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Immune Modulation by Volatile Anesthetics

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ABSTRACT

Volatile general anesthetics continue to be an important part of clinical anesthesia worldwide. The impact of volatile anesthetics on the immune system has been investigated at both mechanistic and clinical levels, but previous studies have returned conflicting findings due to varied protocols, experimental environments, and subject species. While many of these studies have focused on the immunosuppressive effects of volatile anesthetics, compelling evidence also exists for immunoactivation. Depending on the clinical conditions, immunosuppression and activation due to volatile anesthetics can be either detrimental or beneficial. This review provides a balanced perspective on the anesthetic modulation of innate and adaptive immune responses as well as indirect effectors of immunity. Potential mechanisms of immunomodulation by volatile anesthetics are also discussed. A clearer understanding of these issues will pave the way for clinical guidelines that better account for the impact of volatile anesthetics on the immune system, with the ultimate goal of improving perioperative management.
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IN recent decades, the field of immunology has progressed substantially, elucidating many of the cellular and molecular mechanisms underlying human immune responses.[1,2] During the same period, significant insights have been gained to better understand the action of general anesthetics.[3–6] General anesthesia can be administered using inhalational anesthetics, intravenous medications, or most frequently a combination of both. All of these forms of anesthesia have been found to modulate the immune system and exert effects on innate and adaptive immunity.[7–12] A comprehensive evaluation of the impact of anesthetic regimens on the immune system can help refine current perioperative management.

This review focuses on the effects of inhalational anesthetics, specifically volatile anesthetics, on the immune response. Volatile anesthetics play a significant role in clinical anesthesia throughout the world. Furthermore, the volatile nature of these compounds extends their influence to not only the immune system of the patients, but also that of the physicians, nurses, and other personnel in the perioperative setting.[13] Both *in vitro* and *in vivo* studies[9,14–17] have been conducted to answer various questions regarding how volatile anesthetics impact immunity. For example, what is the effect of anesthesia on postoperative infection? Is it the emotional and physical stress before and after the surgery or general anesthesia *per se* that predisposes patients to postoperative complications? Should the impact on immune system be part of the decision-making when choosing anesthesia regimens? Is there a benefit from immunosuppression in the ischemic setting? Do volatile anesthetics hasten the process of metastatic disease? Compared to *in vitro* and animal studies, there are fewer human studies due to the challenge in isolating a single variable in the clinical setting. Nevertheless, we sought to present a comprehensive review of *in vitro* studies and *in vivo* investigations with both small animals and humans. Figure 1 shows some of the direct immune modulations by volatile anesthetics. Direct modulation impacts innate and adaptive immunity, in which the majority of effector immune cells are natural killer (NK) cells, dendritic cells (DCs), neutrophils, macrophages, and lymphocytes. Table 1 summarizes the effects of some of the commonly used volatile anesthetics on these cells.[7,9,18–44] In addition to the direct effects, volatile anesthetics also impact the neuroendocrine response from the hypothalamic–pituitary–adrenal axis, thereby indirectly influencing the immune response through the secretions of
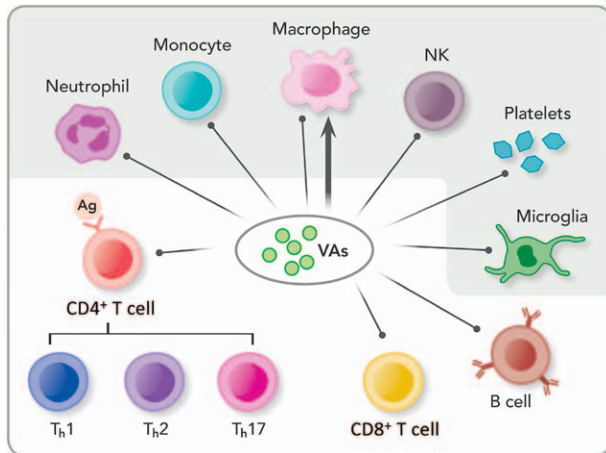
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Fig. 1. Direct immune modulations by volatile anesthetics (VAs). Depicted here are immune cells responsible for the innate (*shaded*) and adaptive (*unshaded*) immunity. VAs have been shown to suppress innate immunity by impairing or suppressing neutrophil adhesion, monocytes, macrophages and natural killer (NK) cells and affecting resident cells in tissues, such as platelets and microglial cells. VAs also suppress adaptive immunity by decreasing lymphocyte proliferation, such as cluster of differentiation (CD) 4 positive (CD4+) and 8 positive (CD8+) T cells as well as B cells. Note that VAs can have both inhibition (shown as a *line with a dot*) and potentiation (shown as a *line with an arrowhead*) effects on macrophages, depending on the site of infection or inflammation. Ag = antigen; T_h1 = T helper cell type 1; T_h2 = T helper cell type 2; T_h17 = T helper cell type 17.

immunomodulator hormones such as catecholamines and glucocorticoids.[45] Both direct and indirect modulations of immunity by volatile anesthetics are covered in this review.

