HHS Public Access

Author manuscript

Semin Cancer Biol. Author manuscript; available in PMC 2020 August 01.

Published in final edited form as:

Semin Cancer Biol. 2019 August ; 57: 19–26. doi:10.1016/j.semcancer.2018.09.008.

Metabolism and Epigenetics of Pancreatic Cancer Stem Cells

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Keywords

pancreatic cancer; cancer stem cells; epithelial-to-mesenchymal transition; stemness; acinar-ductal-metaplasia; metabolism; epigenetics

Introduction

Pancreatic Cancer (PDA) is an aggressive malignancy, usually diagnosed at advanced stages and with a dismally low 5 year survival rate of less than 9%[1]. Early disease spread and local invasion combined with the high incidence of chemoresistance and lack of effective immunotherapy, makes PDA the 3rd leading cause of cancer-related death in the United States [2, 3].

Cancer stem cells (CSC) are undifferentiated quiescent cells characterized by their ability to self-renew coupled with unique plasticity and metabolism [4]. In PDA, CSC are thought to comprise a small subpopulation within the tumor reported to be responsible for driving tumorigenesis and progression of the disease [5]. Emerging evidence suggests that CSC play an important role in disease recurrence and metastatic events and may represent the primary source of resistance to chemotherapy and radiation [6, 7]. The origin of pancreatic CSC remains unknown, but recent data cites local factors present in the tumor microenvironment as supportive of cellular persistence in a relatively undifferentiated state which may favor their development [8–15]. The classical CSC model proposes a hierarchical origin where the bulk of the tumor is constituted by non-CSC and a apical small portion is constituted by CSC that serve as a quiescent, self-renewing pool that can differentiate and replenish the non-CSC in the tumor ([16, 17] Figure 1).

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All authors have read the manuscript and report no conflicts of interest.

Recent attention has focused on links between epigenetics and metabolism of CSC as potential mediators of their renewal capacity and chemoresistance suggesting possible new drug targets for these difficult-to-eradicate cells [18]. Because epigenetics represents a clear link connecting environmental effects and gene expression, this new arena of research could provide clues connecting known risk factors such as smoking and diet to the development of PDA [19, 20]. This review will focus on the metabolic and epigenetic features of pancreatic cancer CSC. A better understanding of this cellular subpopulation's functional and phenotypic characteristics will allow us to develop more effective therapeutic strategies.

Cancer Stem Cell properties in PDA

Our understanding of the complexity of cancer at the cellular and molecular level has significantly expanded, yet the underlying mechanism aiding in evasion and resistance to therapy remains largely elusive. Advances such as the advent of single cell sequencing has revealed that tumors are composed not of single clones, but of a vast array of cellular subpopulations. The basis for the generation of the large cellular tumor heterogeneity remains, however, largely undetermined. It is believed that amongst the cancer cell population, a fraction of the cells hold stem-cell-like characteristics including capacity to not only replicate, but produce progeny that are unique from themselves [21, 22]. The CSC hypothesis has been postulated for decades, stating that a small portion of undifferentiated quiescent cancer cells with limited growth were the source of differentiated cancer cell progeny. Along with the ability to self-renew, this CSC population has unique plasticity and metabolism, as well as enhanced chemoresistance [23, 24].

CSC in PDA were empirically defined by two major techniques, using tracing of genetic lineage markers [25] or by assessment of tumorigenesis in limiting dilution after transplantation into immunodeficient mice [26, 27]. CSCs were identified in other malignancies including lung, ovarian, and prostate cancer using similar methods [28–32]. The property that few or single cells from one subpopulation of tumor cells and not from others could reproduce an entire intact cancer is felt to reflect the stem-like potential of and therefore phenotypic core of CSCs but does not provide a reliable method to identify cells or follow their development in the tumor microenvironment (TME). [33–35]. In an effort to study CSCs *in-situ*, Driessens *et al.* used clonal analysis of squamous skin cancer in which single tumor cells were genetically labelled to follow their behavior within the TME [25]. They demonstrated that while most cells had a relatively limited proliferative capacity, a small population of cells persisted long-term and eventually their progeny constituted the majority of the tumor. Unfortunately no universal cell markers have been identified yet to unequivocally and reliably distinguish CSC populations in the TME. Cell surface markers including various combinations of CD34, CD44, CD133, ESA, ALDH1 and cMet have been shown to be associated with various CSC characteristics including limiting dilution transplantability [8, 28, 35, 36] (figure 2). Nevertheless, expression of these markers varies significantly among different cancer types and investigators [36, 37]. In PDA a small subset of tumor initiating cells were originally described by Li *et al.* using a xenograft mouse model transplanting subpopulations of cells from PDA patients into immunodeficient mice. They found that a small group of cells labelled as $CD44^+$, $CD24^+$, ESA^+ could recapitulate features of the original tumor when injected into mice, while the larger population of cells

