Pancreatic Cancer and Microenvironments: Implications of Anesthesia

Subjects: Anesthesiology

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Pancreatic malignancy is a lethal neoplasm, as well as one of the leading causes of cancer-associated mortality, having a 5-year overall survival rate of less than 10%. The average life expectancy of patients with advanced pancreatic cancer does not exceed six months. Although surgical excision is a favorable modality for long-term survival of pancreatic neoplasm, metastasis is initially identified in nearly 80% of the patients by the time of diagnosis, making the development of therapeutic policy for pancreatic cancer extremely daunting. Emerging evidence shows that pancreatic neoplastic cells interact intimately with a complicated microenvironment that can foster drug resistance, metastasis, or relapse in pancreatic cancer. As a result, the necessity of gaining further insight should be focused on the pancreatic microenvironment contributing to cancer progression. Numerous evidence reveals that perioperative factors, including surgical manipulation and anesthetics (e.g., propofol, volatile anesthetics, local anesthetics, epidural anesthesia/analgesia, midazolam), analgesics (e.g., opioids, non-steroidal anti-inflammatory drugs, tramadol), and anesthetic adjuvants (such as ketamine and dexmedetomidine), might alter the tumor microenvironment and cancer progression by affecting perioperative inflammatory or immune responses during cancer surgery.

pancreatic cancer tumor microenvironment anesthesia

1. Introduction

Pancreatic cancer (PC) is a lethal malignant neoplasm. It is considered one of the leading causes of cancer-associated mortality, having a 5-year overall survival rate of less than 10% [1]. The average life expectancy of patients with advanced PC does not exceed six months [2]. Several factors related to the poor prognosis of PC include insignificant symptoms, shortage of early diagnostic biomarkers, rapid progression of the disease, increased metastatic propensity, and the disease's tendency toward resistance to both chemotherapy and radiotherapy [3][4]. Early resection of the neoplasm is potentially the most successful treatment regime for such aggressive malignancy. However, by the time of diagnosis, metastasis is initially identified in approximately 80% of the patients, making PC treatment extremely challenging [5][6]. Despite several studies outlining various signal pathways involved in PC progression, the mechanisms of tumor progression are poorly understood.

The pancreatic microenvironment plays an important role in tumorigenesis [7]. As cancer progresses, alterations of surrounding tissue stroma develop rapidly. A key role of any non-transformed tissue stroma is to maintain a homeostatic response to shelter the immune system, the vascular system, and connective tissue components. Cancer hijacks the physiological responses to build a tumor microenvironment beneficial for cancer progression [7].

The pancreatic microenvironment includes the surrounding desmoplastic stroma, such as the epithelial-mesenchymal transition (EMT), and immunosuppressive pathways [7]. Evidence reveals that anesthetics or analgesics might alter the tumor microenvironment and the progression of the cancer by affecting perioperative inflammatory or immune responses during PC surgery [8][9]. Soliz et al. reported that propofol anesthesia was associated with no or low-grade complication compared with desflurane anesthesia in PC surgery [10]. In addition, in a retrospective study, researchers found that desflurane anesthesia was associated with poorer survival than propofol anesthesia in PC surgery [11]. Zhang et al. demonstrated that intraoperative intravenous lidocaine infusion increased survival in PC surgery [12]. Therefore, anesthesiologists may improve clinical outcomes by using preferential anesthetics.

2. Patient Factors: Hyperglycemia and Obesity

2.1. Hyperglycemia

Diabetes mellitus (DM) and PC are intimately related, as high blood glucose levels promote PC proliferation, invasion, EMT, and metastasis [13][14]. In addition, insulin resistance, hyperinsulinemia, hyperglycemia, and chronic inflammation are the mechanisms of type-2-DM-associated PC [15].