Innate Immunity

The innate immune response is mediated by innate immune cells that are activated when protective barriers, such as the skin or other mucosa, have been compromised due to infection or injury. Cytokines, chemokines, and inflammatory mediators are secreted by both resident tissue cells and the recruited innate immune cells. They bring forth initial responders: neutrophils, monocytes, and NK cells, as well as the complement pathways that enhance or amplify the immune responses. Surgery, sepsis, ischemia, and even the stress of being in the hospital or undergoing surgery can trigger reactions of the innate immune system. Volatile anesthetics have been found to exert a number of effects on innate immunity,[9,18,46–48] mainly through neutrophils, DCs, NK cells, and resident tissue macrophages.

Neutrophils

Neutrophils are the most abundant granulocytes, and their numerous functions play a significant role in an inflammatory reaction.[49] They are generally the first and most lethal effector cells recruited to an inflammation site. Phagocytosis and oxidative burst, which leads to rapid production of

Table 1. Immunosuppressive and Immunoactivating Effects of Volatile Anesthetics*

Immune Cell Type	Effect	Volatile Anesthetic
Neutrophil	Decreased cell number, adhesion	Sevoflurane[18–22] Isoflurane[19–21,23] Halothane[18–21]
	Increase cell number	Desflurane[24]
PBMC/ macrophage	Decreased cytokine release (interleukin-1B, TNF-α, interleukin-6, interleukin-8, interleukin-10)	Sevoflurane[25,26] Isoflurane[25,27]
	Decreased phagocytosis, ROS, chemotaxis	Halothane[18]
	Decreased cell number	Sevoflurane[28] Desflurane[28]
	Reversed nitrous oxide immune suppression	Sevoflurane[7]
	Enhanced nitrite production	Isoflurane[27]
	Increased cell number, respiratory burst	Halothane[29]
NK cell	Decreased cytotoxicity	Sevoflurane[9,30–32] Isoflurane[9,30–33] Halothane[9,30–32]
	Decreased response to interferon-γ	Isoflurane[25,30,34–36] Halothane[25,30,34–36]
	Decreased cytokine release	Sevoflurane[34]
	Biphasic (increase then decrease cell number)	Desflurane[24]
T lymphocyte	Decreased cell number, proliferation, change in T_h1/T_h2 ratio	Isoflurane[37,38]
	Decreased T_h1	Sevoflurane[31]
	Increased T_h1	Desflurane[24] Sevoflurane[39]
	Promoted cell-mediated immunity	Sevoflurane[39]
B lymphocyte	Decreased cell number, increased B-cell damage	Sevoflurane[40,41] Isoflurane[40] Desflurane[40]
Other	Increased cortisol	Isoflurane[37]
	Decreased platelet–immune cell adhesion	Desflurane[42]
	Decreased microglial cytokine release	Isoflurane[43]
	Decreased monocyte chemoattractant	Isoflurane[44] Halothane[44]
	Increased platelet–immune cell adhesion	Sevoflurane[42]

*Unshaded and shaded entries are considered immunosuppressive and immunoactivating, respectively.

NK = natural killer; PBMC = peripheral blood mononuclear cell; ROS = reactive oxygen species; T_h1 = T helper cell type 1; T_h2 = T helper cell type 2; TNF-α = tumor necrosis factor-α.

oxygen radicals, destroy foreign entities and damage native tissues. With this in mind, the impact of volatile anesthetics on this aspect of innate immunity can be viewed both positively and negatively.

The impaired function of neutrophils after exposure to volatile anesthetics was observed in several studies.[18,26,47]

Sevoflurane was found to decrease the number of reacting polymorphonuclear cells (PMNs).[18] Reactive oxygen species (ROS) production and chemotaxis were affected after exposure to sevoflurane, desflurane, halothane, and enflurane.[18] Since halothane and enflurane are no longer used clinically, we will deemphasize their discussions in this review. Isoflurane and sevoflurane at clinical concentrations decreased neutrophil adhesion to human endothelial cells by inhibiting activation of PMNs.[19] However, in the active state, PMNs are stimulated to roll and adhere to the endothelium of the vasculature within the inflamed tissue; thus, free neutrophils may not accurately reflect the active population.[50] In contrast, the suppression of neutrophil adhesion after exposure to volatile anesthetics may positively affect the deleterious effects of PMNs in the ischemic setting. Isoflurane and sevoflurane have been shown to impair the postischemic adhesion of PMNs in the intact coronary system of isolated reperfused guinea pig hearts, and their inhibitory effects may be beneficial to cardiac function during general anesthesia.[20,21]