could not. Although those cells constituted less than 1% of the original tumor they were a 100 times more tumorigenic than their non-CSCs counterparts [28]. In recent years additional PDA CSA specific cell markers have been characterized including CD133, CXCR4 and cMet [28, 38, 39]. Using these markers and various cell sorting techniques, researchers have begun to unfold some of the phenotypic characteristics unique to PDA CSC. Hermann *et al.* characterized $CD133^+$ cells as CSC-like and gemcitabine-resistant and identified this population as essential for metastasis formation [39]. Isolation of cMet positive cells from human pancreas cancer specimens yielded cells with heightened tumorigenic potential as well as self-renewal capacity [38]. In addition to unique surface markers, PDA CSC were found to have high ALDH1 activity, a detoxifying enzyme which is essential for the early differentiation of stem cells [38]. Recent studies have shown that high levels of ALDH1 may provide protection against chemotherapy and represent a target in battling chemoresistance [40].

A subpopulation of Pancreatic cancer CSC, derived from parental PDA cell lines were demonstrated to have increased aggressive behavior. Bao *et al.* characterized the performance of triple positive $CD44^+$, $CD133^+$, $EpCAM^+$ cells regarding migration and growth in addition to self-renewal [41]. More than 1500 genes were differentially expressed between triple positive and triple negative cells. In this study they used siRNA to demonstrate that the exacerbated aggressive behavior in this triple positive CSCs derived from MiaPaCa2 and L3.6pl cells was dependent on FoxQ1 expression. Additionally, xenograft tumors silenced for FoxQ1 in MiaPaCa2 cells displayed a clearly impaired ability to promote tumor development and growth [41].

Plasticity of CSC in PDA

Cellular plasticity is defined as the ability of the cells to alter their phenotypic state including differentiation status within a hierarchal order in response to environmental signals [4]. In the normal pancreas, acinar cells undergo trans-differentiation in response to injury, transcription factor activation, and/or metabolic or inflammatory stress, all of which promote conversion of cells to a more embryologic primitive duct-like state, a process known as ADM (Acinar-to-Ductal-Metaplasia) [42, 43]. This conversion is entirely reversible as these cells can re-differentiate back to their acinar origin when the promoting stimulus is removed, and the inhibition of ADM can prevent pancreatic regeneration (Figure 1 and [44, 45]). But if ADM happens in the presence of oncogenic KRAS mutations, the process becomes irreversible and promotes the formation of intraepithelial neoplastic regions in the pancreas, a prelude to malignant degeneration [46]. Some have proposed that persistence of cells in this trans-differentiated state, along with accumulation of further genetic mutations, is the origin of CSC in PDA [47]. The most common mutations found in PDA are aberrant activation in KRAS and inactivation of TP53, SMAD4, among others. [48]. Activation of some of these oncogenic signaling pathways influence metabolic reprogramming within the cell [49].

In PDA, a similar plasticity has been demonstrated for both CSC and non-CSC as shown by several studies where tumor cells undergo phenotypical changes in response to environmental signals [43]. CSC can change from a less differentiated stem-like phenotype

to the highly active differentiated cells that constitute the bulk of the tumor. The resulting metaplastic cell can undergo further changes when exposed to sustained stimuli and become more mesenchymal and even potentially metastatic cells [41, 50] (figure 1).

Along with plasticity CSC exhibit relative quiescence which contributes to its therapeutic resistance. Quiescence is a non-proliferative state, defined as a reversible G-zero step of the cell cycle. These quiescent cells are thought to be in an actively preserved state from which the cells can escape and re-enter the cell cycle, which protects them from chemotherapeutics and often mediates their effects during cellular replication [51]. Entry and escape from the cell cycle are regulated both by epigenetic and metabolic cues from the TME and recent data has suggested that p53 is critical in supporting a stem cell quiescence state [52].

Metabolic plasticity in cancer cells and Cancer Stem Cells

Metabolic reprograming was recognized several decades ago as one of the hallmarks of cancer cells [53, 54]. Namely, rapidly proliferating tumor cells switch to the use of aerobic glycolysis to produce ATP displaying high consumption of glucose; features known as the “Warburg effect” [55]. Tumor cells are capable of having higher metabolic rates than their normal counterparts, utilizing glucose, glutamine, several amino acids and even fatty acids as substrates [56]. Thanks to their metabolic plasticity cancer cells quickly adapt to the challenges posed by the microenvironment reciprocally contributing to the heterogenous cellular metabolic landscape of the tumor niche.

