Effects of Anesthetics and Analgesics on Natural Killer Cell Activity

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Surgical excision of cancerous tumors and the human stress response can lead to metastasis of tumor cells. Furthermore, the medications used during the perioperative period (eg, opioids and anesthetic agents) have been shown to inhibit or suppress natural killer (NK) cell activity, one of the body's main defenses against spread of cancer. There are currently no anesthetic regimens that have been shown to completely reverse surgical stress-induced suppression of NK cell activity. However, there may be anesthetic techniques that attenuate surgical suppression of NK cell activity. This article reviews the effects of various anesthetics and analgesics on NK cell activity and suggests techniques to attenuate the suppressive effects of these compounds.

Keywords: Analgesics, anesthetics, cancer, morphine, natural killer cells.

Cancer is the body's growth system gone awry. Nevertheless, the body's immune system can identify and combat cancer and its metastases. Natural killer (NK) cell activity has been identified as one method by which the body attacks tumor cells and thereby prevents metastases. However, surgery and anesthesia have been demonstrated to suppress NK cell activity, thereby placing patients with cancer at risk of metastasis.

NK Cell Function

As Figure 1 shows, NK cells are a vital part of our innate immunity. Cells of the innate system (shown at left in Figure 1), such as phagocytic cells and NK cells, recognize protein or tissue that is not mammalian in a general way. The response that the innate immune system generates against invaders is immediate but does not improve with repeated exposure to the same foreign protein. In contrast, cells of the adaptive immune system (shown at right in Figure 1), such as immunoglobulins, react with exquisite specificity to small portions of foreign proteins. Our body makes approximately 10^9 different antibodies to recognize and destroy any potential foreign protein. The response that the adaptive immune system generates is delayed so that a sufficient number of antibodies can be produced to mount an effective response. However, once produced, the cells are able to generate a stronger response upon repeated exposure to the foreign protein.

Natural killer cells are responsible for the destruction of not only tumor cells but also cells infected with certain

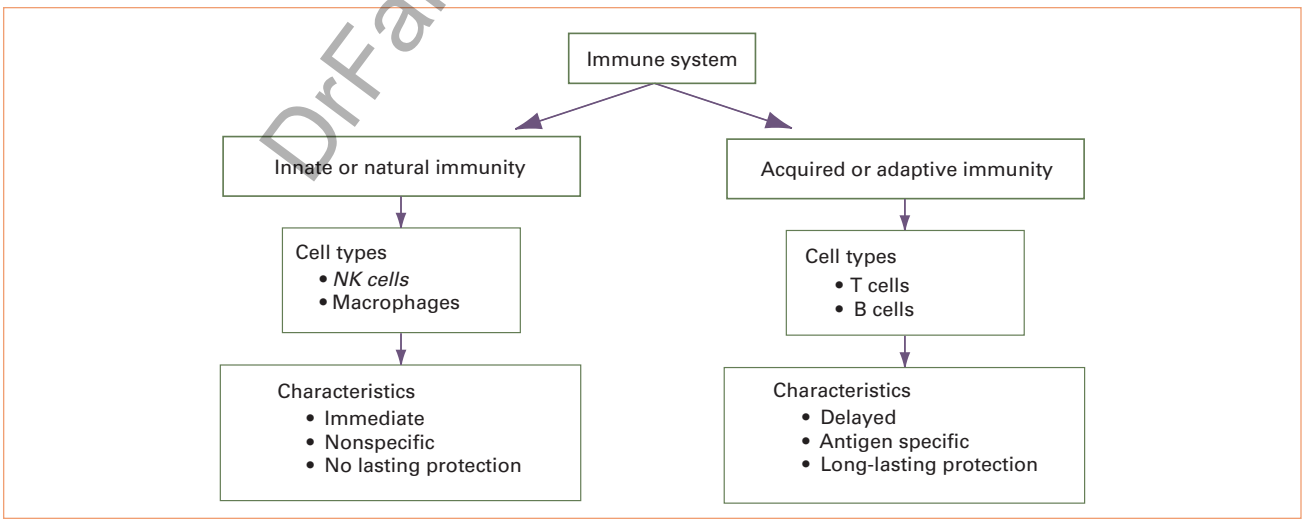

Figure 1. Immune Responses Consist of 2 Categories: Innate Immune Responses and Adaptive Immune Responses.