2.1.1. Laboratory Studies

Recently, Otto et al. attributed a role to the type-2-DM-related hyperglycemic inflammatory micromilieu in the acquisition of malignancy-associated alterations in premalignant pancreatic ductal epithelial cells, thus providing new insights into how hyperglycemia might promote PC initiation [16]. It is well-known that EMT of pancreatic ductal epithelial cells develops in correlation with hyperglycemia or macrophages [17][18]. Moreover, hyperglycemia aggravates microenvironment hypoxia, accelerates EMT, and then promotes the metastatic ability of PC. PC is generally hypoxic due to its avascular morphology, and PC cells express high levels of HIF-1α and MMP-9 for promoting tumor growth, invasion and metastasis in a hypoxic environment [19]. In addition, the accumulation of HIF-1α induced by hyperglycemia might promote pancreatic glycolysis to facilitate cancer progression [20]. Zhou et al. reported that the high-glucose microenvironment accelerated PC growth [21]. With regard to the VAs, Guo et al. reported that isoflurane promoted glucose metabolism through upregulation of *miR-21* and suppressed mitochondrial oxidative phosphorylation in ovarian cancer cells [22]. Dong et al. reported that dezocine, an opioid analgesic, promoted glucose metabolism and impaired the proliferation of lung cancer cells [23]. However, Codd et al. reported that opioid agonists did not elevate blood glucose and lacked an insulin-reducing effect [24]. Han et al. reported that indometacin, an inhibitor of cyclooxygenase (COX)-2, ameliorated high-glucose-induced proliferation and invasion via upregulation of E-cadherin in PC cells [25]. Current laboratory data on the effect of anesthesia on glucose metabolism in PC are limited, and further investigation is required.

2.1.2. Clinical Studies

Insulin resistance, hyperinsulinemia, hyperglycemia, and chronic inflammation are the mechanisms of type-2-DM-associated PC [15]. Recently, type 2 DM was shown to reduce the likelihood of cancer survival, and was

significantly correlated with comorbidity and poor prognosis in patients undergoing PC surgery [15]. In addition, metformin may lower the probability of PC. By contrast, insulin therapy may amplify the probability of PC [15]. In another study, approximately 85% of PC patients exhibited impaired glucose tolerance associated with DM and had a reduced overall survival rate [26]. Elderly patients with new-onset DM are at higher risk of developing PC than the general population [26]. Therefore, new-onset DM and hyperglycemia serve as important screening tools to diagnose asymptomatic PC and improve PC survival [26]. Sandini et al. reported that preoperative blood glucose ≥ 140 mg/dL was associated with poor long-term outcomes in patients undergoing resection for PC [27]. Conti et al. reported that anti-diabetic drugs represented a significant protective factor against mortality among older adults with metastatic PC [28]. However, in a recent meta-analysis study, blood glucose, fasting blood glucose, and glycated hemoglobin (HbA1c) levels were not associated with the survival of patients with PC [29].

Liu et al. reported that the blood glucose levels of the DM patients in the propofol group were significantly lower than those in the sevoflurane group during gastric cancer surgery. This result indicated that the effect of propofol on glucose metabolism under surgical stimulation was less than that of sevoflurane [30]. Epidural blockade with bupivacaine attenuated the hyperglycemic response to surgery by modifying glucose production in colorectal surgery [31]. Current clinical data on the effect of anesthesia on glucose metabolism in PC are limited. Further investigation is required to determine the effects of anesthetics and analgesics on glucose metabolism in PC (**Figure 1**).