The results from *in vivo* studies largely parallel those from *in vitro* investigations. Exposing mice to 1.4% isoflurane before or after stimulation with lipopolysaccharide for 30 min decreased PMN levels in the bronchial alveolar fluid.[23] Neutrophils were noted to concentrate perivascularly, but were inhibited from migrating directly to the affected site. The neutrophil-attracting C-X-C motif chemokine ligand 1 (CXCL1) and CXCL2/3, which belong to the early signaling molecules for PMN recruitment in immune response, were also found to decrease in the same study. Mice injected with a sublethal dose of influenza A showed fewer physical signs and symptoms of infection after exposure to halothane.[51] A delay in appearance of neutrophils in lung tissue was demonstrated. This protective effect from halogenated volatile anesthetics was shown in a recent study[52] to be the anesthetic-induced reduction in type I and type II interferon production. Similarly, in a rat model of liver transplantation, sevoflurane was found to attenuate neutrophil renal injury and decrease neutrophil infiltration, as well as decrease plasma tumor necrosis factor-α (TNF-α) and interleukin-6 levels.[53] In a murine model of zymosan-induced peritonitis, isoflurane diminished the amplitude of PMN infiltration and down-regulated a panel of proinflammatory cytokines.[54] In a human study, sevoflurane at twice the minimum alveolar concentration (MAC) induced leukocyte rolling, but decreased neutrophils in the peripheral blood samples.[22] Despite the aforementioned evidence of the suppressive effects of volatile anesthetics on PMNs, contradictory data exist due to the immune complexity and variation inherent in the clinical setting. A study comparing sevoflurane and propofol in combination with fentanyl noted an overall similar inflammatory response, including increased interleukin-8, decreased interleukin-17, and decreased cellular adhesion.[55] Additional research, particularly human studies, is necessary to determine the clinical impact of volatile anesthetic effects on neutrophil function.

Macrophages

Peripheral blood mononuclear cells (PBMCs) include both lymphocytes and monocytes, which become macrophages upon migration into a tissue. Macrophages are phagocytic scavengers of innate immunity, similar to neutrophils.[49] As resident cells in the tissues, however, macrophages are often the first responders to infection, sending recruitment signals to other effector cells.

In vitro studies revealed suppressive effects of volatile anesthetics on PBMCs and macrophages. Sevoflurane and isoflurane at concentrations of 1.5 to 2.5 MAC suppressed the release of interleukin-1β and TNF-α from human peripheral mononuclear cells stimulated by NK–sensitive tumor cells.[25] Despite its potent inhibitory effect on inflammatory cytokines, sevoflurane does not reduce the proliferation of human PBMC.[7] Interestingly, the same study suggested that sevoflurane might have a beneficial effect by alleviating the immunosuppressive effect of nitrous oxide, which inhibits the proliferation of PBMC.[7]

A number of *in vivo* studies also demonstrated that volatile anesthetics could be either detrimental or beneficial, depending on the setting of inflammation with or without an infection. In a ventilated pig model, sevoflurane and desflurane were shown to decrease macrophage levels in bronchial alveolar fluid, and the overall cellular infiltration was also reduced.[28] Isoflurane at 1.0 MAC after lipopolysaccharide exposure decreased macrophage release of TNF-α and interleukin-1β.[27] Sevoflurane decreased cytokine release, specifically interleukin-6, interleukin-8, and interleukin-10, in patients undergoing cardiac surgery.[26] Decreased pulmonary sequestration of white blood cells was noted as well. In contrast to suppressions caused by volatile anesthetics, a study involving isoflurane and sevoflurane administered at 1.5 MAC for more than 2 h showed significant increases in interleukin-1β, macrophage inflammatory protein-2 (MIP-2), interferon-γ, and TNF-α in rat alveolar macrophages under mechanical ventilation.[56] Postexposure of 1.0 MAC isoflurane 4 h after lipopolysaccharide-induced endotoxemia in rats attenuated the systemic release of TNF-α and interleukin-1β, but simultaneously enhanced the nitrite production in cultured alveolar macrophages.[27] Altogether, it appears that the complexity of *in vivo* studies has resulted in uncertainties regarding the relationship between macrophage function and volatile anesthetic exposure. Table 2 summarizes some of the reported effects of volatile anesthetics on several proinflammatory and antiinflammatory cytokines.[22,24,43,52,57–109] Future in-depth mechanistic studies are needed to reconcile many of the observed discrepancies.

Natural Killer Cells

NK cells, unlike neutrophils and monocytes, are a component of innate immunity originating from the lymphoid

Table 2. General Anesthetic Effects on Several Key Pro- and Antiinflammatory Cytokines*

Anesthetics	Proinflammatory Cytokines				Antiinflammatory Cytokines			
	Interleukin-1β	Interleukin-6	TNF-α	Interferon-γ	Interleukin-1α	Interleukin-4	Interleukin-10	TGF-β
Isoflurane	↑[57–63] ↓[43,63-68]	↓[61,64,65]	↑[59-61,63] ↓[62,64-67]	↑[62,63]	—	—	↑[63,69,70]	↑[71–73]
Sevoflurane	↓[74–79]	↑[80–82] ↓[22,76,79,83–86]	↑[81,82,87] ↓[74–79,83,84,88–90]	↓[91]	—	No effect[92–94]	↑[74,77,87] ↓[79,94]	↑[95,96] ↓[88,97]
Desflurane	↓[89,98] No effect[63]	↑[99] No effect[82,98]	↓[89,98]	↑[100]	↑[101]	No effect[24]	↑[102] ↓[100]	—
Halothane	↑[103]	↑[103]	↑[103,104]	↑[105] ↓[52,106]	—	↑[107,108]	No effect[109] ↓[106]	↑[73]

*Up-arrows indicate activation or potentiation, and down-arrows indicate suppression or inhibition.
TGF = transforming growth factor; TNF = tumor necrosis factor.

lineage of white blood cells.[49] They are large granular lymphocytes that play a critical role in the defense against viral infection as well as oncologic disease. Because surgery and general anesthesia are often necessary in the treatment of cancer, extensive research has been conducted to determine the effect of volatile anesthetics on the NK cell population.