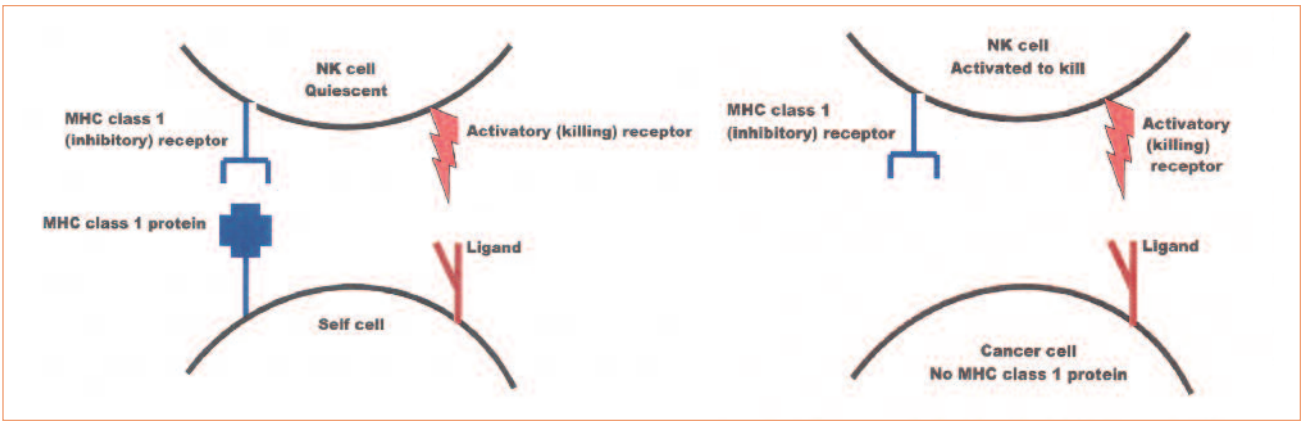

Figure 2. Drawings of the Interactions Between NK Cells and Potential Target Cells
NK indicates natural killer; MHC, major histocompatibility complex.

viruses. NK cells recognize "self" and "non-self" cells through a variety of inhibitory and activatory receptors and are able to kill "non-self" target cells without prior sensitization.[1-3] Current knowledge regarding the mechanisms by which NK cells recognize and kill their target is reflected by Karre[4] in the "missing self" model. Based on this model, the presence of "self" surface markers (major histocompatibility complex, or MHC, class I proteins) on potential target cells inhibit the NK cell attack. In the absence or down-regulation of the MHC class I protein, NK cells attack (Figure 2). The NK cells express inhibitory and activatory receptors. As shown in Figure 2, if an NK cell encounters another cell that expresses MHC class 1 receptors (self-receptors), the NK cell is inhibited from destroying the cell. If, however, an NK cell encounters a cell without the MHC class 1 receptor, such as would occur in cancer cells, the NK cell is bound to the target cell (Figure 2B). Binding initiates receptor activation, increasing intracellular calcium levels and resulting in the release of granules from the NK cell. The granules contain a pore-forming protein, so target cell death occurs by the creation of vacuoles in the target cell membrane.

Many cancer tumor cells express low levels of MHC class I proteins or none at all, thus making them targets for NK cells. The process of tumor lysis by NK cells consists of (1) binding of tumor for targeting, (2) programming of bound tumor for lysis by NK cells, and (3) tumor cell destruction with the separation of NK cells from tumor targets.