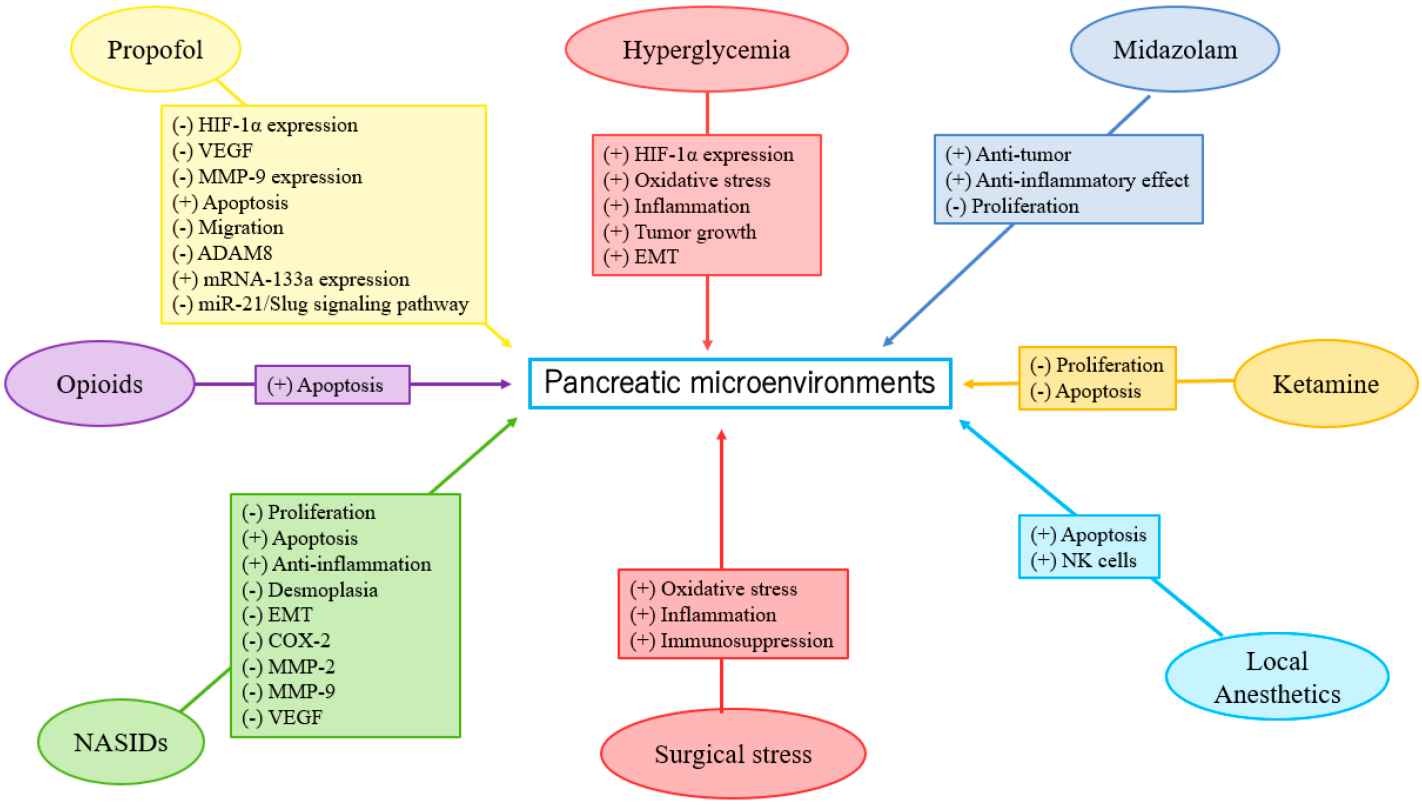

Figure 1. Anesthesia in pancreatic microenvironments.

2.2. Obesity

Obesity-associated adipose tissue inflammation may play a central role in the development of PC and the promotion of PC growth [32]. Chronic inflammation, hormonal effects, circulating adipokines, and adipocyte-mediated inflammatory and immunosuppressive microenvironments are involved in the association of obesity with PC [33]. The tumor-promoting effects of obesity occur at the local level via adipose inflammation and associated alterations in the microenvironment, as well as systemically via circulating metabolic and inflammatory mediators associated with adipose inflammation [34].

In a review article, Heil et al. reported that anesthetics with the effect of inhibiting obesity-induced inflammation may improve postoperative outcomes [35]. Eley et al. concluded that VAs, ketamine, opioids, propofol, and regional anesthesia have been shown to modulate parts of the immune system in patients with obesity [36].