CSC metabolic pathways have recently attracted a lot of interest since they pose an emerging source of new therapeutic targets in cancer. CSC’s distinct metabolic configuration is postulated to enhance tumorigenesis improving fitness of the cancer cells as a means of adaptation to nutrient or oxygen deprived conditions [57, 58]. As a relatively quiescent cell, CSCs also have vastly lower needs for energy and material to generate biomass as compared rapidly proliferating cells. Unsurprisingly, many 0differences exist between the metabolism of CSC and non-CSC in various tumor types [59]. As an example, CSCs appear to be more versatile than the non-CSC counterpart and able to use several energy source metabolic pathways [59]. Considerable controversy exists regarding the metabolic profile of CSC in many tumor types, as opposing reports in ovarian cancer for example, describe both oxidative phosphorylation (OXPHOS) and glycolysis dependence of the CSC metabolism [60, 61]. Additionally, extensive evidence suggests that metabolism of CSCs is tumor type specific with some relying on a glycolytic program such as nasopharyngeal and liver cancers [62, 63] while others use OXPHOS such as pancreatic [64], glioma [65] [60], lung [66] or colon cancer [67]. It is possible that CSCs have adapted a relatively plastic metabolism that can adjust to the settings in which the cells reside. If oxygen is available, the more energetically efficient OXPHOS is used rendering a higher number of ATP molecules per glucose molecule. In hypoxia or stress, the cell can revert to a glycolytic programing or even in some cases utilize mitochondrial fatty acid oxidation [68]. This likely renders downstream effectors of metabolism including epigenetic changes, which will be discussed later, context-dependent and variable-based on the current conditions of the specific TME.

Metabolism in Pancreatic Ductal Adenocarcinoma

Metabolic rewiring in cancer cells is largely influenced by oncogenic pathways which promote pro-growth programs such as glycolysis and activation of glycolytic enzymes [69, 70]. In PDA, this is nearly universally driven by activating mutations in the KRAS oncogene, which results in constitutive downstream signaling [71]. In a seminal paper by Ying *et al.*, the authors used an inducible and reversible transgenic mutant KRAS mouse model to demonstrate that KRAS activation drove the initiation and maintance of PDA by its regulation of anabolic glucose metabolism [72]. In a follow-up study, Viale *et al.* demonstrated that turning off KRAS signaling led to initial tumor regression, followed by relapse from a small surviving cancer cell population. Metabolic and transcriptional characterization of these cells demonstrated that those cells had stem-like features and relied more heavily on OXPHOS rather than glycolysis for survival, suggesting a potentially important difference between CSC and non-CSC metabolism in PDA [72, 73].

In fact, efforts to target CSCs based on mitochondrial metabolism have been met with some success. A study by Sancho *et al.* observed that CSCs were highly dependent on mitochondrial OXPHOS and underwent rapid apoptotic death when treated with the mitochondrial inhibiting drug, metformin [74]. Interestingly, non-CSC cells which were predominately glycolytic exhibited cell cycle arrest, but little cell death. It was noted in this model of CSC enrichment that there was a relative lack of plasticity in CSC metabolism, demonstrating the potential vulnerability of CSC metabolism.

Along with differences in metabolic programing, CSCs rely on different metabolic substrates when compared to their differentiated counterparts for maintenance of cellular function. In culture, PDA is exquisitely reliant on the amino acid glutamine, which is necessary for tumor growth and persistence [75]. Unlike traditional cellular metabolism in which glutamine is used primarily as an anaplerotic substrate for the tricarboxylic acid cycle (TCA), glutamine carbon from the TCA cycle is shuttled from the mitochondria through the cytosolic malic enzyme pathways to maintain bioenergetics and cellular redox state. Perturbation of the metabolic enzymes involved led to suppression of PDA growth both *in vitro* and *in vivo* [75]. Further studies specifically addressing PDA CSC confirmed their reliance on glutamine for maintenance of a proper cellular redox state and found that when glutamine was unavailable, cells became more sensitive to radiation. Glutamine deprivation also negatively impacted other processes including their capacity for self-renewal and expression of stem-related genes, suggesting another potential therapeutic opportunity [76].

Proteomic and metabolomic profiling have shown additional metabolic alternatives used by CSCs, demonstrating reliance on both fatty acid and mevalonate pathways for CSC survival in PDA and other cancers [77, 78]. Using neutralizing antibodies against the fatty acid receptor CD36 in orthotopic models of human oral carcinoma, Pascual *et al.* demonstrated reduction of the metastatic potential of CSC [77]. Similarly, the proteomic comparison of cell-line-derived pancreatic CSCs with their parental cells revealed an increased dependence on fatty acid synthesis and mevalonate pathways. Inhibition of these mechanisms resulted in greatly reduced proliferation of these CSC compared to non-CSC [79]. Somewhat

paradoxically, the CSC population had higher expression of proteins involved in glycolysis, again suggesting the possibility that their metabolism is context dependent.

Altogether these findings demonstrate important differences between the metabolomic profile and nutrient utilization of PDA CSC and PDA non-CSCs. Importantly, there also appears to be differences in metabolic weakness observed among difference CSCs suggesting a metabolic heterogeneity which may mirror that seen in PDA cell lines [80]. Furthermore, these studies shed some light on the ability of CSCs to survive in hostile environments. Improved understanding of their metabolomic plasticity is needed to further investigate therapeutic targets and explore impacts on downstream effectors including alterations in epigenetics.

Epigenetics and Pancreatic Cancer Stem Cells

Epigenetic changes within cells do not involve genetic sequence alterations but instead entail DNA and chromatin structural/chemical changes promoting or repressing DNA transcriptional accessibility. These changes occur as a result of both intrinsic and extrinsic signals which ultimately affect the overall phenotypic state of the cell and represent an important way in which cells interact with environmental factors [19].