In vitro studies show that isoflurane and sevoflurane suppress NK cell cytotoxicity and cytokine-associated NK cell activation.[9,30–32] Isoflurane decreased the NK cells' response to interferon; sevoflurane decreased cytokine release, specifically TNF-α.[25,30,34] It was unclear whether NK cell functions could be fully restored postoperatively with supplemental interferon.[32,110] A previous human study indicated that NK cell activity decreased for several days postoperatively.[47] A more recent *in vivo* study on dogs also showed a significant decrease in NK cytotoxic activity, measured by the percentage of NK cell–induced apoptosis and narcosis in canine thyroid adenocarcinoma cell line 24 h after isoflurane anesthesia compared to the baseline values and the control group without anesthesia.[33] The decreased responses to interferon after exposure to isoflurane were also supported by other *in vivo* studies.[30,31,34–36] A decrease in NK cell number and a shift in cell-mediated immunity away from NK cell promotion were reported.[31,34] A recent meta-analysis of NK cell function and anesthetic exposure in 189 patients noted significant data heterogeneity without a conclusive association between anesthetic modulation and NK cell functions and called for further clinical investigations.[111]

Other Resident Tissue Cells

Resident cells in tissues, such as alveolar macrophages, platelets, and glial cells, can also be affected by volatile anesthetics, thereby affecting the immune response. Alveolar cells are in direct contact with volatile anesthetics. In rat alveolar type II cells in primary culture, isoflurane reduced cell secretions of interleukin-6, MIP-2, and monocyte chemoattractant protein-1, but did not change total protein secretion.[44] Although levels of interleukin-6 and MIP-2 were largely restored to baseline in 4 to 24 h after anesthetic exposure, monocyte chemoattractant protein-1 remained suppressed at 24 h.[44]

Platelets also play a significant role in the immune response, as they are critical for cellular adhesion. After blood was incubated with 1 or 2 MAC sevoflurane for more than an hour, the binding of platelets to lymphocytes, neutrophils, and monocytes was enhanced, and the expression of P-selectin on platelets increased.[42] However, the same treatment with desflurane resulted in a reduction in lymphocyte–platelet, neutrophil–platelet, and monocyte–platelet conjugates.[42] Similar phenomena were also observed in a previous study.[112] Another independent study suggested that neither desflurane nor sevoflurane caused significant changes in adenosine diphosphate-stimulated platelets even though sevoflurane increased the expression of P-selectin in unstimulated platelets.[113]

Microglia, which are resident neural immune cells, were recognized recently to contribute to neuroinflammation and postoperative delirium and cognitive decline. The immune-activated microglia not only changed cell number, size, and shape but also released the proinflammatory cytokines such as TNF-α, interleukin-1β, interleukin-6, and interferon-γ. *In vivo* experiments in young mice with repeated exposures to clinical concentrations of sevoflurane showed activation of microglia and accumulation of interleukin-6 and TNF-α, with associated cognitive impairment.[82] The same study also found that these detrimental changes were absent in adult mice, suggesting selective vulnerability in a particular age group. Repeated exposures to desflurane did not lead to microglia activation and interleukin-6 and TNF-α accumulation in either young or old mice. In cultured H4 human neuroglioma cells, isoflurane was found to induce caspase-3 activation, cause mitochondrial dysfunction, promote ROS accumulation, induce apoptosis, and reduce cell viability.[114–116] Strategies to target these isoflurane-induced events have been demonstrated.[115,116]

In other studies, beneficial effects to reduce neuroinflammation are noted from preconditioning with volatile anesthetics. Isoflurane suppressed the proinflammatory cytokine interleukin-1β in the mouse brain after intraperitoneal injection of lipopolysaccharide.[43] In adult mice, exposure to isoflurane was found not to produce neuroapoptosis but

reduce astroglial processes.[117] A more recent study[64] showed that isoflurane preconditioning inhibited the up-regulation of toll-like receptor 4, which is known to regulate microglia activation and microglia production of proinflammatory factors.

Overall, because of the complexity of various tissue responses to volatile anesthetics, the anesthetic effects on innate immunity remain an active area of investigation.