2.2.1. Laboratory Study

Incio et al. reported that obesity-induced inflammation and desmoplasia promoted PC progression and resistance to chemotherapy [37]. Until now, there have been no laboratory studies on the effects of anesthetics in obesity-induced inflammation and PC progression, and further investigation is necessary.

2.2.2. Clinical Studies

Recently, Zorbas et al. showed that obesity was significantly associated with higher risk of postoperative complications and mortality in patients with body mass index ≥ 40 after pancreatoduodenectomy [38]. Li et al. reported that the lean body-weight-based dosing of propofol had more potent antioxidant and anti-inflammatory effects on morbidly obese patients than the total body-weight-based dosing during anesthesia induction [39]. Until now, there have been no clinical studies on the effects of anesthetics in obesity-induced inflammation and PC progression, and further investigation is necessary.

3. Tumor Factors: EMT, Hypoxia-Inducible Factor-1α (HIF-1α), Matrix Metalloproteinases (MMP)-9 Expression, Inflammation, Apoptosis, Autophagy, and Oxidative Stress

3.1. EMT

The development of EMT originates in the conversion of epithelial cells to motile mesenchymal stem cells [40], which is based on many essential processes involving embryonic progression, tissue formation/fibrosis, and wound repairing [40]. Moreover, the initiation of EMT contributes to tumor growth, therapy resistance, and tumor spreading [40]. In the case of high EMT expression in tumors, deterioration of overall outcomes and metastases is inevitable. [40][41][42][43]. However, research on the direct effects of specific anesthetics on EMT of PC is currently lacking, and further investigation is required.

3.1.1. Laboratory Studies

Anesthesia and analgesia may affect EMT [25][44][45][46][47][48][49][50][51][52][53][54][55][56][57][58][59][60][61]. Studies have reported that propofol suppressed EMT in esophageal cancer, choriocarcinoma, breast cancer, thyroid cancer, lung cancer, gastric cancer, hepatocellular carcinoma (HCC), renal cell carcinoma (RCC), prostate cancer, and oral squamous cell carcinoma cells [45][46][47][48][49][50][51][52][53][54]. By contrast, Ren et al. reported that desflurane induced EMT and metastasis in colorectal cancer through deregulation of the miR-34a/LOXL3 axis [44]. Opioids promoted EMT in breast and lung cancers via mu- or delta-opioid receptors [55][56]. Zhang et al. showed morphine-induced EMT in esophageal carcinoma cells [57]. However, sufentanil inhibited EMT by acting on NF-κB and Snail signaling pathways to inhibit proliferation and metastasis of esophageal cancer [58]. Lidocaine suppressed EMT in ovarian cancer cells [59]. However, high concentrations of levobupivacaine significantly increased EMT in the A549 lung cancer cell line, and enhanced metastasis in mice [60]. COX-2 inhibitors may suppress EMT in oral squamous cell carcinoma [61]. Han et al. reported that indometacin reduced the expression levels of MMP-2, MMP-9, and vascular endothelial growth factor (VEGF) by upregulation of E-cadherin, inhibiting proliferation and invasion of PC [25]. Zheng et al. observed the benefit of EMT inhibition due to the use of chemotherapy in PC treatment [62]. To the best of researchers' knowledge, NSAIDs may inhibit EMT expression in PC. Propofol may inhibit EMT, but VAs may promote EMT in different cancers. On the other hand, opioids and LAs may induce uncertain effects (both positive and negative) on EMT. Laboratory research on the direct effects of specific anesthetics on EMT in PC is currently lacking. Further investigation is needed (see existing studies in **Table 1** and **Figure 1**).

Table 1. The existing studies on the effects of anesthetics/analgesics on clinical outcomes and pancreatic microenvironments.

