Regulatory T cells: A possible promising approach to cancer recurrence induced by morphine

L. Gong, C. Dong, W. Ouyang, Q. Qin

Department of Anesthesiology, The Third Xiangya Hospital of Central South University, Tongzipo Road 138#, Changsha 410013, Hunan, China
Department of General Surgery, The First Xiangya Hospital of Central South University, Xiangya Road 87#, Changsha 410008, Hunan, China

Abstract
Cancer recurrence is one of the most important causes of cancer-related deaths. In present, it has been revealed that there exist some factors especially opioids being able to affect the recovery of cancer patients in a long period. As the most commonly used potent analgesics in practice, morphine appears to be of crucial importance in the regulation of neoplastic tissues by modulating immune responses and promoting angiogenesis. Indeed, regulatory T cells have been shown to inhibit the response of the immune system to tumor and thereby to worsen prognoses. Some reliable evidences indicate that morphine acts directly on regulatory T cells through VEGFR 2 and opioid receptors present in, both of which play a vital role in the cancer recurrence. In addition, morphine might have a noticeable effect on regulatory T cells by regulating the function of some other immune cells or cytokines, TGF-β and IL-2 for instance. Thus, this paper speculates that morphine could induce cancer recurrence by disturbing the behavior of the regulatory T cells and provides a logical reasoning.

Introduction
In the past several decades, cancer has been a malady all around the world. Based on the GLOBOCAN 2008 estimates, about 12.7 million cancer cases are estimated to have occurred in 2008 [1]. And it has become the primary and second leading cause of death in economically developed and developing countries respectively [2]. In addition, metastatic disease is regarded as one of the most important factors inducing cancer-related deaths [3]. Previous researches have showed that many factors such as surgical stimulation, blood transfusion, low temperature, narcotic drugs and so on were related to the cancer metastases [4,5]. Recently, two epidemiologic studies have revealed that the rate of cancer recurrence was significantly lower than in patients undergoing general anesthesia with opioid analgesia in both breast and prostate cancer [6]. It suggested that opioids could favor cancer recurrence.

Opioids have long been used as the mainstay of treatment of cancer-related pain and are an important modality for the prevention of perioperative pain. Among these opioids, morphine is believed to be the most commonly used potent analgesics. Impressively, morphine administration, both perioperative and chronic, has been shown to suppress body immunity [7]. And the immunomodulation is mediated by opioid receptors [8] either in nervous system [9] or immunocompetent cells such as neutrophils, NK cells, macrophages and equally in T cells [10]. Morphine can add directly to these immune cells alter their protein expression profile and function [11]. In addition, morphine is associated with an aberrant stimulation of tumor growth triggered by the stimulation of angiogenesis in cancer patients [12]. As a result, morphine could facilitate cancer recurrence, but laboratory data available at the moment do not draw a clear picture of morphine as a tumor promoting agent.

Regulatory T cells (Tregs), specialized T cells, are CD4+ CD25+ and express the transcription factor Foxp3 [13]. Previous studies showed that Tregs could inhibit the activation of the immune system and even shut off the normal immune system response to the tumor; In addition, vascular endothelial growth factor receptor 2 (VEGFR2) is selectively expressed by regulatory T cells [14]. And VEGFR2 plays a critical role in angiogenesis on the process of tumor growth, invasion and metastasis. These suggest that Tregs favor cancer recurrence involving in immunosuppression or angiogenesis that confer metastasis advantage. Interestingly, naloxone, a kind of opioid receptor antagonists, improved the anti-tumor immunity of BALB/c mice, corresponding to inhibition of the regulatory T cells [15]. Therefore, we guess that Tregs bridge opioids and cancer recurrence.

The hypothesis
According to lots of valuable research results, we hypothesize that morphine could act directly on regulatory T cells by VEGFR2
and opioid receptors present in. Both are of particular importance due to their role in cancer recurrence. Moreover, morphine may also affect regulatory T cells by regulating the function of some other immune cells or cytokines, such as TGF-β, IL-2. And in all, we propose that morphine could favor cancer recurrence by regulating regulatory T cells. The effective pathway to prevention and therapy of cancer recurrence should consider measures against regulatory T cells.

**Evaluation of the hypothesis**

Morphine is currently one of the most effective drugs available clinically for the management of severe pain associated with cancer. Apart from its analgesic action, morphine appears to be important in the regulation of neoplastic tissue. Accumulating evidence suggests that morphine can promote the dissemination of malignant cells by stimulating angiogenesis and impairing immune function.

