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Perioperative Clinical Interventions That Modify the Immune Response in Cancer Patients

María F. Ramírez[1], Johannes M. Huitink[2], Juan P. Cata[1*]

[1]Department of Anaesthesiology and Perioperative Medicine, The University of Texas MD Anderson Cancer Centre, Houston, USA;
[2]Department of Anaesthesiology, VU University Medical Centre, Amsterdam, The Netherlands.
Email: *jcata@mdanderson.org

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ABSTRACT

The immune system plays a pivotal role against cancer. The development of a successful immune response involves the balance between the Th1 (antitumor) and Th2 (protumor) responses. Once this balance is lost, diseases such as cancer may become apparent. Surgical stress, volatile anaesthetics, opioids and blood transfusions are known to favour a Th2 response that manifests as immune suppression. During surgery the load of circulating malignant cancer cells is increased by tumour manipulation. These cancer cells can migrate and seed in distant tissues and form metastasis. Also, some cancer patients may present with micrometastasis that may become invasive if left untreated. Therefore, the perioperative period is a moment of immunological vulnerability in cancer patients. A better understanding of the factors that affect the Th1/Th2 balance may allow anaesthesiologists to identify patients at high risk for cancer recurrence. This review describes the perioperative interventions that can alter the Th1/Th2 balance, during the perioperative period of oncological surgery.

Keywords: Neoplasm; Surgery; Anaesthesia; Cytokines; Neoplasm Recurrence; Immune Response; Opioids; Volatile Anaesthetics

1. Introduction

The immune system plays a pivotal role in clearing new forming malignant cells and it does so by favouring antitumor mechanisms such as the production of cytokines. These cytokines have not only the ability of inducing cancer cell death directly but also by stimulating the function of cells such as natural killer cells and cytotoxic lymphocytes [1].

CD4 T helper cells are lymphocytes that strongly modulate the response of the immune system against cancer cells proliferation and tumour growth. They are classified into Th1 and Th2 cells based on their function and cytokine profile [2]. Th1 cells release IFN-γ, IL-2, and TNF-a (Th1 cytokines); incontrast, Th2 cells secrete IL-4, IL-5, IL-10, and IL-13 cytokines (Th2 cytokines). Mosman *et al*. [3] established the Th1/Th2 balance paradigm to better understand the relevance of the Th1 and Th2 cytokines in different physiological or pathological disorders (**Table 1**). A shift towards Th1 polarization (**Figure 1**) is the expected response against cancer. For instance, IL-2, the prototypical Th1 cytokine, has shown anticancer activity by augmenting cytolytic activity of NK cells, by inducing IFN-γ, and by activating macrophages [4]. In contrast, Th2 cytokines promote matrix metalloproteinase expression, invasiveness, and metastasis [5].

Cancer patients may suffer from significant immunosuppression that is characterized by a predominant Th2 state. This is the result of the cancer itself [6] malnutrition, chemotherapy, stress, concurrent diseases, medicationsand surgery [7]. The latter remains as one of the main therapeutic options for a large number of solid cancers but unfortunately, there are perioperative factors that alter the balance between the Th1 and Th2 cytokines favouring a predominant Th2 (protumor) state. Those factors include surgery-induced stress, anaesthetics, analgesics and blood transfusion. Thus, it is important to highlight the concept perioperative immunosuppression because it is the time in which dormant [8] and occult tumours [9] and circulating tumour cells [10] have increased possibilities of seed and growing even after the primary tumour has been resected [11]. It has been hypothesized that avoiding some or all those factors would

*Corresponding author.

Table 1. Th1 and Th2 cytokines and their main functions.

Th1 cytokines		Th2 cytokines	
IFN-γ	Enhances the microbicidal function of macrophages. Promotes the differentiation of naive helper T cells into Th1 cells. Activates polymorphonuclear leukocytes, cytotoxic T cells, and NK cells.	IL-4	Regulates antibody production, haematopoiesis, and inflammation. Promotes the differentiation of naive helper T cells into Th2 cells. Decreases the production of Th1 cells.
IL-2	Promotes clonal expansion and development of T and B-lymphocytes. Induces expression of adhesion molecules. Enhances the function of NK cells.	IL-10	Inhibits synthesis of Th1 cytokines such as IFN-γ and IL-2. Inhibits antigen-presenting cells.
IL-15	Induces activation and cytotoxicity of NK cells. Activates macrophages. Promotes proliferation and survival of T and B-lymphocytes and NK cells.	IL-8	Promotes neutrophils chemotaxis and degranulation. Promotes tumour angiogenesis.
IL-21	Regulates proliferation and differentiation of T cells, B cells, and NK cells. Potently regulates cellular-mediated immunity and directs cytotoxic T lymphocytes and NK cell effector activity in the clearance of tumours.	IL-13	Inhibits inflammatory cytokine production. Induces immunoglobulin E secretion from B-lymphocytes.

