Similarly, *BRCA2* is essential in restoring damages to double-stranded DNA. *BRCA2* mutations can cause alterations of *TP53* tumor suppressor genes, leading to pancreatic tumorigenesis[13]. Loss of *SMAD4* (an effector of the transforming growth factor β signaling pathway) promotes pancreatic cancer progression and increases rate of metastasis[14]. *SMAD4* inactivation in PDAC is also associated with poor prognosis and short overall survival[14].

Nevertheless, the genetic alterations in PDAC are still unable to explain the complex immune evasion in PDAC, indicating that other more pertinent underlying factors may be the driving force for immune-evading PDAC.

HISTONE DEACETYLASES IN CANCER

Epigenetic abnormalities are also crucial in carcinogenesis and the pathophysiology of cancer. Histone modification is one of the essential epigenetic processes involved in tumorigenesis and progression[16]. Histone acetylation is strictly controlled by a balance between histone acetyltransferase and histone deacetylases (HDAC) with opposing enzymatic activities. Histone acetylation is associated with an increased transcription level, while deacetylation is correlated with its repression. Histone deacetylation increases the ionic interactions between positively charged histones and negatively charged DNA, this limits the access to transcription machinery and represses gene transcription[17]. HDACs also remove acetyl groups and repress the transcription of essential genes such as tumor suppressor genes[18]. HDACs can also regulate the transcription of tumor suppressor gene *via* the formation of corepressor complexes or direct interaction with the transcription factors[19]. Notably, HDACs may also deacetylate

nonhistone proteins, resulting in dysregulation of cellular homeostasis including cell-cycle progression and apoptosis[18,19]. There are 18 potential HDACs grouped into four classes, based on their homology to yeast proteins. Class I (HDAC 1–3 and 8), Class II (HDAC 4–7, 9 and 10) and Class IV (HDAC 11) HDACs are zinc dependent while Class III HDACs are nicotinamide adenine dinucleotide (Figure 2). Class III HDACs are also referred to as sirtuins (SIRT 1–7) (Figure 2)[20].

The dysregulation of post-translational histone modification, especially histone acetylation, leads to gene transcription dysregulation. Overexpression of HDAC results in significant suppression of tumor suppressor genes, contributing to tumor growth and progression[17,20]. In PDAC, more than half of PDACs were stained positive for HDAC 1. The high expression of HDAC 1 has been correlated with a poorer distant metastasis-free survival[21]. Separately, another study also showed that overexpression of HDAC 1 was linked to a lower overall survival[22]. Treatment with HDAC 1 inhibitors decreased the invasion and metastasis ability of PDAC[21]. In addition, HDAC 2[23], HDAC 7 [24] and HDAC 8[24] overexpression is commonly found in PDAC.

Recently, HDAC has been highlighted for its contribution towards immune evasion. For example, HDAC 3 transcriptionally regulates programmed death ligand 1 (PD-L1) expression[25]. It is reported that higher expression of HDAC 3 is positively correlated with increased PD-L1 expression[25]. Such phenomena suppress immune cells that carry PD-L1 receptors, thus disputing immunosurveillance[25]. HDAC overexpression is also a common observation among other immune-evading solid tumors[17]. In particular, the high expression HDAC 1 is found in gastric and prostate cancers; while HDAC 2 overexpression is associated with gastric, cervical and breast cancers[17]. HDAC 1–3 are highly expressed in renal cell cancer and Hodgkin's lymphoma[17]. Overexpression of HDACs is linked to a significant decline in overall survival and prognosis[20]. It is believed that mutation or loss of HDAC expression is correlated with increased oncogene expression[17]. For instance, *Rb* tumor suppressor gene needs the concomitant action of HDAC to suppress transcription of other essential oncogenes. Loss of HDAC reduces the protective effect of *Rb* tumor suppressor gene[26]. Due to the roles and targetability of HDACs, targeting HDAC has garnered much attention as an effective anticancer therapeutic strategy.