Adaptive Immunity

Adaptive immune responses are distinct from innate immunity because they are generated by clonal selection of lymphocytes.[118] There are two broad classes of adaptive immunity: humoral immune responses, which are mediated by macromolecules (such as antibodies and antimicrobial peptides) made by B lymphocytes, and cell-mediated immune responses, which are carried out mainly by T lymphocytes. Given the variety of lymphocytes and the multiple mechanisms involved in their recognition and response to antigens, investigations into the impact of volatile anesthetics on the adaptive immune system have been challenging. In general, volatile anesthetics induced a decrease in proliferation of lymphocytes or an increase in lymphocyte apoptosis.[9,119–121]

T Lymphocytes

Cell-mediated immunity within the adaptive response includes T lymphocytes (T cells), distinguished from other lymphocytes by the T-cell receptor, which can be modified and tailored for specific antigens.[49] T-cell precursors originate in the bone marrow and then travel in an immature state to the thymus to fully mature. From that point, they circulate in the blood and throughout the secondary lymphoid tissues, such as lymph nodes, in search of antigens sequestered there by antigen-presenting cells that have traveled from infected sites. Upon activation, T cells proliferate and differentiate. T helper (T_h) cells remain in the lymph nodes. There are three subsets of T_h cells: T_h1 cells that magnify inflammation *via* soluble protein secretion and macrophage stimulation; T_h2 cells that stimulate B lymphocytes to mature and produce antibodies; and the more recently discovered T_h17 cells that produce interleukin-17, interleukin-17F, and interleukin-22 and secrete interleukin-21 to communicate with the cells in the immune system.[122,123]

Different anesthetics have been found to produce varied effects on T_h cells[37,100] even though exposure to volatile anesthetics has generally resulted in a decrease in the number and proliferation of T cells.[9,47,124] It is often difficult to discern whether the decrease in the number and proliferation of T cells is related to a decrease in interferon-γ, an increase in cortisol, impaired antigen presentation, surgical insult, or a combination of all these factors. Patients exposed to isoflurane or propofol had drastically different T-cell responses.[37] Those exposed to isoflurane showed no change in their T_h1/T_h2 ratio, but did show an increase in cortisol, a known promoter

of T_h2 cells.[37] A recent clinical trial on 40 breast cancer surgeries[24] showed that desflurane can preserve T_h1/T_h2 ratio as well as the ratio of their cytokine products interleukin-2/interleukin-4. A separate study, however, reported a decrease in the T_h1/T_h2 ratio in patients who underwent isoflurane anesthesia.[38] Another study compared patients who received spinal anesthesia and desflurane general anesthesia[100] and showed that desflurane, but not bupivacaine, increased the T_h1/T_h2 ratio, mainly due to an increase in T_h1 responses in patients.[100] Exposure to sevoflurane alone was associated with a decrease in T_h1 cells and in the T_h1/T_h2 ratio postoperatively.[31] However, adding a spinal block to sevoflurane general anesthesia in surgery was noted to preserve the T_h1/T_h2 balance and thereby reduce the promotion of tumor metastasis in a mouse tumor model.[31] In hepatocellular carcinoma patients, neuraxial anesthesia, specifically epidural, combined with general anesthesia, was found to be superior to general anesthesia alone in promoting antitumor T_h polarization, including shifting the T_h1/T_h2 balance toward T_h1 and decreasing T_h17.[39] Although further investigation is certainly needed to clarify the inconsistent effects of volatile anesthetics on the T-cell–mediated immune responses, accumulating evidence seems to suggest that a proper selection of suitable anesthetic methods can mediate the balances of T_h subsets or even benefit the balance of antitumor responses.

B Lymphocytes and Complement System

Similar to T cells, B lymphocytes (B cells) can modify their cell surface receptors or immunoglobulins to recognize specific pathogens.[49] Data regarding the effects of volatile anesthetics on B cells, however, are relatively scarce. A previous study implied that surgical trauma or associated perioperative conditions, not the specific anesthetic agent employed, was the dominant factor responsible for most postoperative specific humoral immunity impairment.[47] A more recent study, however, seemed to suggest that isoflurane, sevoflurane, and desflurane could induce B-cell damage due to calcium release from the endoplasmic reticulum.[40] A study on mice also found that sevoflurane significantly decreased the level of splenic B cells.[41]

Complement-mediated immunity plays a role in both innate and adaptive immunity. It can act as an extension of the immunity provided by the B cells and the antibodies that they produce. To date, there are few reports concerning the effects of volatile anesthetics on the complement system. The combination of anesthesia and surgery was recognized as being associated with a decrease in complement levels, which may represent complement pathway activation.[47] Patients exposed to halogenated volatile anesthetics developed specific IgG1 autoantibodies that were likely cleared by classical activation of the complement system, while anesthetic-induced hepatitis patients developed specific IgG4 autoantibodies that escaped clearance because of their small size or by direct inhibition of complement activation.[125]

