Research progress on the impact of opioids on the tumor immune microenvironment (Review)

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Abstract. Opioids have been extensively used in cancer pain management because they can significantly improve the quality of life of patients with advanced cancer. However, recent evidence suggests that opioids can also modulate the tumor immune microenvironment by interacting with opioid receptors on immune cells, potentially regulating tumor progression and efficacy of cancer treatments. Notably, morphine can exhibit a dose-dependent effect on tumor immunity in pancreatic cancer and renal cell models, with lower doses potentially promoting tumor migration and invasion of pancreatic cancer cells, whereas higher doses shows the effect of inhibiting migration and invasion through distinct molecular pathways. The present review therefore comprehensively explored the mechanisms by which opioids can regulate the tumor immune microenvironment, focusing on their effects on immune cells, oxidative stress and angiogenesis. It also examined the interactions between opioids and other analgesics, along with their potential impact on immune modulation. All relevant articles and materials were retrieved from PubMed using the key words 'opioids', 'immune system', 'T cells', 'monocytes', 'macrophages', 'lymphocytes', 'natural killer cell', 'immunotherapy', 'immune cell function' and 'dose dependent effect'. The immunosuppressive effects of opioids, particularly through the μ-opioid receptor, can suppress the activity of natural killer cells, impair antigen presentation and promote the function of regulatory T cells (Tregs). These effects may contribute to tumor progression and metastasis. The severity of these immunosuppressive effects appears to be dose-dependent and can vary among different tumor types. There is evidence to suggest that tumors with higher immune responsiveness will experience more pronounced suppression, including the reduction of tumor angiogenesis, resulting in a decrease in tumor volume and decrease in tumor metastases. Furthermore, the combination of opioids with other analgesics, such as non-steroidal anti-inflammatory drugs, has the potential to exacerbate immunosuppression, which can in turn increase the risk of infections. Therefore, although opioids are essential for pain management in patients with cancer, their potential to modulate the immune microenvironment and promote tumor progression requires careful consideration. Clinicians should evaluate the advantages and disadvantages of opioids, especially regarding emerging immunotherapies, to minimize their potential negative effects on the outcomes of cancer treatments. Future studies are recommended to prioritize the development of strategies that optimize pain management whilst preserving immune function, such as receptor-specific opioid formulations or adjunctive therapies targeting immunosuppressive pathways.

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1. Introduction

Opioids, such as morphine, fentanyl, oxycodone and methadone, are a class of psychoactive compounds targeting central

and peripheral opioid receptors, are widely applied in the management of cancer-associated pain due to their potent analgesic effects (1-3), including the management of moderate to severe cancer pain and the management of pain at the site of primary and metastasis (4-6). The use of opioids have significantly improved the quality of life of patients with cancer (7,8). However, recent studies suggest that opioids may interact with immune cells within the tumor microenvironment, potentially affecting tumor progression and treatment responses (9,10).

Although there is ample evidence indicating certain immunomodulatory effects of opioids (10,11), including their effects of reducing T cell activity, suppressing the activity of NK cells and inhibiting B cell activity to reduce antibody production. Notably, these effects appear to vary across opioid types, with morphine showing the most pronounced effects. However, the specific mechanisms by which they can influence the tumor immune microenvironment remain to be fully elucidated. There are great knowledge gaps regarding the immunomodulatory effects of different opioids on various tumor models and outcomes of cancer treatments. Additionally, the interactions between opioids and novel immunotherapies, such as immune checkpoint inhibitors, require further exploration.

The present review aims to systematically evaluate the effects of opioids on the tumor immune microenvironment, emphasizing their potential immunomodulatory roles across different tumor types and their potential interactions with immunotherapies. The present review also integrates recent research findings to offer actionable insights for the clinical use of opioids, particularly in achieving effective pain management whilst preserving immune function in patients with cancer.

To the best of our knowledge, current literature has only rarely delved into the dose-dependent effects of opioids on the immune system, as they mainly instead focused on the effects of opioids on pain management. A number of the previous studies have mentioned the dose-dependent effects of opioids (11,12). In the present review, by elucidating the dose dependent effects and dual effect of opioids on the tumor immune microenvironment at different doses and cancer types, with particular attention to threshold concentrations observed in clinical and experimental practice, it explored the mechanisms by which opioids can regulate tumor progression under different conditions. In addition, the effects of opioids on immune cell function at different doses were discussed in detail. From this perspective, the present review hopes to reveal the potential immunosuppressive mechanism of opioids in patients with cancer.