Type of Anesthetics/Analgesics	Effects
Clinical studies Propofol/VAs	Propofol was associated with no or low-grade complication compared with desflurane in PC surgery [10]; propofol anesthesia was associated with better survival than desflurane anesthesia in PC surgery [11].
NSAIDs	In a systematic review of observational studies, there was no signification association between aspirin use and mortality risk in PC [63]; aspirin use reduced risk of PC [64]; aspirin was associated with improved overall survival and improved disease-free survival in PC surgery [65].
Opioids	High opioid consumption was related to decreased survival rates in newly diagnosed stage IV PC patients [66]; opioid prescription was associated with poor overall survival among PC patients [67]; there was an insignificant relationship between intraoperative opioid use and decreased survival in PC surgery [68]; administration of opioids was associated with prolonged survival in older adult patients with PC [69].
LAs	Intraoperative administration of intravenous lidocaine was associated with improvement of overall survival in PC patients [12]; intraoperatively epidural ropivacaine infusion was associated with survival improvement in PC patients [70]; perioperative lidocaine administration might be beneficial to the function of

Type of Anesthetics/Analgesics	Effects
	NK cells in PC surgery [71]; peridural anesthesia with ropivacaine might improve the oncological outcome of PC patients [72].
Experimental studies Propofol	Propofol attenuated malignant potential by inhibiting HIF-1α and VEGF expression [73]; PC cell growth was inhibited by propofol via suppression of MMP-9 expression [74]; propofol inhibited migration and induced apoptosis [75]; propofol induced apoptosis in PC cells in vitro [76]; propofol inhibited PC progression by downregulating ADAM8 [77][78][79]; propofol suppressed proliferation and invasion of PC cells by upregulating microRNA-133a expression [80]; propofol inhibited growth and invasion of PC cells through regulation of the miR-21/Slug signaling pathway [81].
NSAIDs	Indometacin ameliorated high glucose-induced proliferation and invasion by upregulating E-cadherin (EMT) in PC cells [25]; aspirin counteracted PC stem cell features and desmoplasia and gemcitabine resistance [82]; COX-2 inhibition promoted an immune-stimulatory microenvironment in preclinical models of PC [83]; sodium salicylate inhibited proliferation and induced G1 cell cycle arrest in human PC cell lines [84]; indometacin inhibited proliferation and activation of pancreatic stellate cells through the downregulation of COX-2 [85].
Opioids	Fentanyl decreased gene expression of PC stem cell markers and increased expression of apoptosis-related genes [86].
LAs	High concentrations of ropivacaine or bupivacaine revealed antiproliferative potency in PC cells [87].
Midazolam	Midazolam exhibited antitumor (anti-proliferation) and anti-inflammatory effects in a mouse model of PC [88].
Ketamine	Ketamine significantly inhibited proliferation in PC cells [89]; ketamine significantly inhibited proliferation and apoptosis in PC cells [90].

A review article showed that HIF-1α expression enhanced PC cell proliferation through multiple mechanisms by inducing neoplastic features and mediating tumorigenic crosstalk between tumor and stromal cells [91].

HIF = hypoxia-inducible factor; Las = local anesthetics; MMP = matrix metalloproteinases; NSAIDs = non-steroidal anti-inflammatory drugs; PC = pancreatic cancer; Vas = volatile anesthetics; VEGF = vascular endothelial growth factor.

3.2.1. Laboratory Studies

Propofol could attenuate PC cells' malignant potential by inhibiting HIF-1α and VEGF expression [73]. VAs enhance angiogenesis through HIF-1α activity in prostate and lung cancers [92]. Isoflurane upregulated the levels of HIF-1α and exerted a protumorigenic effect on a human RCC cell line [93]. However, in the neuroglioma cell line, sevoflurane decreased HIF-1α expression via *miR-210*, while desflurane downregulated HIF1-α and MMP-9 expressions via *miR-138* and *miR-335*, respectively [94]. Opioids were shown to promote tumor angiogenesis in a breast cancer cell by stimulation of δ-opioid receptors in breast cancer cells, leading to activation of HIF-1α and expression of COX-2 via PI3K/Akt stimulation [95]. However, Koodie et al. reported that morphine suppressed tumor angiogenesis by inhibiting HIF-1α expression in mouse Lewis lung carcinoma cells [96]. Okamoto et al. showed that HIF-1α activation conferred resistance to lidocaine-induced cell death in the RCC cell line [97]. Zhou et al. revealed that inhibition of HIF-1α by meloxicam (a selective COX-2 inhibitor) could suppress angiogenesis and enhance

apoptosis of HCC cells [98]. To the best of researchers' knowledge, propofol may reduce HIF-1α expression in PC. Based on the limited data, further investigation is required and encouraged to determine the effects of VAs, LAs, and NSAIDs on HIF-1α expression in PC (**Table 1** and **Figure 1**).