NK Cell Activity and Cancer Metastasis

Characterization of the role that NK cells play in inhibiting metastatic cancer began almost 3 decades ago. Barlozzari and colleagues[5] studied large granular lymphocytes, the morphologic parent group of the NK cell, and demonstrated the cytotoxic activity of large granular lymphocytes in the elimination of metastatic tumor cells that were circulating in the vasculature. Subsequently several rodent studies showed that host resistance to tumor metastasis depends on NK cell activity. In experimental metastasis models, retention of intravenously inoculated tumor cells is substantially greater, as is formation of tumor colonies in rodents with reduced NK cell activity, compared with those with normal NK cell activity.[6-8]

For example, a sophisticated study backcrossed severe combined immunodeficiency (SCID) mice, which lack functional T and B cells, with a strain of mice that express NK cells; the authors developed a strain that had no adaptive immune function (ie, T and B cells) but did have functional innate immunity via macrophages, mast cells, and NK cells.[7] There are 2 important points to be considered regarding this backcrossed strain: (1) manipulation of NK cells is more effective since the monoclonal antibody for the NK cell receptor is very specific and (2) the confounding activity of the adaptive immune system, present in all of the previous research, is eliminated. This strain of mouse was used to explore the role of NK cells in experimental tumor metastasis. In mice treated with the anti-NK cell receptor antibody (an antibody that rendered the NK cells inoperable), the intravenous injection of human leukemia cells produced 40 times the number of tumor cells lodged in the spleen compared with untreated mice. By 7 weeks, 40% of circulating leukocytes were human leukemia cells in the mice treated with the anti-NK cell receptor antibody. This was a powerful study in that contributions of the adaptive immune system were eliminated and numerous additional assays were employed to corroborate the results, such as measurement of NK cell activity in both treated and untreated mice. This study clearly demonstrated the specific role of NK cells in inhibiting cancer metastasis.

The function of NK cells as metastatic tumor eradicators in humans was established through various studies that investigated mortality related to NK cell activity after therapy for cancer. For example, Konjevic and Spuzic[9] found in a comparison of preoperative levels of NK cell activity that patients with a diagnosis of stages I to III

breast cancer had significantly lower NK cell activity than did healthy controls ($P < .001$). Furthermore, they found that individuals with stage IV cancer had lower NK cell activity than those with stages I, II, or III, suggesting that NK activity is inversely correlated to the stage of disease.

This same inverse correlation between NK cell activity and cancer stage was found in patients with prostate cancer.[10] The NK cell activity was correlated to the prostatic cancer markers, prostate specific antigen (PSA), a marker of tumor load, and tissue polypeptide specific (TPS) antigen, a marker of cancer activity that is elevated during metastasis. The NK cell activity was shown to be lower as the serum marker levels of cancer load and metastatic progression increased. Thus, by using quantifiable markers of cancer progression and metastasis, it was shown that NK cell activity decreases as cancer progresses. Taken together, these findings suggest that lower NK cell activity is associated with increased cancer metastasis.

Surgery-Induced Suppression of NK Cell Activity

Surgery is used for both palliative (debulking) and curative treatment of cancer. Surgical resection of solid tumors provides a major opportunity for cure in many patients; for colorectal cancers, resection is the only potential for cure.[11] However, surgery is also associated with the risk of metastasis.[12] Surgery has been shown to suppress NK cell activity in rats[13,14] and to increase experimental metastasis to the liver[15,16] and lungs[12,17,18] of rats intravenously injected with tumor cells. Moreover, human studies have demonstrated that surgery suppresses NK cell activity for as long as 7 days, and preoperative NK cell activity values may not return for up to 2 weeks.[11,19,20] The mechanism underlying the phenomenon of surgery-induced impairment of NK cell activity has not yet been clearly characterized.