Indirect Effectors of Immunity

Volatile anesthetics can indirectly affect immunity through their impact on stress hormone levels as well as other effectors of immunity. Stress is inherent in the perioperative setting and a known modulator of the immune system. The major stress hormones include endogenous glucocorticoid (*e.g.*, cortisol in humans and corticosterone in nonhuman animals) and catecholamines (*e.g.*, epinephrine and norepinephrine), which can be released to result in systemic immune activations. Surgery-induced inflammatory response and alteration in cell-mediated immunity were found to be more pronounced after a balanced volatile anesthesia when compared to total intravenous anesthesia.[120] The effects were attributed to the enhanced stress response in patients undergoing anesthesia with a volatile agent.[120] Volatile anesthetics also often cause hypotension and transient hypoxia,[126,127] which promote tissue inflammation and increase cellular adhesion. These can, in turn, depress the T_h1 phenotype or promote cell-mediated immunity.[46] Glycemic control in the perioperative environment is another topic of significant debate, and volatile anesthetics can exert direct effects on immunity by manipulating glucose control. Blood glucose levels were found to be higher in patients anesthetized with a combination of sevoflurane and fentanyl *versus* those anesthetized with propofol and fentanyl.[55] Isoflurane was also noted to inhibit normal insulin production and produce a hyperglycemic response.[128–130] The observed hyperglycemic response in isoflurane anesthesia was thought to be a consequence of both impaired glucose clearance and increased glucose production.[129]

Potential Mechanisms of Immunomodulation by Volatile Anesthetics

Although specific targets of volatile anesthetics in the immune system have not been well defined, molecular and cellular events involved in immune modulation by volatile anesthetics have been identified, including a reduction in the number of immune cells due to cell death and the suppression of immune activities (fig. 2). In reality, with the heterogeneity in immune responses, immunomodulation is likely more complicated than what is shown in figure 2. For instance, cross talks may occur among different pathways, such as interactions between ROS and inducible nitric oxide synthase (iNOS). Understanding individual pathways and their relationships will facilitate mechanistic understanding of immune modulation by volatile anesthetics.

Lymphocytes are more prone to apoptosis than other immune cells.[131] Apoptosis is initiated by the mitochondria-triggered pathway (intrinsic pathway) or the
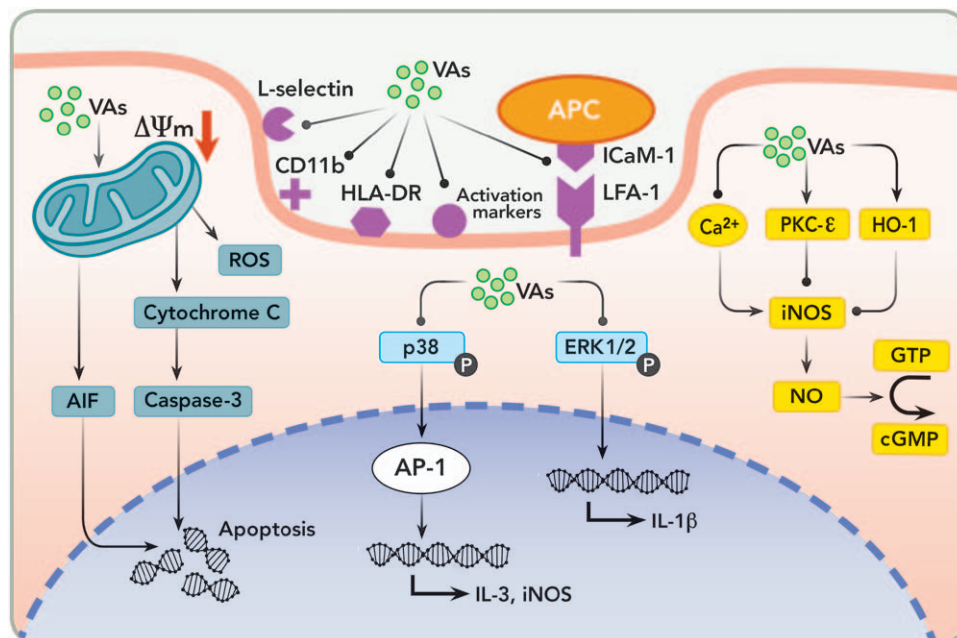

Fig. 2. Potential mechanisms involved in the immunomodulation by volatile anesthetics (VAs). Depicted here are schematic representations of major immunomodulation pathways affected by VAs. The *thick solid line* shows the cytoplasmic membrane and the *dashed line* marks the nuclear membrane. The *pink shaded areas* are cytoplasmic and extracellular space, and the *light purple shaded area* is the cell nucleus. *Lines with arrowheads and dots* at the end represent "activation" and "inhibition," respectively. $\Delta\Psi$m = mitochondrial membrane potential; AIF = apoptosis-inducing factor; AP-1 = activator protein 1; APC = antigen-presenting cell; cGMP = cyclic 3′,5′-guanosine monophosphate; DR = antigen D related; ERK = extracellular signal–regulated kinases; GTP = guanosine triphosphate; HLA = human leukocyte antigen; HO-1 = heme oxygenase 1; ICAM-1 = intercellular adhesion molecule; IL-1 = interleukin-1; IL-3 = interleukin-3; iNOS = inducible nitric oxide synthase; LFA-1 = lymphocyte function-associated antigen 1; NO = nitric oxide; PKC = protein kinase C; ROS = reactive oxygen species.