Recently, Yue et al. demonstrated that HIF-1α positively regulated miR-212 expression and resulted in pancreatic ductal adenocarcinoma progression [99]. Propofol inhibited ovarian cancer cells growth and glycolysis by elevating miR-212-5p expression [100]. Higher miR-212-5p expression showed a neuroprotective effect in rats with isoflurane-induced cognitive dysfunction by inhibiting neuroinflammation [101]. He et al. reported that δ-opioid receptor activation modified miR-212 expression in the rat kidney under prolonged hypoxia [102]. Until now, there have been no laboratory studies on the effects of anesthetics on miR-212 expression and PC progression; further investigation is necessary.

3.2.2. Clinical Studies

In a systemic review and meta-analysis, Raji et al. found that miR-212 could be a novel potential biomarker in cancer diagnosis and prognosis [103]. High levels of miR-212 indicated poor prognosis in PC, and low levels of miR-212 indicated poor prognosis in other cancers [103]. Until now, there have been no clinical studies on the effects of anesthetics on HIF-1α or miR-212 expression and PC progression; further investigation is necessary.

3.3. MMP-9

MMPs are part of the zinc-dependent proteolytic metalloenzyme family that may play a role in the early diagnosis and prognosis of PC. The higher expression of particular MMPs may also correlate with metastatic disease and/or poorer prognosis [104][105][106][107]. MMP-9, well-known as one of the most investigated MMPs, corrupts the extracellular matrix components, resulting in pathophysiologic alterations [108]. Impairment of MMP-9 expression and regulation affects various dysfunctions, including tumorigenesis, and MMP-9 suppression can be targeted in anticancer therapeutics [108]. Anesthesia may affect MMP-9 expression [74][94][109][110][111][112][113][114][115].

3.3.1. Laboratory Studies

Yu et al. reported that propofol inhibits PC growth by suppressing MMP-9 expression [74]. Sevoflurane and desflurane inhibited glioma cell proliferation and migration via downregulation of MMP-9 [94]. Sevoflurane and desflurane reduced the invasion of colorectal and neuroglioma cancer cells through downregulation of MMP-9 [94][110]. Moreover, sevoflurane inhibited the proliferation and invasion of HCC cells through downregulation of MMP-9 [111]. Zhang et al. showed that fentanyl inhibited tumor growth and cell invasion in colorectal cancer by downregulation of miR-182 and MMP-9 expression [112]. In addition, the antitumor effects of morphine are associated with a reduction in the level of MMP-9 [113]. Both lidocaine and ropivacaine inhibited TNFα-induced invasion of lung adenocarcinoma cells in vitro by blocking MMP-9 expression [114]. Based on the limited data, further investigation is needed to clarify the effects of anesthetics and analgesics on MMP-9 expression in PC (**Table 1** and **Figure 1**).

3.3.2. Clinical Studies

Wang et al. reported that MMP-9 in the propofol group was significantly lower than in the sevoflurane group in lung cancer patients who received surgery [109]. In breast cancer patients, Kashefi et al. reported that novel NSAIDs may reduce MMP-2 and MMP-9 expression, which promotes angiogenesis and metastasis [115]. In summary, propofol may reduce MMP-9 expression in PC. Based on the limited data, further investigation is required to determine the effects of anesthetics and analgesics on MMP-9 expression in PC (**Table 1** and **Figure 1**).