One hypothesis suggests that surgery itself exerts a toxic effect on NK cells. For example, Pollack and Lotzova[14] demonstrated that NK activity was diminished both in total rate and quantity of attacks during the perioperative period. Other surgical mechanisms of suppression suggest a multifactorial impairment of perioperative NK cell cytotoxicity. Erythroblasts generated at the time of surgery may compete for tumor target binding sites and thus block NK cytolytic mechanisms. These mechanisms can act synergistically to make the patient vulnerable to metastasis.[13]

Taken together, these data support the following conclusions. First, an association between NK cell activity and metastasis has been shown in both animals and humans. Animal models have provided causal evidence that both experimental and spontaneous tumor metastasis depend on NK cell activity. Human studies support this relationship. Second, surgery-induced suppression of NK cell activity has been shown in both animals and humans. Hence, one may conclude that surgery-induced suppression of NK cell activity may increase the risk of metastatic cancer. The underlying mechanism of surgery-induced NK cell suppression, however, remains elusive.

Effects of Stress, Pain, and Anxiety on NK Cell Activity

Surgical manipulation of the tumor may not be the primary cause of perioperative suppression of NK cell activity. Pain and anxiety, which are common in the perioperative period and are associated with the diagnosis of cancer, also have an effect on NK cell activity. Acute stress evokes immediate immunologic responses in the body that affect NK cell activity. For example, acute stress induced in rats by a swim stress test promotes tumor-enhancing effects after 1 to 8 hours.[12] The physical response is believed to be neurohormonal such that acute emotional stress activates the sympathetic-adrenal-medullary axis and the hypothalamic-pituitary-adrenal axis.[21,22] Subsequent release of glucocorticoids and catecholamines from the adrenal cortex has been shown to induce suppression of NK cell cytotoxicity. Correspondingly, stress-induced suppression of NK cell activity has been shown to be reversed by a chemical sympathectomy or by β-receptor antagonists.[21,23]

Painful stress-induced suppression of NK cell activity has also been associated with a decreased resistance to metastasis. For example, the stress of intermittent foot shock has been shown to suppress NK cell activity[24,25] and to decrease survival after the injection of a mammary ascites tumor.[26] These findings suggest that pain can, through unexplored mechanisms, suppress NK cell activity.

Effects of Analgesics and Anesthetics on NK Cell Activity

Page and colleagues[27] suggested that the pain of undergoing and recovering from surgery stimulates surgery-induced decreases in NK cell activity and host resistance to metastasis. Moreover, their findings suggest that adequate treatment of pain can attenuate surgical suppression of NK cell activity. For example, morphine reduced the rates of metastases to a greater degree when dosed preoperatively than with postoperative dosing.[27] Furthermore, fentanyl and indomethacin, a nonsteroidal anti-inflammatory drug, were shown in rodents to have a positive effect on the NK cell activity in operative subjects but shown to be suppressive in the nonsurgical subject.[28]

These findings by Page et al are congruent with other rodent models that suggest moderate doses of opioids attenuate NK cell suppression[29] and with human models that suggest the same. For example, Yeager and colleagues[30] examined the opioid effect on NK cell activity using low- and high-dose morphine. Their data suggested

a continued suppression in NK cell activity in subjects treated with high-dose morphine after the 48-hour mark but not in the low-dose–treated subjects. A dose-dependent effect on NK cell activity by opioids was also observed when large-dose and small-dose fentanyl was compared in human subjects.[31] The data suggested a return to preoperative levels of NK cell activity in the small-dose fentanyl group by 48 hours, whereas the large-dose fentanyl group had continued suppression of NK activity past 48 hours.

Other anesthetics have been suggested to affect NK cell activity as well. Melamed and colleagues[32] examined the NK cell suppressive activity of ketamine, thiopental, halothane, and propofol and found that all agents except propofol suppressed NK cell activity under nonsurgical conditions. Interestingly, their results also suggested that NK cell suppression caused by ketamine could be attenuated by use of a β-receptor antagonist, congruent with findings by Irwin et al.[23] Likewise, Sacerdote and colleagues[33] examined opioid agonists and antagonists and found that morphine and, to a lesser extent, codeine suppressed NK cell activity.