2. Methods

The present review systematically retrieved the materials from PubMed (https://pubmed.ncbi.nlm.nih.gov), using key words 'opioids', 'immune system', 'T cells', 'monocytes', 'macrophages', 'lymphocytes', 'natural killer cell', 'immunotherapy', 'immune cell function' and 'dose dependent effect'.

Inclusion criteria: i) The present review included all original studies, systematic reviews and meta-analyses associated with cancer immunotherapy, opioid mechanisms of action and their effects on the immune system; ii) Studies involving the effects of opioids on the immune system, cancer growth or immunotherapy effects, including *in vitro* cell experiments, animal experiments and clinical studies, were all included; iii) studies must address the use of opioids and analyze their effects on immune cells [including T cells, macrophages, natural killer (NK) cells] or immune-related molecules (such as IL-2 and IFN-γ); iv) studies need to have control groups (such as individuals or cell/animal models not using opioids) to compare the effects of opioids on the immune system; v) at least one indicator of immune function (such as cytokine level, immune cell activity and tumor microenvironment change) must be reported; and vi) Literature between January 2000 and November 2024.

Exclusion criteria: i) The content of the study was not relevant, namely if the study did not explore the interaction between opioids and the immune system or if it placed too much focus on the analgesic effects of opioids but did not involve immune regulation; ii) insufficient or low-quality data, such as if the study did not provide complete experimental data, lacked control groups, had too small sample sizes or were of low methodological quality (such as drop-out rate >20%); and iii) non-English literatures, to avoid translation bias.

3. Mechanisms of opioids and their impact on the tumor immune microenvironment

Mechanisms of opioids. Opioids are commonly administered for the management of severe pain, because they can primarily target the μ, κ, δ and nociception (NOP) receptors (13). Amongst these, the μ receptor, with its two subtypes μ1 and μ2, is predominantly responsible for the key analgesic effects of opioids (14,15). In addition, they have also been implicated in opioid addiction (16). The μ1 receptor associated with central analgesia, euphoria and opioid use dependence (17). The μ2 receptor primarily mediates physiological processes, such as respiratory depression and inhibition of gastrointestinal motility (18). By contrast, the κ receptor and its three subtypes (κ1, κ2 and κ3), which are also involved in analgesia and sedation, exhibit relatively milder respiratory depression effects compared with these exerted by the μ receptor (19). The δ receptor is associated with anti-anxiety and antidepressant effects, whilst the NOP receptor is involved in regulating various responses, including reward and depression (20).

Introduction to the impact of opioids on the tumor immune microenvironment. Opioid receptors, including μ, δ, κ and NOP, are involved in regulating a number of physiological activities, such as analgesia, memory modulation, respiratory control and angiogenesis (21,22). A number of studies have suggested that opioids may contribute to the oxidative stress response within the breast cancer and human neuroblastoma tumor microenvironment (23-25), promoting the production of reactive oxygen species (ROS) (26,27). As a major mutagen, ROS can increase the risk of tumor development in opioid users (23,28). Additionally, opioids may exacerbate the oxidative imbalance, particularly in patients with cancer who frequently exhibit heightened oxidative stress due to concurrent inflammation (29). This suggests that opioids could cause greater harm to patients with cancer compared with healthy individuals. Table I presents a functional overview of opioid receptors in the tumor immune microenvironment.

Opioids can modulate immune functions through both direct and indirect pathways, influencing the body's response

Table I. A summary of the functions of opioid receptors in the tumor immune microenvironment.

Opioid receptor	Main function	Impact on Tumor Immune Microenvironment	Key studies/findings	(Refs.)
μ	Central analgesia, respiratory depression	Promotes tumor growth by enhancing angiogenesis and suppressing immune cell activity (such as natural killer cells and T cells)	Morphine binding to μ receptors increases tumor invasiveness by modulating macrophage activity and promoting M2 polarization	(12,34,37)
κ	Analgesia, mild respiratory depression	Inhibits angiogenesis by reducing VEGFR2 and neurophilin 1 expression, thereby potentially suppressing tumor growth	κ receptor agonists exhibit anti-angiogenic properties, suggesting potential therapeutic applications in cancer treatment	(51-53)
δ	Anti-anxiety, antidepressant effects	May promote the proliferation and metastasis of cancer cells through pathways, such as Janus kinase/STAT, in specific cancer types	δ receptor activation can stimulate the metastasis and progression of breast cancer cells	(50)
Nociception receptors	Regulates reward, depression, anxiety	Modulates various physiological responses, including immune suppression, though its direct impact on tumors is less studied	Involved in complex signaling pathways that may indirectly influence tumor immune microenvironment	(18)

to tumor cells (9,30). Direct effects occur when opioids bind to opioid receptors on immune cells, directly regulating their physiological activity, which is primarily mediated through μ receptors. By contrast, indirect effects are mediated through the inhibitory effects of opioids on the central nervous system, affecting various receptors within the sympathetic nervous system. They can involve D1 receptors, ultimately affecting peripheral Y1 receptors to inhibit spleen NK cell cytotoxicity (9,30). Previous animal studies and studies on human CD3+ T cell and leukemic T-cell lines have demonstrated that μ receptor activation can suppress the activity of NK cells and inhibit the mitogenic responses of T cells (31-33). In addition, it can also suppress the mitogen responses of B cells in mice following an *in vivo* administration (34).