PDA cells exhibit markedly altered epigenetic profiles and often have mutations within chromatin regulatory proteins [81]. Epigenetic context also controls the process of epithelial-mesenchymal transition (EMT), which is important in pancreatic cancer metastasis formation [82, 83]. Recent comparison of pancreatic metastases to the liver, lung, and peritoneum with primary tumors has revealed fundamental anatomic site-specific epigenetic signatures within the tumor cells [84]. Partly based on these ideas, many groups have begun to investigate whether inhibition of epigenetic regulatory processes could contribute to the development of new pancreatic cancer therapeutics [85, 86].

PDA CSC are thought to be related to the process of EMT through master transcription factors including Zeb1 acting within the proper epigenetic context [82, 83, 87]. Multiple groups have targeted different aspects of epigenetic and chromatin regulation, including DNA methylation, histone methylation, and acetylation and demonstrated concurrent inhibition of CSC function or CSC elimination [88–90].

Aberrant methylation of functionally relevant genes is a hallmark of pancreatic cancer [91]. This process is mediated by DNA methyltransferases (DNMT) which is frequently found upregulated in PDA [92, 93]. PDA CSC selected by flow cytometry label retention, nonadherent sphere growth conditions, and by CD133 expression have higher overall DNA methylation levels than the remaining cancer cells [94]. This correlates with higher expression levels of the DNA methyltransferase, DNMT1. When DNMT1 was pharmacologically inhibited or genetically deleted using a CRISPR-Cas9 approach, the CSCs demonstrated increased commitment and progression through the cell cycle along with epithelial-like differentiation [94]. At least part of this phenotypic switch is due to the hypomethylation of the miR-17–92 miRNA cluster after DNMT1 inhibition. In a separate study, Kwon *et al.* combined 5-aza-2-deoxycytidine (5-aza-dC), a DNA methylation

inhibitor, with ionizing radiation *in vitro* and *in vivo* [95]. They observed dose-dependent reduction in the population of CSCs in the MiaPaCa-2 and Panc1 cells, reduced self-renewal markers, including Oct4, Nanog, and Sox2. These observations correlated with inhibition of their migration and tumorigenic properties [95]. Efforts to disrupt DNA methylation should form a part of our therapeutic approach to disrupt the pancreatic CSC compartment.

Gene expression is partly regulated by the combination of covalent histone modifications, including histone acetylation and methylation, that mark inactive heterochromatin or active euchromatin. Screening of compounds that inhibit ZEB1-mediated EMT identified the histone deacetylase (HDAC) inhibitor, mocetinostat, as a compound that synergizes with gemcitabine to inhibit *in vivo* pancreatic xenograft growth by disrupting EMT and the CSC phenotype [96]. Similarly, inhibition of HDACs with trichostatin A and vorinostat increased Panc-1 and MiaPaCa-2 cell death, promoted epithelial differentiation, disrupted tumorsphere formation, and subcutaneous tumor xenograft growth [97]. In a separate set of experiments, analysis of gemcitabine-resistant Panc1 cells showed dysregulation of multiple histone-modifying enzymes [98]. Among these, the histone methyltransferase (HMT) G9a played a key role in maintenance of the CSC subpopulation and chemotherapy resistance partly through production of the cytokine IL-8. Higher levels of G9a expression also correlated with poor survival in a cohort of pancreatic cancer patients [98]. Disruption of histone 3 lysine 27 (H3K27) methylation by enhancer of zeste homolog 2 (EZH2), a component of the Polycomb Repressor Complex 2 (PRC2), also disrupts pancreatic CSC tumorsphere growth and sensitizes the cells to gemcitabine by increasing the expression of cell surface nucleoside transporters [99, 100]. These preliminary studies in established pancreatic cancer cell lines suggest that interference with histone modifications can successfully inhibit the CSC state and potentially synergize with existing chemotherapy to stop pancreatic tumor growth. It will be important to replicate these findings in more high-fidelity models of pancreatic cancer including primary patient-derived xenografts and tumor organoids.

Metabolic and Epigenetic interactions in CSC

While the primary function of cellular metabolism is energy production, the sequalae of nutrient utilization and production of metabolites produce downstream effects that can additionally contribute to tumorigenesis by influencing gene expression and cell signaling [101]. This has been suggested as mechanism by which CSC maintain relative plasticity by up or down regulating genes under epigenetic control based on the environment in which they exist [19]. There are several substrates and cofactors for epigenetic enzymes that vary as a direct result of changes in OXPHOS or glycolysis which enhance or repress the enzymatic function [101]. Reciprocally, expression of specific metabolic genes could be the consequence of epigenetic dysregulation [102–105]. In PDA, several mechanisms in CSC and non-CSC appear to be involved in the crosstalk between the epigenetic and metabolic pathways ultimately contributing to cellular plasticity and enhanced tumorigenesis.