HDAC INHIBITORS AS CANCER THERAPY

HDAC inhibitors bind directly to the active sites on HDAC enzymes, and inhibit the deacetylation effect of HDAC. Each HDAC inhibitor contains a cap, connecting unit, linker and a zinc-binding group that chelates the cation in the target HDAC[27]. HDAC inhibitors can be classified based on their specificity towards HDACs, namely the pan-HDAC inhibitors, Class I or Class II specific inhibitors. HDAC inhibitors can change the acetylation status of both nonhistone proteins and chromatin, causing a viable gene expression alteration, induction of apoptosis and cell cycle arrest[27]. HDAC inhibitors can target not only the tumor cell itself, but also the tumor microenvironment and immune milieu, making the use of HDAC inhibitor a promising strategy to eradicate immune evaded PDAC[27].

The overexpression of HDACs in cancer allows cancer cells to have increased sensitivity to HDAC inhibitors, leading to the induction of growth arrest, differentiation inhibition and eventual tumor cell death without compromising the nontumor cells[27]. Given PDAC's therapeutic resistance to conventional therapy, it is not surprising that the use of HDAC inhibitor as an alternative treatment option has been studied. Ivaltinostat (CG200745), a pan-HDAC inhibitor, demonstrates inhibitory effects on PDAC tumor growth by upregulating proapoptotic proteins BAX and p21[28]. Treatment of PDAC cells with belinostat (PXD101), a Class I and II HDAC inhibitor, also induces cell cycle arrest and tumor regression [29]. A Phase I clinical study using escalating doses of dacinostat (LAQ824), another pan-HDAC inhibitor, showed that the drug was well tolerated by PDAC patients[30]. A significant accumulation of histone acetylation was reported among the patients treated with dacinostat[30]. However, most patients in this trial discontinued dacinostat treatment due to disease progression[30], indicating an unresolved limitation of prescribing HDAC inhibitor as monotherapy for pancreatic cancer.

In combination, HDAC inhibitors show a better effect with other chemotherapeutic agents. The combination of two Class I HDAC inhibitors, romidepsin and ricolinostat (ACY-1215), showed potent synergy with gemcitabine in a panel of PDAC cell lines[31]. Combination of entinostat (Class I HDAC inhibitor), vorinostat (Class I and II HDAC inhibitor) and cyclooxygenase (COX)-2 inhibitors showed complete stalling of PDAC cell growth[32]. In addition, the use of vorinostat and trichostatin A (Class I and II HDAC inhibitor), showed induction of apoptosis in caspase-independent pathways, even for antineoplastic drug-resistant PDAC cell lines[24]. Combination of trichostatin A and proteasome inhibitor PS-341 downregulated antiapoptotic factors and synergistically induced apoptosis[33]. In a separate study, trichostatin A together with silibinin demonstrated a synergistic growth inhibitory effect on PDAC cells by inducing G2/M cell cycle arrest and apoptosis[34].

Meanwhile, the combination of ivaltinostat, gemcitabine and erlotinib significantly reduced PDAC tumor size up to 50%[28]. Ivaltinostat enhanced gemcitabine sensitivity in gemcitabine-resistant pancreatic cancer cells[28]. The use of valproic acid (Class I HDAC inhibitor) confers a synergistic effect with gemcitabine on PDAC cells, lending support to the postulation that targeting HDAC may be a promising strategy to overcome therapeutic resistance and circumvent immune evasion strategies[35].