Existing evidence suggests that opioids may have dual effects on tumor progression, depending on the concentrations applied and the tumor cell heterogeneity profile (35,36). Previous studies on morphine have indicated that μ receptor expression in Lewis lung carcinoma cells may be crucial to these mechanisms, influencing tumor growth and metastasis by regulating apoptosis and VEGF signaling. As a result, opioid antagonists may represent a novel therapeutic option for cancer treatment (9,12,34). The following sections discuss the mechanisms of various opioid receptors and their potential effects on the immune system.

μ receptor. μ receptor agonists are considered immunosuppressive agents that can hinder the body's ability to combat cancer cells, particularly by promoting angiogenesis (37). Morphine, as a μ receptor agonist, also shows an agonistic effect on δ and κ receptors. However, it shows a low drug selectivity on δ and κ receptors compared with μ receptors (38). Therefore, morphine is primarily the predominant μ receptor agonist. Previous studies have shown that activation of morphine-induced μ receptors can promote breast cancer cell proliferation both *in vivo* and *in vitro* (37,39). Morphine can also regulate the polarization of macrophages toward an M1 or M2 (alternative) activation state *in vitro*. A previous study on murine bone marrow cells documented that morphine can inhibit macrophage M1 polarization *in vitro* (40). In addition, morphine was found to inhibit M2 macrophage (alternative) activation *in vitro*, including the processes of antigen uptake and caused morphological changes, such as decrease in perimeter, area and aspect ratio, increase in roundness, circularity and solidity (40). An experimental study on breast cancer indicated that morphine can decrease macrophage M2 polarization through blocking the activation of IL-4, which may lead to breast cancer progression (41). However, other studies on morphine have indicated that it can inhibit tumor invasiveness by modulating the production of macrophage proteases in the tumor microenvironment. Specifically, morphine affects the production of certain proteins such as inhibiting the production of MMP-9 and MMP-2 by inhibiting the nitric oxide (NO)/NO synthase (NOS) system] in MCF-7 breast cancer cells and pancreatic cancer (42,43). The NO/NOS system serves an important role in tumor progression, NO, as an important bioregulatory mediator in the human body, is produced in the body by the action of NOS, exhibiting the

function of inducing extracellular matrix degradation (44,45). MMP-9 breaks down the extracellular matrix (ECM) and the basement membrane, which are structural components that provide physical barriers to multiple tumor cells, including giant cell tumor of bone (GCTB), non-small cell small lung cancer (NSCLC) and breast cancer. By degrading these barriers, MMP-9 enables tumor cells to invade surrounding tissues and spread to other parts of the body, increasing tumor invasiveness and metastasis (46,47). Therefore, by inhibiting the production of MMP-9 by inhibiting the NO/NOS system, morphine may exhibit an inhibitory function against tumor metastasis and invasiveness.

Previous studies have demonstrated that morphine can exert a dual effect on the proliferation of pancreatic cancer cells. In murine experiments, the tumor volume was found to be significantly increased in the low-dose morphine group (at doses of 0.5 mg/kg), whereas it was significantly smaller in the high-dose morphine group (at doses of 5 mg/kg) compared with that in the control group. The underlying mechanism was proposed to be mediated through the p38/JNK pathway. Specifically, low concentrations of morphine in this concentration led to an increase in phosphorylated JNK, whilst the phosphorylation of p38 was reduced. By contrast, higher concentrations of morphine reversed these aforementioned processes, resulting in increased p38 activation and decreased JNK activation (48). Another previous *in vitro* study reported that in renal cell carcinoma, when using morphine at a dose of 2 nmol to 3.5 μmol in serum concentrations, converted to clinical dosage at 10-2,450 mg/day, it exerted no significant proliferative effects. However, after increasing the dose to 50 μmol in serum concentrations, which equated to a commonly used clinical dose of 35 mg, morphine promoted the migratory ability of renal cell carcinoma cells (49). Therefore, it is essential to carefully consider the pharmacokinetic and tolerance effects of morphine during its administration. A clinical trial on patients with cervical cancer have been previously performed assessing the effects of morphine combined with ketamine (morphine, 1 mg/kg/day; ketamine, 1 mg/kg/day) and morphine alone (1 mg/kg/day) for pain management, where both groups yielded a decrease in CD4+ and CD4+/CD8+ ratios. This was proposed to be achieved by modulating T cell activation and cytokine expression, specifically by inhibiting the secretion of IL-2, IFN-γ and IL-17, through the Janus kinase 3/STAT5 pathway (50).