3.4. Inflammation, and the Immune System

Inflammation, apoptosis, and autophagy can provide cellular defense, and impairments of these processes (rendering them deficient or overactivated) lead to pathological effects. Inflammation induces secretion of various cytokines and chemokines, and recruits various immune cells in reaction to oxidative stress or infection sites. Reflexively, enhancement of reactive oxygen species (ROS)-generation via inflammatory immune cells provokes oxidative stress and tissue injury. In addition, chronic inflammation not only produces high numbers of inflammatory mediators but also gives rise to oxidative stress [116]. Inflammatory processes have emerged as key elements in PC development and progression [117][118]. The relationship of chronic inflammation and cancer, as revealed in the pioneering work of Rudolf Virchow, has been observed for more than 150 years, especially in PC progression [118]. However, even in malignancy without preceding inflammation, cancer-induced inflammation, secretions of inflammatory factors, and immune cell infiltration are main characters in tumor initiation and advanced metastasis [118]. Anesthesia and analgesia may impact cellular immunity and inflammation during surgery, and thus affect cancer outcomes [119][120][121][122][123][124][125].

3.4.1. Laboratory Studies

A recent laboratory study has shown that propofol enhances anti-inflammatory reactions and stimulatory effects on immune responses, which may be a potential benefit in the prevention of tumor recurrence. However, clinical evidence of the tumor suppression effects is inconclusive. [126]. Opioids influence the nervous system indirectly, as well as release biological amines that potentially impair innate immunity by suppressing natural killer (NK) cell cytotoxicity. [127]. However, a mu-opioid receptor (MOR) partial agonist, buprenorphine, intercepted the inhibition of NK cell cytotoxicity and progression caused by surgery in a rat mammary adenocarcinoma cell line [128]. Additionally, neoplasm is related to inflammation, and anti-inflammatory properties are identified in LAs. LAs may be able to reduce metastasis risk, but the molecular mechanism is not fully understood. [129]. With regard to NSAIDs, aspirin was associated with a decreased expression of markers for progression, inflammation, and desmoplasia in PC cell lines [82]. NSAIDs also reduced inflammation and induced apoptosis in rat osteosarcoma cells in vitro [130]. Thus, NSAIDs may attenuate inflammation in PC. Further laboratory research is necessary (see extant research in **Table 1** and **Figure 1**).

3.4.2. Clinical Studies

The surgical treatment of PC is complicated by the prolonged nature of the surgery, the magnitude of the surgical stress, inflammatory response, immunosuppression, anesthesia-/epidural-induced hypotension, and blood loss, all of which cause oxidative stress [92][131]. In a retrospective study based on clinical pathological analysis, Huang et al. showed that the survival probability was reduced in patients with TNM stage III to IV, lymph node metastasis, higher $CD4^+IL\text{-}17^+$ level, and lower $CD8^+$ expression, which implied that the tumor immune microenvironment may affect the outcome of PC [132]. Recently, Li et al. reported that high systemic immune-inflammation index levels were regarded as negative with regard to PC overall survival and cancer-specific survival [133]. Yamaguchi et al. demonstrated that propofol reduced the number of $CD8^+$ T cells, whereas sevoflurane augmented the percentage of regulatory T cells in lung-cancer surgery patients [121]. Sevoflurane was revealed to devastate multiple pulmonary functions by releasing a series of inflammatory secretions in lung cancer patients undergoing perioperative one-lung ventilation [134]. However, another clinical study reported that sevoflurane inhibited pulmonary inflammatory cytokines [135]. Propofol combined with epidural anesthesia and epidural analgesia demonstrated less interference with the immune system (compared to propofol with intravenous analgesia) and led to fast recovery in patients undergoing radical resection of pulmonary carcinoma [125]. However, in a clinical study, Fant et al. reported that thoracic epidural analgesia with bupivacaine inhibits the neurohormonal but not the acute inflammatory stress response after radical retropubic prostatectomy [136]. Based on the published data, further investigation is required to determine the effects of anesthetics and analgesics on inflammation and cellular immunity in PC progression (**Table 1** and **Figure 1**).

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