Important to the anesthesia community, Sacerdote and coworkers continued investigation of interactions between analgesics and NK cell suppression. Their findings in mice under nonoperative conditions, rats under operative conditions, and—most important—humans under operative conditions suggested that tramadol, an analogue of codeine, was an effective analgesic that did not suppress NK cell activity.[33] In the clinical trial, patients undergoing abdominal surgery for removal of uterine carcinoma were anesthetized with thiopental, fentanyl, isoflurane, and nitrous oxide in oxygen. Immediately after the end of surgery, 1 group of patients was administered tramadol, and the other group was administered morphine. Although both drugs provided comparable postoperative pain management, tramadol significantly preserved activity of NK cells postoperatively compared with morphine ($P < .01$).

The finding that tramadol may preserve NK function when used with an inhalation agent is important because research clearly indicates that inhalation agents alone or in combination with most intravenous opioids suppress NK cell activity. The preponderance of evidence from in vitro, in vivo, animal, and human studies suggests that halothane,[34-36] isoflurane,[37-39] and sevoflurane[40,41] suppress NK cell activity. For example, NK cell function in animals is suppressed when halothane or isoflurane is administered to nonsurgical animals. Furthermore, NK cell suppression is not overcome by the administration of compounds that are known to enhance NK cell function.[37] Moreover, isoflurane-induced NK cell suppression unrelieved by immune stimulants was reported to occur in humans undergoing surgery.[38,42]

Earlier research suggested that epidural anesthesia may be less immunosuppressive compared with general anesthesia; however, more recent studies have not completely supported that hypothesis.[43-45] Findings of Procopio and colleagues[46] in an examination of lidocaine epidural anesthesia compared with isoflurane general anesthesia in human subjects not undergoing surgery showed no benefit for epidural anesthesia. Furthermore, lidocaine epidural anesthesia in patients with and without pain suggested that epidural anesthesia suppressed NK cell activity.

On the other hand, recently published research by Wada and colleagues[41] reported an attenuation of surgical suppression of NK cell activity using a combined anesthetic technique. Mice that were administered spinal anesthesia (bupivacaine and morphine) with general anesthesia were shown to have significantly less suppression of NK cell activity compared with mice administered only general anesthesia with or without the addition of systemic morphine.[41]

In contrast, administration of intrathecal morphine without local anesthetic has a dose-related effect on surgical-suppression of NK cell activity. Yokota et al[47] found a significant decrease in NK cell activity on postoperative day 1 in animals receiving 0.5 mg of intrathecal morphine. There was, however, no significant suppression in NK cell activity in control animals, animals receiving 10 mg of intravenous morphine, or animals receiving 0.1 mg of intrathecal morphine.[47] This research further illustrates the dose-dependent effects of morphine on NK cell activity without regard to route of administration.

Summary

In summary, findings from several lines of research support the following: (1) suppressed NK cell activity increases risks of metastatic cancer, (2) surgery suppresses NK cell activity through mechanisms not yet defined, but may be due in part to analgesic and anesthetic agents associated with surgery, and (3) pain and stress suppress NK cell activity. Therein lies the conundrum. Analgesics and anesthetics, which suppress NK cell activity, must be administered to patients undergoing surgery to inhibit surgical pain and activation of the stress response, both of which suppress NK cell activity as well.

The findings of Page et al,[27,28] Shavit and coworkers,[29] and Beilin and colleagues[31] suggest a partial answer to the dilemma. Whereas large doses of analgesics may contribute to postoperative NK cell suppression, adequate and sufficient perioperative pain management mitigates the immunosuppressive effects of undergoing and recovering from surgery. But how to provide adequate and sufficient perioperative pain management with the least negative impact on NK cell activity has not been clearly elucidated. Findings suggest that regional anesthesia may be more advantageous than general anesthesia, yet interpreting findings from research regarding interactions between anesthetics and NK cell activity is difficult given

that much of the research is in vitro, in animals, or in humans under nonsurgical conditions. Clearly, much more research is needed in this area, specifically clinical trials designed to address which anesthetics have the least negative immune and metastatic consequences in patients undergoing surgery. Surgical resection is one of the primary treatments of solid tumors. Continued research in this area may be critical for survival in individuals undergoing surgery for resection of malignant tumors.

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