death-receptor–triggered pathway (extrinsic pathway).[132,133] Sevoflurane and isoflurane were found to decrease mitochondrial membrane potential ($\Delta\Psi$m) in a dose-dependent manner, subsequently triggering the release of cytochrome C from the mitochondrial intermembrane space into the cytosol and eventually inducing apoptosis *via* activation of caspase-3.[14,121,134] The irreversible pan-caspase inhibitor Z-VAD-fmk was shown to block sevoflurane-induced apoptosis.[14] Another distinct mitochondria-mediated molecule, apoptosis-inducing factor (AIF), also initiates apoptosis.[132,133] AIF was originally identified as a mitochondrial flavoprotein that was released into the cytoplasm and subsequently entered the nucleus to cause cell death.[132,133] A recent human study[135] showed that sevoflurane increased AIF in cardiac surgery patients, who also exhibited decreased lymphocyte counts. ROS is another major signaling molecule in the mitochondrial pathway for apoptosis.[70] Sevoflurane was shown to increase the production of intracellular ROS and promote lymphocyte apoptosis.[134] Interestingly, the same study also suggested that propofol might attenuate the sevoflurane-induced mitochondria-related apoptosis.[134] Compared to the mitochondria-triggered pathway, the death receptor–signaling pathway played little role in sevoflurane-induced lymphocyte apoptosis.[14] Thus, it is reasonable to believe that mitochondria are central mediators of volatile anesthetic–associated apoptosis. In addition to apoptosis, cell necrosis could also contribute to the isoflurane-induced decrease in immune cell count.[14]

Adhesion molecules are important for immune cell recruitment and accumulation at inflammatory sites. The human leukocyte antigen heterodimers are cell surface antigen for the T-cell receptor. Volatile anesthetics may interact directly with these molecules to modify their functions or reduce their expression. Immune cell trafficking and penetration depend predominantly on integrin lymphocyte function–associated antigen-1 (LFA-1).[136] Isoflurane and sevoflurane bind to LFA-1 and allosterically block the coupling of LFA-1 to its major interaction partner intercellular adhesion molecule-1 found on antigen-presenting cells. As a result, immune cell adhesion is inhibited.[16,17] It was found recently[137] that isoflurane, but not sevoflurane, had the same inhibitory effect on macrophage-1 antigen (MAC-1), a LFA-1 homologous protein. Structural biology approaches, combined with computational docking and mutations of key residues at the anesthetic binding site in LFA-1 and MAC-1, have shed new lights on how volatile anesthetic binding to a functionally important protein domain (the so-called I domain in LFA-1 and the homologous MAC-1) can allosterically change the binding pocket at a remote location on these immune signaling proteins to change their interaction with intercellular adhesion molecule-1, thereby inhibiting the downstream events of leukocyte recruitment and migration.[137,138] Cluster of differentiation (CD) 11b (CD11b) is another pivotal integrin on the surface of leukocytes. Isoflurane and sevoflurane at clinical concentrations abolished the upward regulation of CD11b on neutrophils and resulted in reduced neutrophil adhesion.[19,21] L-selectin, a cell adhesion molecule belonging to the selectin family, can be found in most leukocytes. Sevoflurane decreased L-selectin expression by 25%, indicating an increased threshold for cellular activation.[139]

Volatile anesthetics mostly suppress, but in some cases up-regulate, iNOS expression and nitric oxide production.[48,140] The suppressive effect is followed by the alteration of the nitric oxide-cyclic 3′,5′-guanosine monophosphate system, which is a major signaling transduction pathway implicated in a wide range of physiologic functions.[140,141] Evidence showed that volatile anesthetics interacted with several upstream mediators of iNOS, including calcium, protein kinase C, and heme oxygenase-1 (HO-1). Isoflurane and desflurane at clinically relevant concentrations mediated the inhibitory effect on iNOS expression by inhibiting mobilization of cytosolic-free calcium, which occurred upon macrophage activation.[48] Treatment or pretreatment with 2% isoflurane induced HO-1 protein expression and caused an induction of HO activity, which correlated with a decrease in iNOS expression and nitric oxide production in lipopolysaccharide-stimulated macrophages.[142] Blockade of HO activity reversed these effects.[142] Pretreatment with 2% isoflurane inhibited overexpression of iNOS and accumulation of nitrite induced by lipopolysaccharide and interferon-γ in macrophages.[143] The isoflurane preconditioning effect may be mediated by isoform protein kinase C-ε.[143] It was noted that lipopolysaccharide stimulation in combination with interferon-γ resulted in increased nitrite release after exposure to isoflurane,[48] indicating that supplementary interferon-γ is able to overcome any inhibition of normal macrophage function. The notion was further reinforced by the study showing the reversal of volatile anesthetic–induced impairment to macrophage chemotaxis and H_2O_2 production upon addition of interferon-γ.[47]