Animal models of NSCLC have shown that morphine (0.1 μg/μl) can promote the proliferation, migration and invasion of H460 cell-induced NSCLC by activating the Src/PI3K/AKT/mTOR signaling pathway, inhibiting the G_2 phase of the cell cycle and suppressing apoptosis (51). Furthermore, another *in vitro* and *in vivo* study has demonstrated that, morphine (1.0 μmol/l) pre-treatment under hypoxic conditions can inhibit the production of the pro-angiogenic factor VEGF in Lewis lung carcinoma cells *in vitro*. *In in vivo* experiments, morphine exhibited an inhibitory effect on angiogenesis. This effect was mediated by morphine's interaction with hypoxia-inducible factor 1, which binds to its hypoxia response element, resulting in the suppression of VEGF production by μ receptor. Another murine study previously reported that morphine (plasma levels maintained between 250-400 ng/ml) can significantly reduce the blood vessel density, branching and length compared with those in the placebo group (52). This suggests that the MOR receptor-mediated processes can inhibit angiogenesis within the tumor microenvironment under certain conditions, thereby suppressing tumor growth. Morphine exhibit a dual effect on promote or inhibit tumor progression in different cancer models, including lung cancer model and breast cancer model, which may be due to the different downstream proteins activated by μ receptors on the surface of different cancer cells, the mechanism underlying the differences in performance among each cancer cell type warrants further exploration.

δ receptor. A previous study has addressed the δ receptor's role in breast cancer progression, with the majority primarily focusing on breast cancer. A mouse study previously indicated that δ receptor agonist (D-Ala^2,D-Leu^5)-Enkephalin treatment promoted lung metastasis by breast cancer cells, through the migratory Janus kinase 1/2-STAT3 axis and by enhancing epithelial-mesenchymal transition (53). Subsequent studies on human breast cancer cells have shown that expression of the δ receptor was increased in breast cancer cells, where the inhibition of the δ receptor was found to suppress cell proliferation, suggesting its role in the proliferation process (53,54). In addition, δ receptor was found to underly the progression of breast cancer by activating the protein kinase C/ERK signaling pathway. Therefore, the δ receptor inhibitors were proposed to serve as an adjunctive treatment for patients with breast cancer (53).

κ receptors. The role of the κ receptor in the tumor microenvironment primarily involved inhibiting angiogenesis, particularly the transformation of vascular progenitor cells into vascular endothelial cells. κ receptor agonists were found to inhibit VEGFR2 expression, thereby suppressing endothelial cell migration and angiogenesis in Lewis lung carcinoma and breast cancer (22,52,53).

Previous studies have shown that the κ receptor is highly expressed in endothelial progenitor cells and endothelial cells, where its activation can reduce the expression of VEGFR2 and neuropilin 1, which are necessary for angiogenesis, by decreasing cAMP production through inhibiting the cAMP/protein kinase A (PKA) pathway (22,52,53). In murine tumor models, κ receptor knockout mice exhibited enhanced tumor proliferation and angiogenesis following lung cancer cell transplantation compared with those in wild-type mice. Consequently, κ receptor agonists may inhibit tumor growth by suppressing angiogenesis (22,52,53).

The anti-angiogenic properties of κ receptor hold potential therapeutic value in cancer treatment. However, κ receptor agonists, such as butorphanol, nalbuphine and dynorphins, pose a risk of drug dependence and tolerance (55,56), necessitating careful consideration in their development and application, particularly for the combined treatment of cancer pain and anti-angiogenesis.

Additionally, another previous study on breast cancer cells found that the expression of κ receptor was significantly increased in breast cancer cells compared with that in non-tumor cells (normal human mammary epithelial cells).

Table II. A summary of the effects of opioids on different types of lymphocytes within the tumor immune microenvironment.