IFN-γ: Interferon gamma; IL: Interleukin; NK: Natural killer.

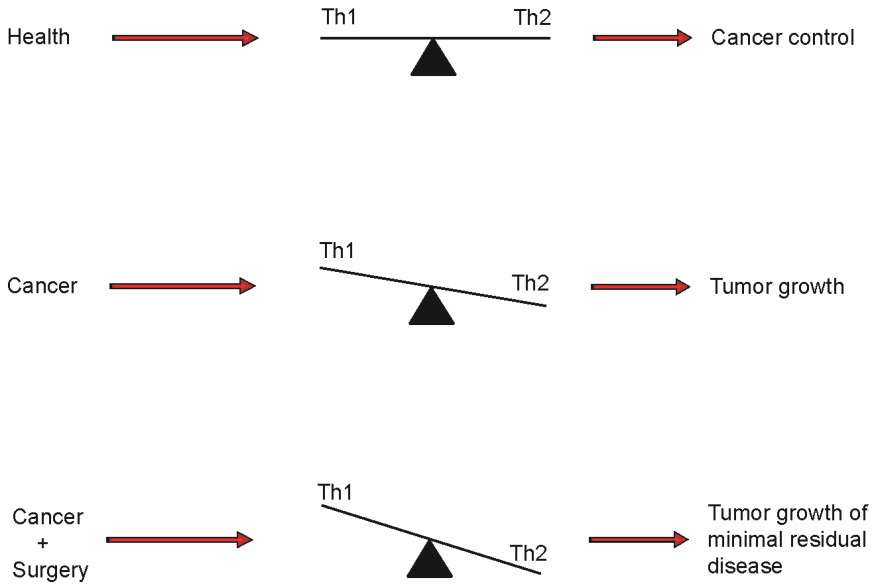

Figure 1. The Th1/Th2 balance in different heath states.

minimally affect the Th1/Th2 balance and perhaps be associated with better oncological outcomes [12].

The purpose of this review is to describe the perioperative variables that modify the Th1/Th2 balance. We will focus on its pattern during the perioperative period and the clinical and long-term implications of the misbalance in oncological surgical patients.

2. The Th1/Th2 Balance during Cancer Surgery: The Th2 Dominant Immune State

Few studies have clearly investigated the Th1/Th2 balance in the perioperative period of cancer surgery. The kinetics of Th1 and Th2 cytokines during the perioperative period remains difficult to study because they are not being measured at their maximum peak and most studies are done during in vitro conditions. Many studies have used immunoassays to measure the concentrations of Th1 and Th2 cytokines in serum/plasma, supernatants of stimulated peripheral blood mononuclear cells or, intracellularly [13,14]. Clinical studies indicate that the Th2 predominant state is the result of a decrease in Th1 cytokine production and enhancement of the Th2 response [14,15]. For instance, in patients with oesophageal cancer, Sato *et al*. [16] observed increased postsurgical serum concentrations of IL-8 and IL-10 that lasted 24 hours. These cytokine profiles were similar to those found in patients with squamous cell carcinoma of the larynx. Strey *et al*.

[17] described the cytokine pattern among patients with hepatic metastases, primary intrahepatic cholangiocarcinoma, and primary hepatic carcinoma. The authors found higher concentrations of IL-10 among patients with extensive and prolonged surgery and among patients with delayed postoperative recovery [17]. An alternative hypothesis to the imbalance can be drawn from other studies in which the predominant Th2 state is the result of a decrease in Th1 response without an increase in the Th2 response [18,19].

Summarizing, the Th2 state associated with surgery is due to an increased of the Th2 cytokines with a relative decrease or no change in the Th1 cytokines.

2.1. Extent of Surgical Trauma

Catecholamines disrupt the Th1/Th2 balance towards a predominant Th2 state [20]. Thus, it is possible to speculate that the balance between Th1 and Th2 cytokines may change according to the magnitude of surgical invasiveness [21]. It is well known that in the context of cancer surgery, minimally invasive techniques have several advantages over open procedures including shorter hospital stay [22] and reduced infection rate [23]. Moreover, the smaller incisions of laparoscopic procedures are considered to produce less overall trauma and immunological disturbances at both cellular and humoral level compared with open surgery [14,24,25]. For instance, in patients undergoing colon cancer surgery, Tsamis *et al*. [26] documented higher serum concentrations of IFN-γ in patients who underwent laparoscopic colectomy than in patients who underwent open surgery. This difference was sustained until the seventh postoperative day [26]. Open oesophageal cancer surgery has been associated with higher concentrations of IL-10 than laparoscopic resection [27].