In murine PDA the metabolic reprograming which occurs in the presence of activated $KRAS^{G12D}$ expression promotes increases in H3 and H4 acetylation, via acetyl-CoA nuclear accumulation after AKT-dependent signaling activation (Figure 3). Acetyl-CoA's availability is influenced by oncogenic reprogramming of the cellular metabolism. There are

two pools of Acetyl-CoA a mitochondrial and a nuclear-cytoplasmic pool. Several substrates contribute to the replenishment of this pool and histone acetylation correlates well with its availability. This histone acetylation is typically associated with active gene transcription and is dysregulated in tumors [106]. Glucose availability as well as acetate and glutamine represent Acetyl-CoA's major contributors [107]. AKT phosphorylation and ACLY (ATP-citrate lyase) demonstrated to be linked to histone acetylation in tumors [106].

Another example of metabolic and epigenetic crosstalk involves Histone methylation and Histone methyltransferases (HMT) which catalyzes transfer of methyl groups to lysine and arginine residues on histones H3 and H4 changing the chromatin structure and gene transcription [108]. The cofactor and methyl source for both HMT enzyme as well as DNMT1, a methyltransferase frequently upregulated in PDA CSC (see epigenetics section) is S-adenosylmethionine (SAM). Surplus of SAM substrates in the cell promotes DNA hypermethylation in CpG islands and can result in gene silencing, particularly of tumor suppressor genes such as SOC2 [109]. When SAM is consumed it produces SAH (S-adenosyl-homocysteine) which in turn inhibits the HMT and DNMT enzymes. In other words, histone and DNA methylation are controlled by the resulting ratio between SAM and SAH within the cell. A recent study found that alterations in metabolism pathway that produce high levels of glycolysis and serine biosynthesis in PDA consequently led to generation of large amounts of SAM which in turn promotes hypermethylation of specific retrotransposon elements associated with transcriptional silencing [110]. Using an inducible transgenic murine model of PDA, Kottakis *et al.* proved the existence of a connection between the loss of the tumor suppressor LKB1 serine-threonine kinase and KRAS signaling activation, events that combined led to the induction of the serine pathway [110]. Specifically, epithelial primary duct cells were isolated from mice bearing $KRAS^{G12D/+}$; $LKB1^{-/-}$ cells; double and single mutants were injected in SCID mice and demonstrated increased tumorigenicity and proliferation compared to the single mutation counterparts. Loss of LKB1 improved glucose consumption of these subpopulations. The entire one carbon-Serine-Glycine pathway showed a strong enrichment by proteomic and sequencing of RNA analysis in the double positive cells. Furthermore, double mutant $KRAS^{G12D/+}$; $LKB1^{-/-}$ cells were dependent on the Serine pathway and had a clear CpG enrichment both of which were shown to strongly correlate with DNA methylation. Retrotransposons were found responsible of the observed gene expression modulatory effects. Moreover, that dependence was resolved when DNMT1 was chemically blocked.

The generation of chromatin modification substrates is an example of the interconnecting link between the epigenetic and metabolic stages within the tumor cell. In parallel to upregulation of DNA methyltransferases, SAM is ultimately generated and the lack of LKB1 finally translates into inhibition of the serine biosynthesis pathway and the DNA methylation mechanism [110]. These observations revealed the clear connection that exists in pancreatic cancer tumorigenesis between LKB1 expression, glycolysis and DNA methylation events.

Histone Acetylation, mediated by histone acetylases (HATs) is a crucial post translation modification that regulates histone activity and increases gene expression. HDACs have the opposite effect mainly promoting gene silencing by chromatin condensation [111]. HATs were shown to play a role in the self-renewal ability of embryonic stem cells [112–114]. The

effect of HAT over PDA CSCs has yet to be determined but the effects of HATs over other CSCs suggests it could affect PDA CSC [113, 115, 116]. Additionally work by Zhao *et al.* reflects the direct effect of acetylation over the metabolic enzyme LDH-A in human PDA [117]. LDH-A is known to be frequently over-expressed in pancreatic cancer. Several studies have highlighted a role for HDAC in relation to CSCs as we previously mentioned [96] another example is in liver cancer where there was a significant decrease in stem markers expression upon specific HDAC3 inhibition [118].

While no studies directly address the role of metabolism in the epigenetic processes that control PDA CSCs, epigenetic activating and inhibiting enzymes require cofactors, substrates and donors that are generated and influenced by metabolic enzymes which exemplifies the interplay between those two processes. Additionally, it is likely that several of these influences will have a different outcome depending on whether they are acting over non-CSCs or CSCs respectively.