Opioid	Lymphocyte	Effect	Mechanism/Outcome	(Refs.)
Morphine	T Cells	Decrease	Inhibits IL-2 production and receptor expression; reduces T cell activity and immune response	(100,101)
	CD8+ T Cells	Decrease	Suppresses IFN-γ production, inhibits STAT-1 pathway activation and leads to impaired antiviral response	(102,103)
	NK cells	Decrease	Suppresses the activity of NK cells through central opioid receptors	(102,103)
	B Cells	Decrease	Suppresses mitogen-induced responses and reduces antibody production	(78,104)
Fentanyl	NK Cells	Decrease	Prolonged post-operative suppression, particularly in cancer surgery	(30)
Buprenorphine	T Cells	No Effect/reversed suppression	Shows no effect or reverses postoperative suppressive effects	(9)
Tramadol	NK Cells	Increase/reversed Suppression	Increases the activity of NK cells or reverses the suppressive effects of surgery	(30)

NK, Natural killer.

The inhibition of PI3K/AKT signaling by using inhibitors Recilisib and Buparlisib, or knockdown of the κ receptor, was found to reduce the viability and migration of breast cancer cells. These findings suggested that κ receptor may serve as a potential breast cancer growth antagonist (57).

4. Impact of opioids on the immune system

Previous studies have indicated that opioids can suppress the immune system, where *in* vitro studies have shown that opioids can damage immune cells, including macrophages and T cells (12,30). Epidemiological studies have also suggested that long-term opioid use may increase the risk of infections (30,34,58). The effects of opioids on immune cells are summarized in Fig. 1 and Table II.

Impact on T cells. Animal and cell studies have demonstrated that morphine can reduce the activity of T cells in mice by inhibiting the lymphocyte IL-2 production and IL-2 receptor expression in the spleen, which in turn reduces T cell activity and impairs immune function (32,59). In addition, cell experiments have demonstrated that morphine can reduce lactate dehydrogenase (LDH) release and the number of CD8+ T cells, whilst increasing the ratio of CD4+/CD8+ T cells (32,59). Another previous study on the effects of morphine on the anti-human immunodeficiency virus properties of CD8+ T cells has indicated that morphine can inhibit the activity of CD8+ T cells by directly binding to μ receptors, which can downregulate CD8+ T cell activity. In addition, morphine can reduce the secretion of IFN-γ by CD8+ T cells, thereby impairing their function. Morphine was also found to reduce the production of IFN-γ by CD8+ T cells and inhibits CD8 T cell-induced expression of the STAT1, further impairing IFN-γ signaling to compromise CD8 T cell activity, resulting in immune dysfunction.

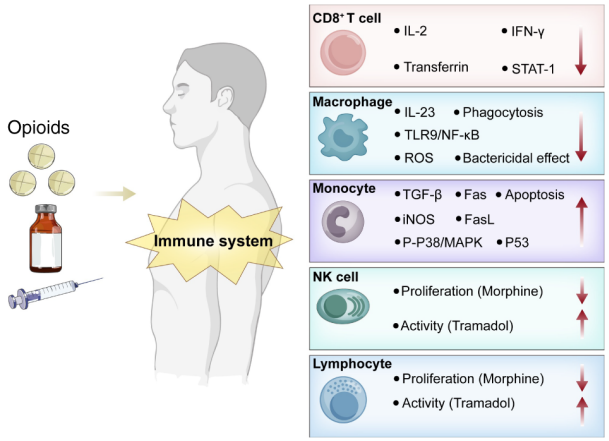

Figure 1. A summary of the effects of opioids on immune cells. Opioids can mediate dual effects on immune system, by the following: i) inhibiting cytokine production in CD8+T cells; ii) interfering with the TLR9/NF-κB pathway in macrophages, leading to the reduction of ROS production and in turn the bactericidal effect; iii) Upregulating apoptosis-related molecules, such as Fas/FasL and p53, inducing the apoptosis of immune cells (such as monocytes) and inhibiting the repair function mediated by TGFβ; and v) Inhibiting lymphocyte proliferation and NK cell activity, whereas tramadol exhibits the opposite effects. TLR, Toll-like receptor; ROS, reactive oxygen species; iNOS, inducible nitric oxide synthase.

Impact on monocytes and macrophages. Morphine can inhibit the macrophage-mediated clearance of pathogens (such as *Streptococcus pneumoniae*) by suppressing the toll-like receptor (TLR)9/NFκB signaling pathway, which increases the risk of infections (60). It can also reduce the production of IL-23 by dendritic cells and macrophages by inhibiting the TLR3 and nucleotide-binding oligomerization domain-containing protein 2 signaling pathways, weakening the body's defense mechanisms (60,61). In addition, recent studies suggest that morphine can significantly increase the

Table III. A summary of the existing conflict effects of opioids.

Conflicts existing	Possible explanations	(Refs.)
μ receptors may promote or inhibit tumor growth	The receptor activation effect is dose-dependent; Anoxic conditions also influence the effect of μ receptor agonists	(48)
κ receptors can reduce angiogenesis to reduce tumor growth, but they are highly expressed in breast cancer cells	κ receptor agonists can reduce VEGF expression and inhibit angiogenesis in endothelial cells; but in breast cancer, κ receptors can promote tumor growth through PI3K/AKT pathway	(30,57)

expression of TLR4, p65, NF-κB and cytokines (IL-6 and TNF-α) in microglia and macrophages (62,63).