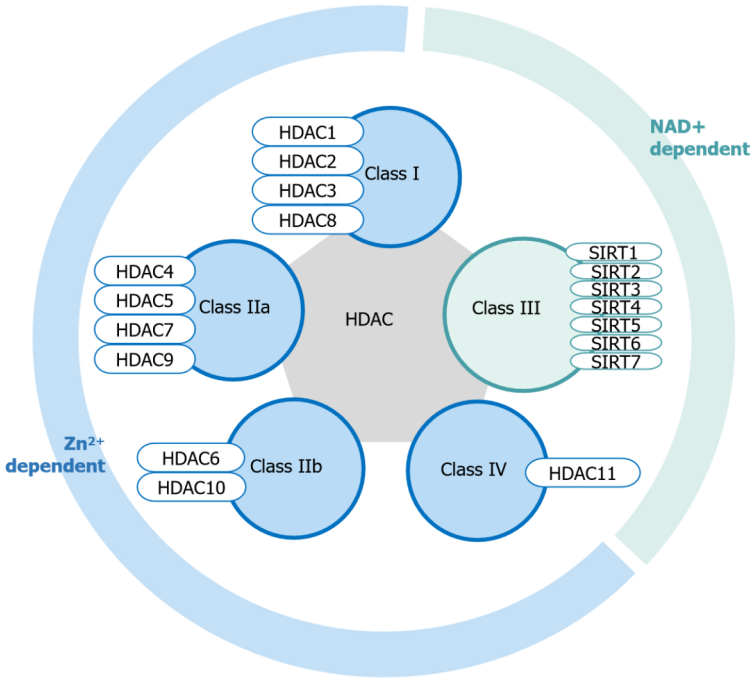

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Figure 2 Histone deacetylases classification. Histone deacetylases (HDAC) can be divided into two major classes, namely Zn-dependent and NAD dependent. Class I (HDAC 1–3 and 8), Class IIa (HDAC 4, 5, 7 and 9), Class IIb (HDAC 6 and 10) and Class IV (HDAC 11) are Zn-dependent HDAC. Class III (SIRT1 to 7) is NAD^+ dependent HDAC. HDAC: Histone deacetylases. The figure in this review paper is created by using BioRender.com by the authors.

HDAC inhibitors demonstrated anti-angiogenic effects by regulating angiogenic related transcriptional factors such as von Hippel-Lindau (VHL), hypoxia inducible factor-1a (HIF-1a) and vascular endothelial growth factor (VEGF)[36]. Rosengren RJ team found novel HDAC inhibitors, Jazz90 and Jazz167, which had a superior potency and anti-angiogenic effects than conventional HDAC inhibitor suberoylanilide hydroxamic acid (SAHA) in prostate cancer cell lines[37]. Independently, Vyas A team synthesised novel SAHA analogues with greater anti-angiogenic effects using the chick chorioallantonic membrane assay[38]. Several clinical trials are ongoing to evaluate the clinical benefits of HDAC inhibitors in targeting angiogenesis in cancer, however, to the best of our knowledge, there is no solid evidence on its benefits among pancreatic cancer patients. More studies are needed to investigate the potential of HDAC inhibitors as anti-angiogenesis agents in PDAC.

In view of their promising combinatory therapeutic efficacy, there has been growing interest in the use of HDAC inhibitors with other therapeutic agents for pancreatic cancer patients (Table 1). However, the use of HDAC inhibitors has been studied in the treatment of lymphoma and other nonpancreatic tumors[39]. For example, HDAC inhibitor has been approved by the FDA for various cancer treatments. Romidepsin[40] and vorinostat[41] have been approved for refractory cutaneous T cell lymphoma while panobinostat[42] (Class I, II and IV HDAC inhibitor) has been approved for multiple myeloma. Likewise, belinostat[42] and tucidinostat[39] (Class I, II, and III inhibitor) have been approved for the treatment of peripheral T cell lymphoma.

HDAC INHIBITORS REVERSE IMMUNE EVASION IN CANCER

HDAC inhibitors enhance immune cell activation

The PDAC tumor microenvironment is composed of regulatory T cells, tumor-associated macrophages (TAMs) and myeloid-deprived suppressive cells (MDSCs) that inhibit ability of cytotoxic T cells (CTLs) in tumor recognition and clearance[6,43]. Cells in the tumor microenvironment can also produce immunosuppressive cytokines including interleukin (IL)-1, IL-6, IL-10, and tumor necrosis factor-α (TNF-α) to cause T cell anergy or tolerance, resulting in immune evasion[44]. Other important cells in the tumor microenvironment include the fibrotic matrix, pancreatic stellate cells and cancer associated fibroblasts (CAFs); all of which can adhere to infiltrating T lymphocytes and prevent their entry into cancer cells, resulting in T cell anergy[44]. In particular, the activated CAFs create a dense stroma that dominates in PDAC, mediating tumor growth and survival by the production of extracellular matrix proteins, growth factors and cytokines[6,45]. CAFs represent the majority type of cells in PDAC stroma and have been acknowledged to be one of the key contributing factors to the immune evasion of cancer cells[45]. CAFs can limit access of infiltrating immune cells to cancer cells through the release of dense