Angiogenesis is important in the growth and metastatic potential of various cancers. Mainly through VEGFR2, VEGF which is secreted by several types of tumors and abundant in the tumor microenvironment exerts its biological effect on vascular endothelium. Both in fact are of particular importance in angiogenesis by improving normal blood vessel development [16]. What's more, Singleton and Moss [17] demonstrated that morphine transactivates the VEGFR and promote angiogenesis. A common trend that emerges is that opioids promote cell proliferation and migration, through activation of MOR and subsequent transactivation of VEGFR, VEGFR2 included. It should be noted that vascular endothelial growth factor receptor 2 (VEGFR2) has been found expressed by regulatory T cells [14]. All above indicates some relation exists between opioid receptor and VEGFR2 in regulatory T cells.

Coincidentally, it has been demonstrated that over expression of VEGF from tumors resulted in elevated numbers of regulatory T cells in the tumor [18]. In addition, a few studies suggest a contribution of VEGF to the induction or maintenance of regulatory T cells [19]. This suggests that morphine may stimulate the VEGFR2 on Tregs, also with the synergic effect of VEGF and further affect tumor metastasis or recurrence. That means regulatory T cells may play a role in angiogenesis in cancer patients just because of the present VEGFR2.

Besides VEGFR2, a possibility that opioid receptors may also present in regulatory T cells is available. It is well known that effects of opioids ultimately depend on the expression of specific receptors, termed μ, δ and κ opioid receptors [20]. There is growing evidence that opioid receptors are expressed by cells of the immune system. In addition, it has been demonstrated that morphine is capable of directly restraining the immunomodulatory function of the immune cells. Just using the whole blood ex vivo mode, opioids modulate immune response by direct modulation results from the effects of opioids on immune system cells [21]. Otherwise, it has been strengthen the concept that opioids exert a marked number of immunomodulatory effects by subtly regulated expression of functional opioid receptors in cells of the immune system, such as lymphocytes and macrophages [22,23]. What's more, long-term intrathecal morphine can upregulate MOR gene expression in lymphocytes [24]. Interestingly, naltrexone, the general opioid antagonist, can improve the anti-tumor immunity by reducing the regulatory T cells in BALB/c mice [15]. So morphine administration may accelerate the regulatory T cells proliferation. And the responses due to morphine treatment may be mediated through direct interaction with the opioid receptors on regulatory T cells.

Beyond acting on the receptors of Tregs, morphine may also affect them by regulating the function of some other immune cells or cytokines. Based on an intensive number of references, two main origins have been describe for regulatory T cells, whose numerical and functional importance have yet to be clarified. Apart from the thymus where Tregs are generated, the periphery where a number of triggers induce the expression of FoxP3 in T cells, appeared to depend on TGF-β for its differentiation. As we all know, TGF-β is closely associated with the levels of corresponding cytokines, which was the cause of the immune alteration. However, opioids can influence the expression both at cellular and molecular level. It has been shown that exposure of PBMC to morphine (1 μM) for 24 h substantially amplified the release of TGF-β in response to LPS or PHA [25]. Moreover, a highly selective μ-opioid agonist DAMGO can induce the expression of TGF-β1 expression at the protein and mRNA levels and further affect the chemokine and chemokine receptor expression [26]. Although the mechanism of how opioids act on TGF-beta is unclear, this may at least provide us a way that TGF-β bridge morphine and Tregs.

In addition, IL-2 is indispensable for the peripheral maintenance of the regulatory T cells. Because CD25low CD4+ nonregulatory T cells actively transcribe the IL-2 gene and secrete IL-2 protein in the physiological state [27]. And nonregulatory naïve T cells toward a regulatory T cell phenotype capable of suppressing proliferation of other T cells, presumably through inhibition of IL-2 production. What's more, chronic morphine treatments inhibit IL-2 promoter activity and protein production [28]. And the decrease in IL-2 production following opioid administration was observed [29]. This may provide another way for us. Overall, these findings demonstrated that regulatory T cells may be regulated by morphine directly or indirectly. Therefore, regulatory T cells may be a possible promising approach to Cancer Recurrence induced by morphine.

**Consequences of the hypothesis and discussion**

Morphine possibly favors cancer recurrence by regulating regulatory T cells. A more appropriate administration of morphine or blockage of regulatory T cells expression would reduce cancer metastasis. It could be suggested that regulating regulatory T cell numbers could constitute an important prognostic factor for cancer patients treated with morphine. Beyond that, Tregs could be a novel target for therapeutic intervention. However, further identification and characterization of the receptors and the signal transduction pathways that account for some of the unique properties of opioid binding and immunomodulation represent major research challenges that lie ahead. And more and more evidences would be found to raise this hypothesis.

**Conflicts of interest statement**

There is no conflicting interest exists.

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**References**