Numerous studies have demonstrated that morphine, as an opioid receptor agonist, can directly downregulate various phagocytic activity and enhance cell apoptosis in a number of cell types, including mouse peritoneal macrophages, bone marrowderived macrophage (BMDM) and peripheral blood monocytes (64,65). In particular, in BMDM, morphine can enhance LPS-induced macrophage apoptosis through a peroxisome proliferator-activated receptor γ-dependent mechanism (65). This interaction inhibits the production of ROS, including superoxide and peroxide, resulting in decreased superoxide anion production. Since these intermediates are involved in the bactericidal mechanism of phagocytes, morphine treatment resulted in decreased phagocytic efficacy and reduced macrophage bactericidal activity (40). Morphine has also been found to inhibit the formation of macrophage colonies in soft agar from cultured mouse bone marrow progenitors (34).

Impact on NK cells. In rat models, the proliferation of NK cells was reported to be significantly suppressed in mice treated with morphine compared with that in controls. Administration of a nucleus accumbens shell blocker reversed the suppressive effects of morphine on the proliferation of NK cells in mice, suggesting that the nucleus accumbens serves a critical role in regulating peripheral immune responses. This process is likely mediated by the activation of sympathetic pathways and dopaminergic neurohumoral immunomodulation, with morphine indirectly affecting NK cells (34,66,67). A previous study demonstrated that morphine can inhibit lymphocyte proliferation and NK cell activity *in vitro* (68), whereas tramadol exhibits the opposite effects (67,68). This effect of tramadol was due to the (+)-enantiomer of tramadol inhibiting serotonin (5-HT) reuptake, increase extracellular 5-HT concentrations in the synaptic cleft, prolonging its combining time with 5-HT receptors and amplifying 5-HT signaling, which can promote immune activation, increase NK cell activity and IL-2 production (67).These findings suggest that different opioids may have distinct impact on the immune system.

Contradictory research findings. Opioids are recognized for their inhibitory effects on immune cell function (12,34), including the suppression of lymphocytes, T cells and monocytes, which may in turn adversely affect the immune system and promote tumor growth. However, the literature also presents significant contradictions regarding these effects. These conflicting findings highlight the dual effects of opioids.

Dual role of μ receptors. μ receptor agonists may promote tumor growth under certain conditions. The activation of morphine-induced μ receptors can promote breast cancer cell proliferation both *in vivo* and *in vitro* (37,39). In addition, low concentrations of morphine in pancreatic cancer led to an increase in phosphorylated JNK, whilst the phosphorylation of p38 was reduced, resulting in an increment in tumor volume (48). However, morphine pre-treatment under hypoxic conditions inhibits VEGF production, which can suppress tumor growth (51,69). By inhibiting angiogenesis and production of M2-polarized macrophages, whilst inhibiting the production of MMP9 by macrophages, morphine can also suppress tumor growth (42,43).

Dual effect of κ receptors. Although κ receptor agonists can inhibit angiogenesis and tumor growth through the cAMP/PKA pathway, they may promote metastasis of breast cancer when activated in breast cancer cells (57,70).

The expression and functional profiles of different receptors, including μ and κ receptors, may vary in different types of tumors, leading to differences in anti-tumor or pro-tumor effects. The existing contradictory information are summarized in Table III.

5. Opioids in different cancer types

Effects of opioids on breast cancer. Previous studies of opioid use in breast cancer have shown that the use of fentanyl, a δ receptor agonist, as anesthetics can reduce NK cell cytotoxicity compared with sevoflurane, during surgery. The use of δ receptor agonists in breast cancer can also promote the metastasis of breast cancer cells (53,71). However, activation of κ receptor has been documented to exhibit an inhibitory effect on estrogen receptor (ER)-positive breast cancer through the κ receptor/ER/X-box binding protein 1 pathway (72).

Effects of opioids on lung cancer. Opioids can inhibit lung cancer angiogenesis through different pathways. In Lewis lung carcinoma murine experiments, κ receptor knockout mice showed increased proliferation and enhanced tumor angiogenesis compared with those in wild-type mice, through the VEGF signaling pathway, indicating that κ receptor may inhibit the blood supply and growth of lung cancer (70). However, in lung cancer cell experiments, morphine may suppress the immune function by upregulating maelstrom spermatogenic transposon silencer (MAEL) expression, increasing the levels of Programmed death-ligand (PD-L)1, TGF-β and IL-10, whilst decreasing IL-2 levels (59).