Accumulating observations suggest links between environmental factors such as smoking, sun and diet with an increased risks of cancer development [119]. The interplay between metabolism and epigenetics may constitute a major factor in many of the observed environment-related malignancies by enhancement of CSC persistence. For example, as previously stated, increase in SAM availability enhances gene silencing through promotion of DNA methylation [110]. On the other hand, recent human studies have established a clear linear association between circulating plasma concentration of SAM with BMI (body mass index) and fat mass, known risk factors for PDA [120, 121]. This suggests a potential molecular mechanism tying metabolism and metabolic changes associated with obesity and epigenetic reprograming which could consequently lead to silencing of tumor suppressor genes thus promoting pancreatic cancer formation. In other words, this provides a clear example of environmental factors promoting cancer development through interplays between metabolism and epigenetics of cancer cells. Another observation linking cancer, metabolism and stem-cells is the finding that the dietary fat palmitic acid, an abundant component of the western high-fat diet, has been linked to increased metastatic potential of CSC in squamous cancer cells [77]. The CSCs expressing CD36 receptor rely on lipids from the diet to increase metastasic events.

Concluding Remarks

Recent findings have expanded our understanding of CSC biology and, as the model of CSC continues to evolve, new therapeutic strategies are emerging aimed at targeting these difficult to eradicate cells. Because of their relative plasticity, it is likely that CSC exist within a spectrum of metabolic and epigenetic states making their study and treatment complex and likely context dependent. Metabolic-epigenetic cross-talk represents a mechanism by which CSC can maintain their plasticity and respond to changes in the local environment including availability of nutrients and oxygen. Strategies to target cellular and metabolic processes of CSC appear attractive, but their nimble nature makes development of resistance a likely result. One strategy developed specifically to target PDA CSC is currently in phase I/II trial and relies on a different approach, turning the body’s immune system

against this cellular subpopulation [122]. Efforts to add metabolic and epigenetic manipulation to this strategy had also been proposed.

It remains to be determined if the specific removal of CSC from a tumor, in addition to conventional chemotherapy against the bulk non-CSC compartment is the missing link to eradicating this difficult to treat disease. A lengthy history of failure to treat this population with traditional chemotherapy and radiation heightens the need to better understand its biology to define new avenues of attack.

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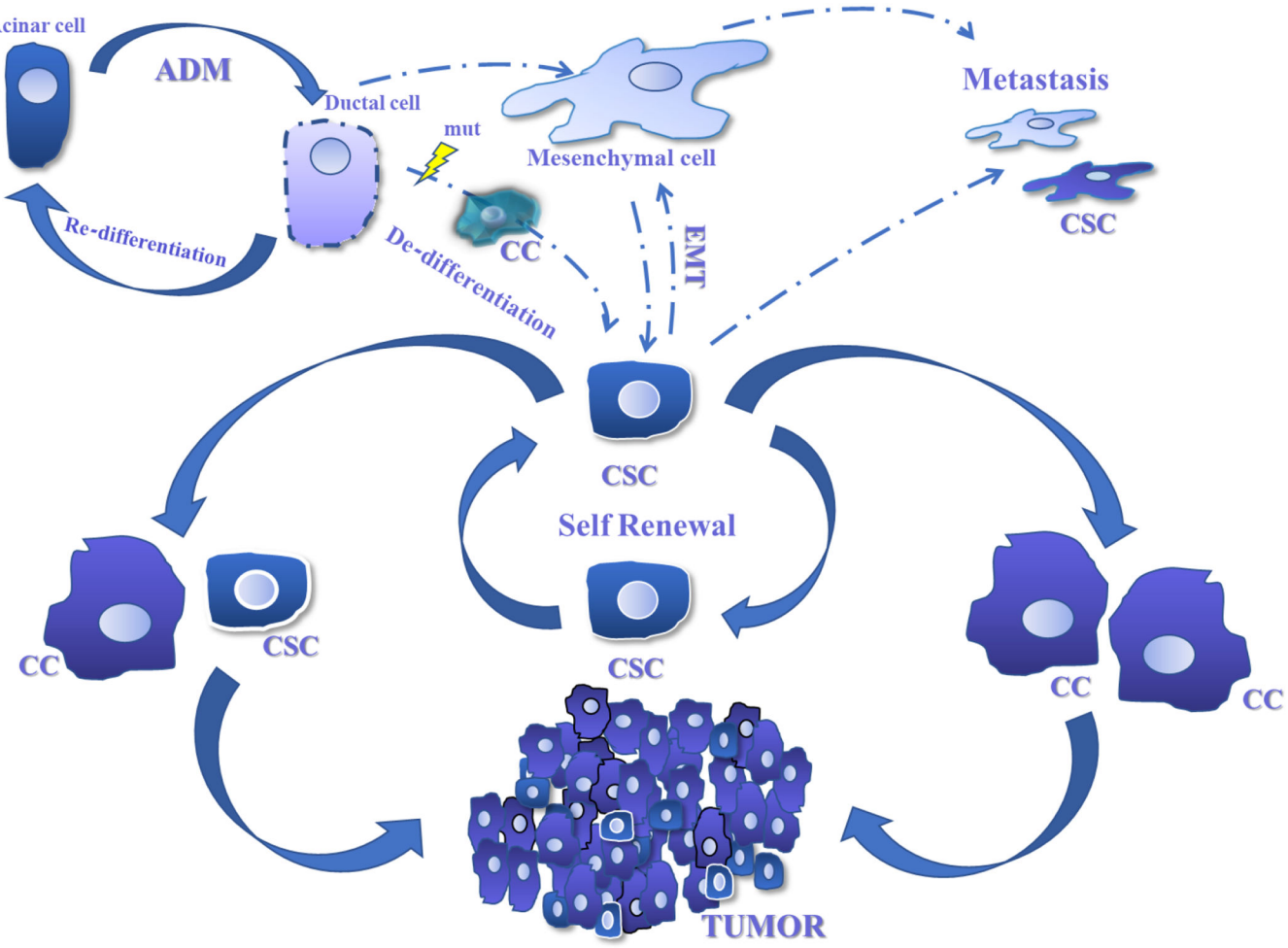

Figure 1. Plasticity of Cancer Stem Cells in Pancreatic cancer.