Whether changes in the Th1/Th2 balance in response to surgical invasiveness correlate with long-term oncological prognosis is basically unknown. However, there are several studies that have tried to address the question of whether the degree of surgical invasiveness in associated to oncological outcomes. For instance, in patients with stage 1 non-small cell lung cancer the overall survival rate, only at 5 years, is better after open thoracotomy than video-assisted lobectomy; however, publication bias has been found in a recent metaanalysis [28]. Interestingly, the rate of systemic recurrences has been reported to be lower than after lobectomy [28]. Data from a large randomized controlled trial comparing open versus laparoscopic resection of colorectal cancers demonstrates that there are no differences in overall and disease-free survival [29]. A retrospective study in patients undergoing oesophageal cancer surgery failed to demonstrate an association between type of surgery (open versus laparoscopic) and overall survival [30]. Similar results were found in gastric cancer surgery [23].

In summary, it seems that the higher the surgical trauma the more pronounced the alteration of Th1/Th2 balance, however; the impact of this imbalance on cancer recurrence and survival after oncological surgery are not clear and needs further study.

2.2. Perioperative Blood Transfusion and Cancer Survival

The concentrations of Th2 cytokines are increased in non-leukoreduced RBC units; hence during the administration of blood there is also infusion of those cytokines [31-33]. To complicate more this matter, the immune system of the blood recipient is able to trigger a significant Th2 response that is caused by the contact of the cellular and not cellular factors present in the transfused units to recipient's leukocytes. For instance, exposure of stored red blood cell (RBC) to whole blood triggers release of IL-10 [34], reduces lipopolysaccharide-induced release of TNF-a [35], and induces regulatory T cell (Treg) activation [36]. Interestingly, the enhanced released of IL-10 is not completely avoided when leukodepleted or autologous blood is used [37]. Moreover, it appears that the plasma non-cellular factors of the transfused units are responsible of a depressed Th1 response whereas the RBCs are involved in the enhanced Th2 response, thus turning the balance to predominant Th2 state.

Several retrospective studies have shown an association between blood transfusions and cancer recurrence [38-40]. Importantly, a meta-analysis demonstrated that blood transfusions in the perioperative period are associated with higher rates of cancer recurrence after colorectal cancer surgery [41]. However, it is unknown if the association between blood transfusions and cancer recurrence is due to a Th1/Th2 imbalance or other biological mechanisms.

2.3. Opioids and Anaesthetics

Opioids, the most commonly used analgesics in the perioperative period, also contribute to the Th1/Th2 imbalance by favouring Th2 over a Th1 response (**Figure 2**). The production of IL-4 and IL-5, increases [42] and that of IL-2 decreases after exposure of T lymphocytes and peripheral mononuclear cells to increasing concentrations of morphine [43]. Moreover, morphine decreases the expression of IL-2 by acting on the mu-receptor [44]. Humans receiving morphine have an increased mRNA expression of IL-4 in peripheral blood mononuclear cells, and in a positive feedback mechanism [45], IL-4 increases the expression of mu-receptors in the same cells [46]. Similarly, a clinical study demonstrated that the administration of fentanyl was associated with a predominant Th2

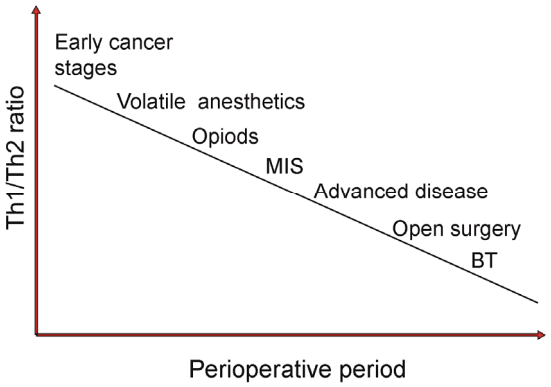

Figure 2. Perioperative interventions that affect the Th1/Th2 balance.

shift [47]. In regards to IL-10, it has been shown that the administration of high-dose morphine to intact animals provokes a sustained increase in IL-10 concentrations [48]. Interestingly, two clinical studies corroborated the findings in animals and indicate that the plasma concentrations of IL-10 are elevated after patient-controlled morphine analgesia and after sevofluraneopioid based anaesthesia [49,50].