Table 1 Investigational histone deacetylases inhibitors in pancreatic cancer patients

HDAC[1] specificity	Intervention	Clinical trial phase	Study start date	Status	Clinical trial reference code
Pan-HDAC	Vorinostat + Marizomib	I	March 2008	Completed	NCT00667082
Pan-HDAC	Vorinostat + Capecitabine + Radiation Therapy	I	October 2009	Completed	NCT00983268
Pan-HDAC	Vorinostat + Gemcitabine + Sorafenib + Radiation Therapy	I	January 2015	Active	NCT02349867
Pan-HDAC	Vorinostat + Radiation Therapy	I and II	March 2009	Terminated	NCT00831493
Pan-HDAC	Vorinostat + 5-fluorouracil + Radiation Therapy	I and II	August 2009	Terminated	NCT00948688
Pan-HDAC	Panobinostat + Bortezomib	II	September 2010	Terminated	NCT01056601
Class I	Entinostat	I	March 2001	Completed	NCT00020579
Class I	Entinostat + Nivolumab	II	November 2017	Completed	NCT03250273
Class I	Entinostat + ZEN003694	I and II	March 2022	Not yet recruiting	NCT05053971
Class I	Entinostat + Molibresib	I	September 2020	Withdrawn	NCT03925428
Class I	Entinostat + FOLFOX[2]	I	January 2021	Withdrawn	NCT03760614
Class I	Tacedinaline + Gemcitabine	II	October 1999	Completed	NCT00004861

[1]HDAC: Histone deacetylases.
[2]FOLFOX regimen consists of folinic acid, 5-fluorouracil, and oxaliplatin.

collagen networks, resulting in a physical hurdle that disrupts T cell dispersal and inhibition of T cell migration in areas of increased collagen deposition, such as that of PDAC tumors[45]. CAFs have been demonstrated to upregulate immune checkpoints on Cluster of Differentiation (CD)4$^+$ T cells and CTLs, thus resulting in reduced immune function of T cells[45]. Within the immunosuppressive tumor microenvironment, PDACs can disrupt the immunogenic effects of CTLs, by which the CTLs that presented in PDACs may be poorly cytotoxic and nonfunctional[46]. Multiplex staining has demonstrated that proximity of T cells to PDACs is correlated with patient prognosis and survival[47]. As a result, exclusion of T cells from the tumor microenvironment correlates with the tumor initiation and progression.

HDAC inhibitors can modulate immune evasion by modulating immune cell functions[48]. HDAC inhibitors can also increase the expression of major histocompatibility complex (MHC) and its costimulatory molecules leading to T-cell activation[48]. For example, AR42 (a pan-HDAC inhibitor) enhances its adaptive immunity through improving the functions and capabilities of CTLs and natural killer (NK) cells in murine melanoma[49]. Meanwhile, trichostatin A suppresses CD4 T cells from undergoing apoptosis, leading to enhanced antitumor effect[50]. Entinostat increases CTL cytotoxic function and T cell signatures in ovarian tumors[51]. Entinostat also reverses CTL–T regulatory (Treg) cell ratios in the ovarian tumor microenvironment, thus facilitating CTL accumulation at the tumor site[51]. Therefore, HDAC inhibitors have a pivotal role in sustaining T-cell-mediated antitumor immunity. Further studies are required to understand their underlying mechanisms in reversing T cell resistance.

HDAC inhibitors enhance tumor immunogenicity

The intrinsic resistance of PDAC tumors to immune eradication is mainly due to its nonimmunogenic characteristic[6,7]. Tumors can further evade CTL-induced tumor lysis *via* immunoediting, or changes in immunogenicity of cancer cells[52]. Host immune system can alter the expression profile of tumors, in turn enabling them to evade immune detection[53]. The development of PDAC has been described to reflect the three Es of cancer immunoediting, which are elimination, equilibrium and escape[6,54]. The elimination phase occurs during cancer immunosurveillance, when immune effector cells are enlisted to the cancerous tissue to eliminate PDAC cancer cells. Immune effector cells, including CTLs can eliminate most of the vulnerable tumor cells, leaving the resistant tumor clones behind. These resistant tumor clones then expand and remain undetected by the immune system. During the equilibrium phase, a unique equilibrium between antitumor and protumor immune cells is sustained until tumor escape mechanisms are established. During the escape phase, an immunosuppressive microenvironment is formed with the presence of TAMs and MDSCs, creating an effective barrier against the effector immune cells such as CTLs[6,54]. Taken together, such immunoediting has allowed PDAC to bypass immune detection, whereby PDAC continues to grow, progress and metastasize.