Mitogen-activated protein kinases (MAPK), including extracellular signal-regulated kinase (ERK), c-Jun *N*-terminal protein kinase, and p38 MAPK, have been implicated in proinflammatory cytokine release.[144] In isolated T cells, sevoflurane inhibited activation of the transcription factor activator protein-1 (AP-1), which was associated with the inhibition of p38 activity and resulted in a decreased interleukin-3 expression.[15] Activation of p38 is known to regulate several inflammation-related genes, including TNF-α, interleukin-β, and interleukin-6. Isoflurane, but not halothane, can activate p38 MAPK in a concentration-dependent manner.[145] Most interestingly, both isoflurane and halothane can greatly enhance the proinflammatory cytokine-induced p38 activations but have little effects on oxidative stress–induced p38 activations,[145] suggesting that the anesthetic action might be upstream of phosphorylation of p38 MAPK. Similarly, phosphorylation of ERK can activate the transcription factor cyclic adenosine monophosphate response element–binding protein, which in turn modulates

many cyclic adenosine monophosphate response element–binding protein–targeted genes. In glial cells, particularly microglia, isoflurane suppressed lipopolysaccharide-induced phosphorylation of ERK 1/2 and the high expression of interleukin-1β mRNA and protein but did not affect nuclear factor-κB or activator protein-1 activation.[43] More molecular biology investigations aimed at dissecting anesthetic effects on each of these pathways will help us better understand the molecular mechanisms of immunomodulation by volatile anesthetics.

Additional Considerations

Oncologic Considerations

Surgical intervention remains a primary treatment for cancer. Anesthetics used during the perioperative period may influence the immune system, directly affect cancer cells, and ultimately modify oncologic outcomes.[146,147] Investigations on whether anesthetics affect the outcome and prognosis of cancer have been carried out on various types of cancer, including ovarian, colon, breast, prostate, and rectal cancer. Several retrospective studies suggested that, in comparison to general anesthesia, regional anesthesia was associated with better outcomes.[148–152] In one study, patients who had radical prostatectomy during general anesthesia using a combination of sevoflurane and nitrous oxide showed more than 20% higher mortality rate than those who received epidural anesthesia.[148] A similar study also showed a decrease in time to tumor recurrence after primary cancer surgery or even to death when using an anesthetic regimen of sevoflurane alone compared to that of intraoperative neuraxial anesthesia combined with postoperative analgesia.[153] However, conflicting data exist. The beneficial effect of regional anesthesia on cancer recurrence was not observed in all types of cancer.[152,154,155] Some studies found no association between volatile anesthetics and death or length of cancer-free survival time.[156,157] Thus, more prospective randomized controlled trials, with careful designs of various anesthetic regimens, are warranted. In addition, in order to optimize anesthesia management strategies for oncologic surgical patients, more mechanistic studies at the cellular level are also needed.[7,158–161]

Positive Immune Modulation by Volatile Anesthetics

Despite the suppressive effects of volatile anesthetics on the function of neutrophils, macrophages, DCs, T cells, B cells, and NK cells, as reviewed above under the subheadings "Innate Immunity" and "Adaptive Immunity," is it possible for volatile anesthetics to enhance the immune system or possibly generate therapeutic benefits? A recent review by Fukazawa and Lee[162] presented compelling evidence of protective effects of volatile anesthetics against ischemic acute kidney injury in both preclinical and clinical studies. The cellular mechanisms of volatile anesthetic–induced kidney protection lie in the anesthetic activation of multiple pathways synthesizing antiinflammatory and cytoprotective signaling molecules, such as releasing transforming growth factor β1, activating CD73 and inducing interleukin-11, generating adenosine, and producing sphingosine kinase and sphingosine-1-phosphate.[71,96,163–165] Antiischemic and antiinflammatory effects of volatile anesthetics were also shown to affect other organs such as the heart, liver, and brain through either pretreatment before prolonged ischemia or after completion of an ischemic insult.[166–169] The protective mechanisms on these organs, however, may differ from those observed in renal protection.[170] Nevertheless, systematic investigations of protective effects of volatile anesthetics against acute kidney injury have led to an important discovery that volatile anesthetics can positively modulate immunity and provide off-label therapeutic effects if dose and exposure time of volatile anesthetics are optimized.[162]

Closing Remarks

The majority of studies reported thus far show that volatile anesthetics have immunosuppressive effects. Whether a short period of immunosuppression has a prolonged effect on patient outcomes merits further investigation. Well-controlled randomized clinical trials are highly desirable, although isolating effects of volatile anesthetics from other factors in a perioperative setting remains challenging. Future studies should take into consideration the surgical procedures involved, the anesthetics and other medications used, and the time dependence in immune modulation and resolution. Because immunosuppression is in general detrimental for cancer patients, but potentially beneficial for septic patients, the choice of anesthesia regimens should be carefully evaluated in the overall planning for the perioperative care.

In vitro– and *in vivo*–level mechanistic studies focusing on how volatile anesthetics modulate various immune responses should continue. These studies not only can provide valuable clues to initiate more complex clinical trials, but also can identify useful biomarkers to detect the detrimental effects of volatile anesthetics.

Desirable off-label effects of volatile anesthetics have been demonstrated in a few areas, but on a large scale, they are underexplored.[162] Whether and how volatile anesthetics positively modulate immune responses and subsequently generate therapeutic benefits to patients warrants further investigations.

Competing Interests

The authors declare no competing interests.

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