Effects of opioids on liver cancer. Morphine, as a μ receptor agonist, can suppress the metastasis and growth of liver cancer cells by upregulating the expression of opioid growth factor receptor and downregulation of μ-opioid receptor and MMP-9 expression (73). Murine experiments have previously reported that tramadol can suppress the growth of orthotopic liver tumors by promoting M1 macrophage polarization in the tumor microenvironment (74).

6. Interactions between opioids and common analgesics

Anesthesia during cancer surgery rarely involves a single anesthetic, such that cancer pain management typically requires the application of multiple drugs (75). There are complex pharmacokinetic interactions between various anesthetics, which significantly affect the patient's postoperative recovery. Opioids can inhibit the proliferation of T cells and hinder the function of B cells through μ receptors and by upregulating the production of proinflammatory cytokines, such as IL-1β and IL-6. By promoting the production of cAMP, μ receptor agonists can inhibit T cell receptor signaling through the PKA/Csk-binding phosphoprotein associated with glycosphingolipid-enriched microdomains/C-terminal Src kinase-leukocyte-specific protein tyrosine kinase pathway, resulting in a decrease in IL-2, which can inhibit the proliferation of T cells (76,77). In addition, they can inhibit the activity of NK cells through opioid receptors in the central nervous system (78). They can also stimulate the metabolism of benzodiazepines, potentially leading to respiratory depression when combined with benzodiazepines (79). When co-administered with certain general anesthetics, such as isoflurane and propofol, opioids may enhance respiratory depression, which causes severe respiratory depression and apnea (80). By contrast, co-administration with NSAIDs may affect drug metabolism through the liver, increasing the risk of gastrointestinal injury and bleeding (81). Combining opioids with alcohol can increase central nervous system depression, potentially leading to confusion and respiratory depression (82). Since patients with cancer may also take antidepressants, co-administration with opioids can result in respiratory depression, confusion, mood instability, drowsiness and other mental symptoms, such as anxiety, depression and hallucinations (specifically false sensory perceptions in the absence of external stimuli) (83). Combining opioids with certain sedatives, including benzodiazepines, may cause hypotension and bradycardia, increasing the cardiovascular burden, especially in elderly patients or those with a history of cardiovascular disease (84). Therefore, careful monitoring of cardiovascular function and the timely adjustment of medication may prevent the aforementioned complications (85).

Clinical scenarios for the combined use of opioids. As common analgesics in clinical settings, opioids have the potential to be combined with non-traditional cancer therapies. Emerging non-traditional cancer therapies, such as immunotherapy, primarily involve immune checkpoint inhibitors, adoptive cell therapy and cancer vaccines (86-88). Cancer immunotherapy is fundamentally based on the inhibition of immune escape mechanisms utilized by tumor cells. Currently, cancer immunotherapies primarily focus on immune checkpoint inhibitors targeting programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte associated protein 4 (CTLA-4) (89). The application of PD-1 or its ligands, PD-L1 and PD-L2 monoclonal antibodies, selectively blocks the interaction between tumor cells and T cells. This restores antitumor immunity and enhances cytotoxic T cell-mediated tumor destruction, which ultimately causes tumor eradication (90). CTLA-4 monoclonal antibodies inhibit the co-stimulatory interaction between CTLA-4 molecules on regulatory T cells and Fc, which induces the death of regulatory T cells, reduces negative T cell regulation and enhances T cell-mediated immune responses (91). Immune checkpoint inhibitor therapy allows T cells to effectively infiltrate into tumor sites and form long-lasting immune responses by activating the body's T-cell immunity (87,92,93).

However, the modulation of immune activity, upregulation of T cell activity and reduction of Treg cell-mediated immunosuppressive activity can increase the risk of autoimmune complications and inflammation, such as checkpoint inhibitor pneumonitis induced by anti-PD-1/PDL-1 immune checkpoint inhibitors (94). To improve survival rates and quality of life, it is common to co-administer opioids and immunosuppressants to patients who commonly experience abdominal and lesion pain (94). Opioids can damage T cells and macrophages, where retrospective analyses of PD-1/PD-L1 concomitant medications have shown that patients with melanoma and NSCLC who receive opioids along with immunotherapy exhibit significantly lower overall survival rates, objective response rates and progression-free survival rates compared with patients who receive immunotherapy without opioids. This combination carries a higher risk of disease progression, gut microbiota dysbiosis and gut barrier dysfunction (95). Therefore, it is necessary to closely monitor changes in gastrointestinal function and inflammation markers when the treatment plan involves a combination of opioid administration and immunotherapy. Alternative treatments should be promptly adopted in the case of impaired gastrointestinal function.