General anaesthetics also have important effects on the immune system (**Figure 2**) [51-53]. Propofol appears to improve or preserve the Th1/Th2 ratio [54,55] which is in distinct contrast to volatile anaesthetics and ketamine [56]. An *in vitro* study in which lymphocytes were obtained from patients exposed to the combination of fentanyl and propofol for 20 minutes and then stimulated with phytohemmagglutinin or lipopolysaccharide demonstrated a predominant Th1 response based on an IFN-γ/IL-10 ratio that was higher than before anaesthesia [52]. In healthy individuals, sevoflurane-N_2O-based general anaesthesia is associated with higher and lower plasmatic concentrations of IL-10 and IL-2, respectively, than is propofol-based general anaesthesia, although these differences seem to be transient and short-lived [57]. These findings are in contrast to those reported by Delogu *et al*., who did not find differences in the systemic concentrations of IL-10 between patients who underwent major surgery under total intravenous anaesthesia versus inhalational anaesthesia [58].

One of the means to reduce or even avoid volatile anaesthetics and decrease opioid consumption is using regional anaesthesia techniques. Thus, several investigators have hypothesized that these techniques would be associated with better immunological profiles and oncological outcomes [59,60]. Wada *et al*. showed, in an animal model, that the addition of spinal block to general anaesthesia decreased the number of liver metastasis induced by surgery. The authors speculated that this effect was related to the preservation of the Th1/Th2 balance after surgery [60]. Whether these findings translate in humans is completely unclear. The use of spinal anaesthesia was not associated with a lower or higher Th1/Th2 ratio compared with general anaesthesia in patients undergoing transurethral prostate resection for prostate hyperplasia. Although the authors did find a transient decrease in the plasma concentrations of IL-2 in the general anaesthesia group patients, these subjects had higher concentrations of the cytokine at baseline than those who had spinal anaesthesia [61]. Le Cras *et al*. found an increase in Th1 cells and decrease in Th2 cells in patients who underwent transurethral resection of the prostate with spinal anaesthesia compared with cancer patient with general anaesthesia, leading to an increase in the Th1/Th2 ratio. Thus, the ratio was higher in patients who received spinal anaesthesia compared with general anaesthesia [62]. Ahlers *et al*. reported similar findings in patients undergoing abdominal surgery. These authors demonstrated that the use of intraoperative epidural analgesia was associated with a higher Th1/Th2 ratio than when epidural analgesia was started postoperatively [63]. Remarkably, these findings are in striking contrast to those recently reported by Viviano *et al*., who found that, in the majority of cancer patients undergoing thoracotomy, the use of epidural anaesthesia was associated with a lower Th1/Th2 ratio than that calculated for patients who received only remifentanil or remifentanil plus clonidine [64]. Finally, a clinical study demonstrated that the use of intraoperative high doses of fentanyl was associated with a reduction in IFN-γ concentrations; interestingly this phenomenon was partially reversed by the used of intraoperative epidural anaesthesia [63].

Whether or not the magnitude of the effect of opioids and anaesthetics on the Th1/Th2 balance is higher to that of cause by surgical stress in unknown. Several authors have hypothesized that the use of regional analgesia would not only ameliorate the stress response associated with surgery and the requirements of aesthetic and analgesic hence maintaining the Th1/Th2 balance but also it would have a significant impact on cancer recurrence [65]. Unfortunately, there is no clinical evidence from randomized controlled trials that indicate that the use of regional anaesthesia or analgesia technique is associated with better recurrence-free survival [66].

In summary, the predominant immunological response during and after surgery is Th2 type, and it is perhaps related to the magnitude of surgical stress and tissue damage and less likely to the type of anaesthesia technique used.

3. Conclusion

In conclusion, the perioperative period of oncological surgery represents a moment of immunological vulnerability characterized by a predominant Th2 response (immune suppression). The magnitude of the Th1/Th2 im-

balance is most likely associated with the degree of surgical stress, the use of volatile anaesthetics, opioids and the administration of blood transfusions. Only retrospective studies have been conducted to assess the impact of regional anaesthesia on cancer recurrence. The results of those studies are controversial and given the lack of randomized control trials, we cannot conclude that a particular anaesthesia technique is associated with higher or lower rates of cancer recurrence. In contrast, strong evidence from a meta-analysis in colorectal patients indicates that blood transfusion are linked to poor oncological outcomes in this patients population.

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