HDAC inhibitors may reverse immune evasion in tumors by enhancing tumorigenicity. Trichostatin A induced suppression of tumor growth by improving the immunogenicity of the metastatic tumor cells in a murine study[21,55]. Trichostatin A also increased the MHC Class I expression that translated into enhanced susceptibility to being killed by cytotoxic T cells[55]. Entinostat altered the tumor microenvironment by increasing the MHC Class II expression and its transactivator[56]. Entinostat also re-expressed the natural killer cell receptor and ligand, leading to a decrease in the immunosuppressive effects by host immune cells[57]. Another study using vorinostat and entinostat revealed that breast and prostate carcinoma cells became more sensitive to T-cell-mediated lysis after treatment with HDAC inhibitors. Treatment with vorinostat increased CTL sensitivity, leading to tumor lysis, demonstrating the enhancement of antigen-specific CTL-mediated killing by HDAC inhibitors[58]. Entinostat can sensitize immune checkpoint inhibitors by ablating MDSC-mediated immunosuppressive effects in PDAC tumor-bearing mice[59]. Such exciting findings have rendered the researchers to launch their human clinical trial to investigate the combination of entinostat with nivolumab (a checkpoint inhibitor) in unresectable PDAC patients (Clinical Trial NCT03250273)[60]. Other studies showed that epigenetic modulators[61,62] (including HDAC) could improve tumor immunogenicity and could be a promising translational intervention in cancer.

Given the high frequency of *KRAS* mutations in pancreatic cancer patients, mRNA vaccine that targets a specific mutant has gained attraction[63]. In theory, mRNA vaccine encodes KRAS mutant-specific antigens into the host's cytoplasm, leading to the eradication of tumor cells with KRAS mutation by host's immune system[63]. mRNA-5671/V941 is being investigated as monotherapy or in combination with immunotherapy for pancreatic cancer patients with *KRAS* mutation (NCT03948763). However, it remains uncertain whether cancer vaccine could be given along with HDAC inhibitors since HDAC inhibitors may also enhance tumor immunogenicity. Barouch DH group demonstrated that the combination of romidepsin, I-BET151 and cancer vaccine enhanced the CTL cell response in a mouse model, indicating the possible synergism between HDAC inhibitor and cancer vaccine[64]. Thus, further studies are warranted to explore the efficacy of cancer vaccine as a monotherapy or in combination with other therapeutic agents.

HDAC inhibitors counteract PD-L1 and PD-1 interaction

Tumor-infiltrating lymphocytes including CTLs produce a high level of programmed death (PD)-1 while PDAC cells counteract by overproducing the specific ligand of PD-1, which is PD-L1. The interaction between PD-1 and PD-L1 results in T-cell depletion[6,65]. Studies have shown that PD-1 and PD-L1 interaction impedes T-cell growth and that tumor-cell-borne PD-L1, and thus induce apoptosis of tumor-specific T-cell clones[66]. Such transformation turns CTLs into a dysfunctional state of exhaustion that characterized by the loss of CTL proliferation ability as well as the loss of CTL cytotoxic functions [67,68]. As a result, CTLs will be downregulated, and tumor cells can then escape the cytotoxic killing by CTLs.

PD-L1 is overexpressed in PDAC and the higher level of PD-L1 has been linked to a poorer prognosis for PDAC patients[52,67]. In addition, a higher HDAC 3 expression has been linked to the increased PD-L1 expression on PDAC cells[25]. HDAC 3 modulates PD-L1 expression *via* the signal transducer and activator of transcription 3 pathway[22]. HDAC 3 inhibitor (RGFP966) reduces PD-L1 mRNA and protein expression levels, thus enhancing immunosurveillance and aiding the reversal of immune evasion[25].