Opioids can damage immune components, such as macrophages and T lymphocytes. However, considering the dose-dependent effects of opioids on the immune system, further studies are needed to explore how opioids can affect the tumor immune microenvironment, which differs from the normal immune composition (96). The long-term effects of opioids on the immune system and the complex immune system within the tumor microenvironment require further investigation.

7. Therapeutic strategies and future directions

Opioids are used in cancer treatment to alleviate patients' pain and improve their quality of life. However, the efficiency of opioids depends on multiple factors, such as the type applied and severity of pain, the patient's overall health status, potential side effects and drug interactions (97). Clinical treatment typically follows the pain management guidelines published by the World Health Organization (WHO) (97). It is necessary to conduct comprehensive pain assessments and select appropriate dosages of analgesics based on the patient's condition and response. The choice of analgesics can be guided by the WHO analgesic ladder. If a single drug is insufficient to control pain, it is recommended to use a combination of

multiple drugs along with non-pharmacological treatments, such as physical therapy, psychological support and alternative therapies such as traditional Chinese medicine, to alleviate the patient's pain. Opioids may cause various side effects, such as constipation, vomiting, drowsiness and respiratory depression (98). Therefore, it is necessary to regularly monitor the patient's pain status, drug efficacy and side effects during the clinical treatment regimen. It is important to take the necessary measures to control these side effects and if necessary, to change the medications or increase their dosage to improve the patient's quality of life. Additionally, since cancer patients may take multiple drugs simultaneously, drug interactions must be carefully monitored.

The study of opioids represents a dynamic and advancing area of research. Researchers are actively pursuing novel drug targets to create innovative non-opioid analgesics and mitigate the adverse effects associated with the administration of opioids. To mitigate the risk of drug abuse and potential addiction, studies are investigating alternative therapies to overcome challenges, such as opioid abuse and dependence (99). In addition, it is crucial to develop selective opioid receptor antagonists to inhibit the potential immunosuppressive effects of opioids. κ receptor activation can exert anti-tumor effects by reducing VEGF production and inhibiting tumor angiogenesis (70). However, the use of receptor antagonists to block κ receptors on breast cancer cells can hinder breast cancer progression and reduce the risk of metastasis (70).

Additionally, advances in drug delivery systems, such as the use of nanotechnology or targeted delivery, can increase local drug concentration, reduce systemic side effects and enhance efficacy. Studies on genetic variations in analgesic responses may facilitate the development of personalized pain management strategies. Before clinical application, the efficacy, safety, tolerance and dependence of analgesics should be extensively investigated to prevent and mitigate their possible side effects.

8. Conclusion

Although opioids are essential for managing cancer-related pain, they serve a complex and dual role within the tumor immune microenvironment. The suppression of immune cell activity and promotion of angiogenesis is of particular importance in cancer, since they may undermine the effectiveness of antitumor therapies. Therefore, a deeper understanding of these mechanisms is crucial for optimizing the use of opioids in cancer treatment to ensure that pain management does not inadvertently compromise treatment outcomes. The following strategies and future research keynotes should be considered to achieve a balance between effective analgesia and optimal cancer pain management.

Personalized pain management plans. It is necessary to develop individualized analgesic plans under the WHO pain management guidelines to minimize opioid dosages whilst ensuring effective pain relief. This requires further development and integration of non-opioid analgesics, adjuvant therapies and non-pharmacological interventions to reduce the dependence on opioids.

Regular monitoring and assessment. Regular assessments of pain intensity, functional capacity and possible opioid-associated side effects are essential, where treatment strategies must be modified as needed to achieve effective pain management whilst minimizing immune function disruption.

Opioid-immune system interactions. The specific pathways through which different opioid receptors influence immune cell function, angiogenesis and tumor progression need to be investigated to inform safer analgesic choices.

Opioid use in conjunction with immunotherapies. The interaction of opioids with immune checkpoint inhibitors and other immunotherapies should be examined to determine their impact on treatment efficacy and patient outcomes.

Development of novel analgesics. It is necessary to explore and develop novel pain management agents that provide effective analgesia with minimal immunosuppressive effects to preserve the integrity of cancer therapies.

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Authors' contributions

YZ and WL were involved in the conception and design of the present review, collection and assembly of data. XH and CM contributed substantially to the conception and design of the study. CM also performed data analysis and data visualization. YC contributed to the refinement of the manuscript's narrative and logic critically reviewed the content. All authors were involved in drafting and revising the manuscript. All authors have reviewed and approved the final version of the submitted manuscript.

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Competing interests

The authors declare that they have no competing interests.

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