Normal pancreatic acinar cells undergo trans-differentiation in response to injury and metabolic or inflammatory stress in a process known as Acinar-to-Ductal-Metaplasia (ADM). Oncogenic mutations can result in failure to re-differentiate leading to malignant degeneration and cancer formation. Cancer Stem Cells (CSC) are poised to originate from de-differentiation of genetically mutated epithelial cells or from non-cancer stem cells. Factors present in the PDA TME favor persistence of CSC and can promote a more malignant phenotype including metastatic potential. CSC can self-renew or produce differentiated progeny which comprise a majority of tumor cells.

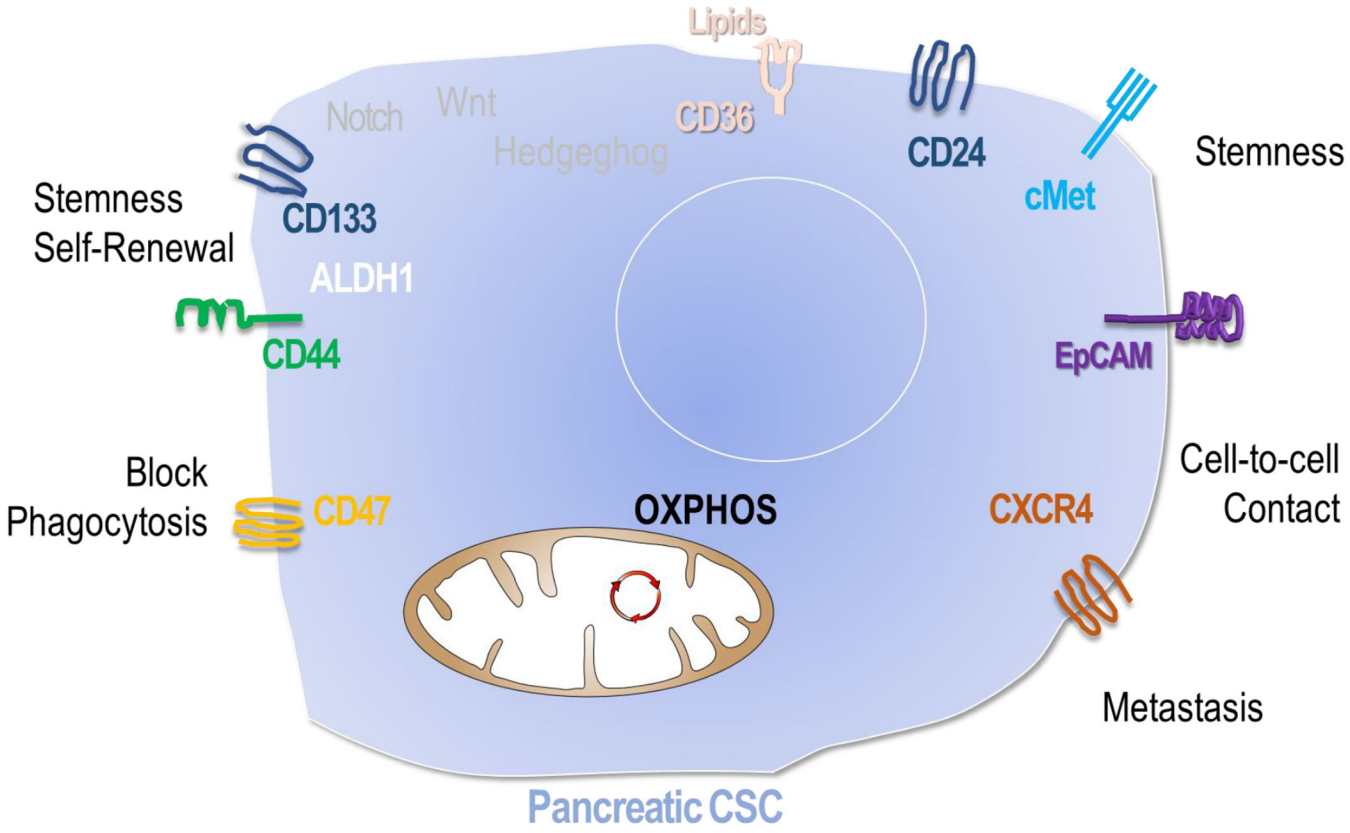

Figure 2. Pancreatic cancer stem cell characteristics.