Another study reported that combination of CG-745 (HDAC Class I and IIb inhibitor) and anti-PD-1 antibody showed synergistic tumor eradication in two syngeneic cancer mouse models[69]. Further mechanistic studies indicated CG-745 increased T-cell activation and macrophage M1 polarization, helping the anti-PD-1 anticancer effect[69]. In addition, HDAC inhibition with entinostat improved the antitumor effect of PD-1 blockade in two syngeneic cancer mouse models[70]. The combination of entinostat and PD-1 inhibitor reduced the tumor burden and improved its survival[70]. Additional analyses indicated that entinostat upregulated PD-L1 in tumors, blocked the immunosuppressive function of MDSCs, and reduced *COX-2*, *inducible nitric oxide synthase* (*iNOS*) and *arginase-1* mRNA expression[70]. Romidepsin enhanced the PD-1 blockade in a murine tumor model, leading to tumor rejection[71]. Individual treatment with romidepsin or PD-1 blocker did not result in significant tumor suppression[71]. Further analyses indicated that romidepsin increased PD-L1 Levels in the tumor[71]. Romidepsin and PD-1 blocker synergized by unleashing the interferon-dependent response in T-cell recruitment to the upregulated PD-L1 tumor cells[71]. Unlike entinostat[70], romidepsin-treated tumor did not alter the MDSC population[71], indicating that HDAC inhibitors have varied impacts on PD-1 and PD-L1 interaction, which can be independent of MDSC modulation. Further study is warranted to explore how HDAC inhibitor affects PD-1 and PD-L1 interaction. Such findings support the notion that HDAC inhibitors can modulate PD-1 and PD-L1 interaction in tumors apart from their canonical role in inhibiting HDAC.