CSC express unique surface and cytosolic proteins that aid in cell surface markers aid in macrophage evasion, self-renewal, stemness, and cell-to-cell in pancreatic cancer. They principally use OXPHOS but possess metabolic plasticity.

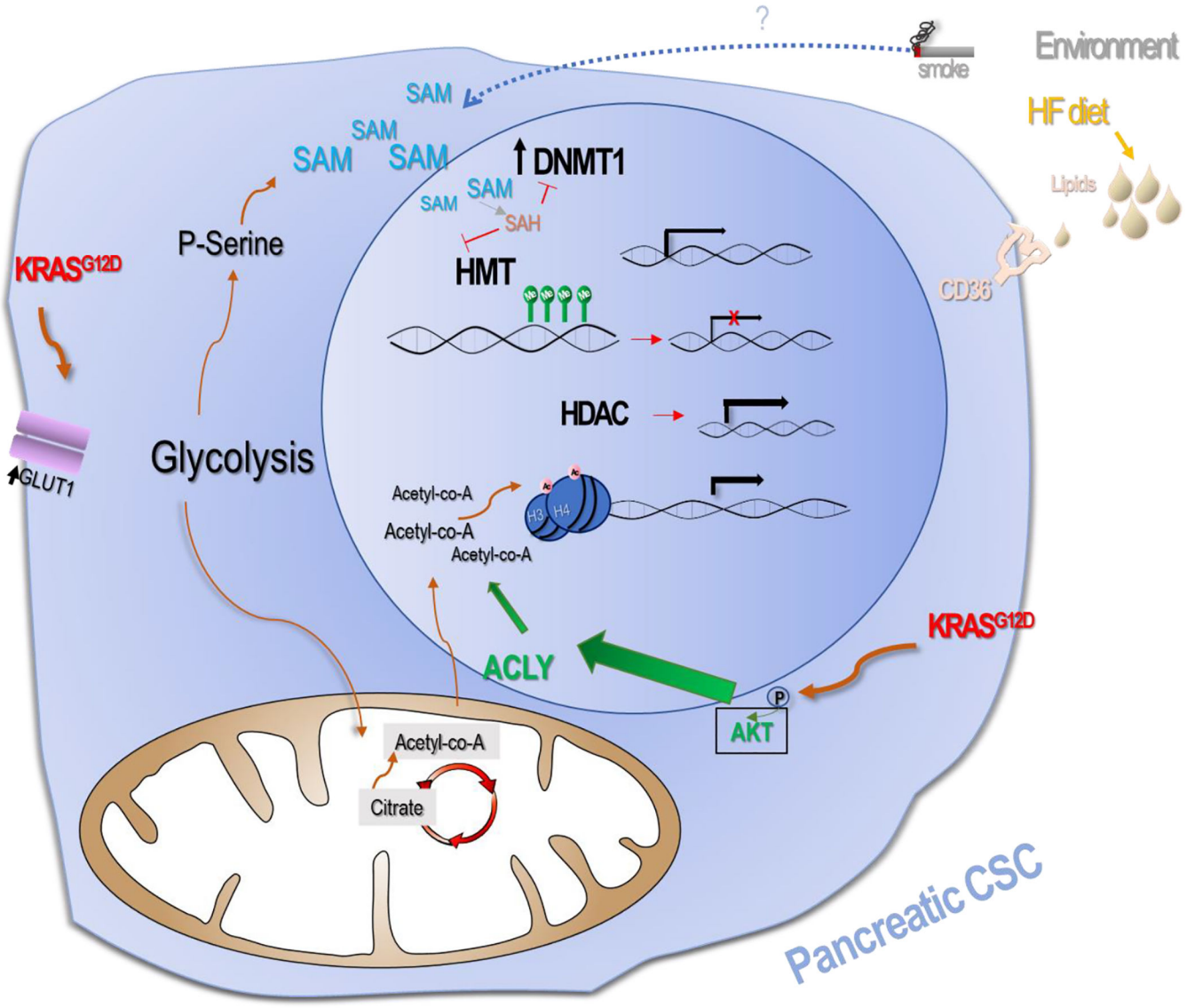

Figure 3. Metabolic-Epigenetic crosstalk in PDA.

epigenetics and metabolic pathways ultimately contribute to tumorigenesis. In murine PDA the metabolic reprograming due to activated $KRAS^{G12D}$ expression promotes increase in H3 and H4 acetylation, via acetyl-CoA nuclear accumulation after AKT-dependent activation. Histone acetylation is usually associated with active gene transcription. CSCs expression have higher overall DNA methylation levels. SAM might contribute to DNA hypermethylation and increase in SAM availability enhances gene silencing through promotion of DNA methylation. DNMTs are overexpressed in several cancers and promote silencing of tumor suppressor genes in PDA. A DNA methylation inhibitor promoted reduced self-renewal marker expression. Additionally, several observations suggest links between environmental factors such as smoke sun and diet with an increased risks of cancer development [119].