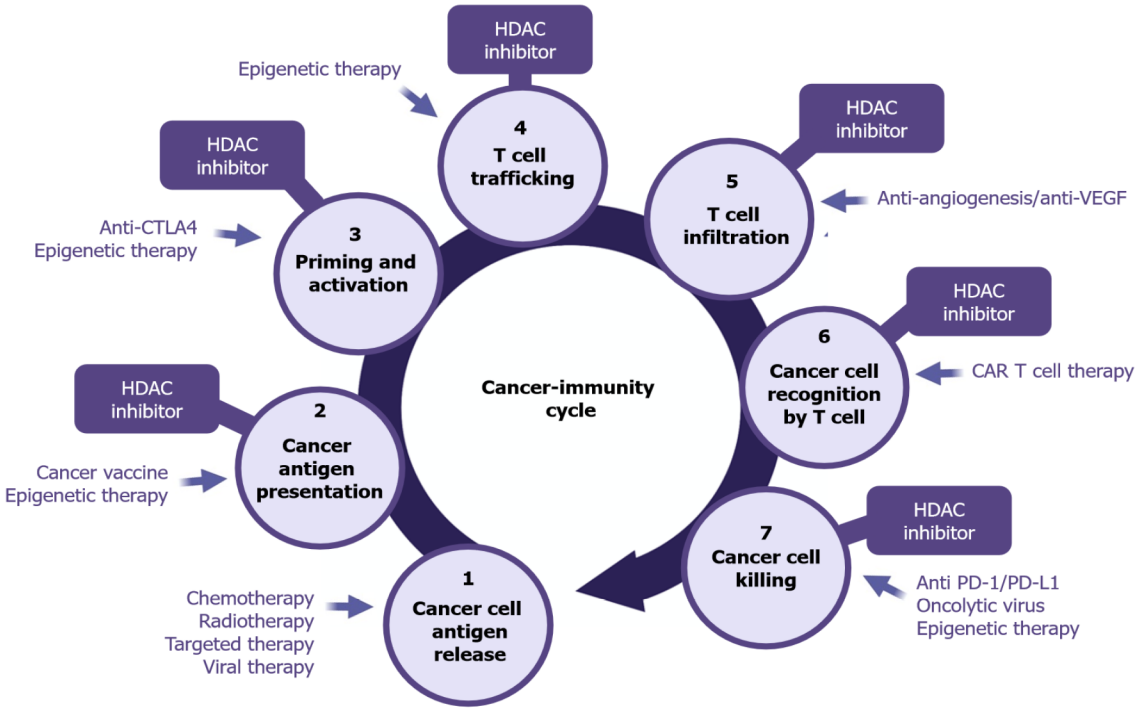

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Figure 3 Role of histone deacetylases inhibitors in targeting cancer immune evasion. Cancer–immunity cycle is a continuously cyclical process to amplify the immune response leading to cancer eradication. The cancer–immunity cycle has seven steps: Step 1: Dying cancer cells release neoantigen (Step 2). These neoantigens are captured by antigen-presenting cells and present the antigens on the major histocompatibility complex to T cells (Step 3), allowing the T cells to be primed and activated. Once T cells are activated (Step 4), T cells are transported to the tumor site and (Step 5) infiltrate the tumor. Once inside the tumor (Step 6), T cells recognize the tumor cells, and (Step 7) kill the tumor cells. Histone deacetylases inhibitors will support Steps 2–7 of the cancer–immunity cycle. Such effects can be synergized with other therapeutic agents. CAR: Chimeric antigen receptor; CTLA4: Cytotoxic T-lymphocyte associated antigen 4; PD-1: Programmed death protein 1; PD-L1: Programmed death ligand 1; VEGF: Vascular endothelial growth factor; HDAC: Histone deacetylases. The figure in this review paper is created by using BioRender.com by the authors.

CONCLUSION

PDAC is often synonymous with a "death sentence". The high mortality and poor outcome of PDAC are mainly due to PDAC being refractory to most forms of contemporary therapeutic strategies. Given that the hallmark of PDAC is a highly dense stroma and immense microenvironment, immunotherapy stands out as a promising novel approach to PDAC treatment. Chen and Mellman proposed that cancer immunity is a series of ongoing cyclical events (Figure 3)[72]. Disruption in the major events in the cancer–immunity cycle leads to immune evasion in cancer[6].

HDAC inhibitors have grained traction in medical research as a promising approach to counteracting immune evasion strategies to strengthen Steps 2–7 of the cancer–immunity cycle (Figure 3). HDAC overexpression as a contributing factor to immune evasion and subsequent carcinogenesis have been increasingly recognized. The use of HDAC inhibitors to eliminate cancerous cells (Step 7 of the cancer–immunity cycle, Figure 3) is also gaining traction. Further research is warranted to investigate the effectiveness of HDAC inhibitors in cancer patients. HDAC inhibitor use may well be the key to a long-awaited treatment regimen for cancer patients. The direction for HDAC inhibitors in cancer treatment seems to lean towards combination therapy (Figure 3), with chemotherapy, radiotherapy or immunotherapy. HDAC inhibitors have been widely used with checkpoint inhibitor antibodies in preclinical models. Such combinations have demonstrated successful enhancement of antitumor efficacy and an increase in immune-cell activation.

Studies on HDAC inhibition to circumvent immune evasion are still limited. Current use of HDAC inhibitor to treat PDAC has had promising results, but studies are often still in the early preclinical stage, with much still unknown about the effect of HDAC inhibitors in PDAC patients. There remain much hope and scope in investigating HDAC inhibitors in clinical trials, which will help shed light on the effectiveness of HDAC inhibitors as an adjunct therapy in PDAC.

The ability of HDAC inhibitors to inhibit histone deacetylation may also have its limitations. HDAC inhibitors have poor physiochemical features and unfavorable pharmacokinetics[73]. HDAC inhibitors may also nonspecifically block angiogenesis, which may disrupt drug delivery through blood vessels to solid tumors[73]. In addition, the anti-inflammatory properties of HDAC inhibitors have been postulated to induce apoptosis among immune cells[73]. Current evidence supports the understanding

that HDAC inhibitors may counter immune-cell suppression and apoptosis by enhancing anti-PD1 blockade effects[25]. Moreover, there must be an intact immune function in the host as a prerequisite for HDAC inhibitors to modulate antitumor immune response[6]. Moreover, HDAC inhibitors have yet to utilize the current advanced drug delivery systems that offer site-specific drug delivery[74] with enhanced tumor targeting and reduced toxicity[73]. We believe that, by targeting HDAC in the immune evaded pancreatic cancer, the greatest therapeutic outcome will emerge.

FOOTNOTES

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