Prevention of Anesthesia-induced Immunosuppression: A Novel Strategy Involving Interferons

Postsurgical suppression of immune defense mechanisms is well recognized clinically. As the immune system was described in ever greater detail at the cellular level beginning in the 1960s, the effect of surgery on the integrity of these systems was examined in parallel. It is clear that surgery compromises a wide range of cell-mediated immune functions and, in particular, cell-mediated cytotoxicity reactions. Surgical trauma in and of itself certainly could be expected to play a role in immune dysfunction, given the large number of chemical signals cavorting about the body after damage to tissues. Inflammation and healing reactions that set in almost immediately in response to this trauma generate another set of cytokines that profoundly affect immune function. A third source of potential compromise for the immune system is the administration of anesthetics that accompany surgical procedures.

A depressive effect of at least some anesthetics on cell-mediated immune activity has been known for at least 20 yr. Anesthetic inhibition of T cell functions was the first to be described, followed very shortly by a description of the effects of anesthetics on natural killer (NK) cells. Surprisingly, it has proved difficult to take advantage of this knowledge in any clinically useful way. But studies like the one reported by Markovic et al., in this issue of ANESTHESIOLOGY may finally point to some effective and (importantly from the patient's viewpoint) safe ways to take advantage of our increased understanding of this relationship. This report is the most recent in a series of incisive and informative studies from this laboratory on the effects anesthetics exert directly on key effector cells in immune responsiveness.

In previous papers these authors focused on the effects of anesthetics on T cell functions. The paper appearing in this issue focuses on NK cells, extending a previous report on the same subject. NK cells remain, in many ways, almost as enigmatic today as when they were first described about 20 yr ago. But their importance in a number of immune parameters, including tumor control, is beyond doubt. Markovic et al. previously reported that interferons α and β (IFN-α/β), administered to mice 5 days before anesthesia and surgical debulking of a melanoma, greatly increased the number of mice achieving a complete response to surgical treatment of the tumor. That study suggested that NK cells were the target for the positive effect of the interferons.

The depressive effects of anesthetics on NK function are well known. In the present study, however, Markovic et al. show convincingly that anesthesia alone (halothane or isoflurane), in the absence of surgery, inhibits the increase in NK function induced by IFN-α/β. Importantly, they show that baseline NK cytotoxicity is not inhibited by these anesthetics; only IFN-inducible cytotoxicity. IFN-α/β is an important regulator of NK activity in tumor-bearing animals. The loss of sensitivity of NK cells to stimulation by IFN-α/β could be expected to compromise substantially the effectiveness of the NK compartment in postanesthetic immune responses. But the really intriguing finding of their study is that NK activity enhanced by IFN-α/β before exposure to anesthetics is not affected by anesthesia! Experiments carried out both in vivo and in vitro (where the NK cells are exposed directly to both IFN-α/β and anesthetic) confirm this important observation. As the authors modestly point out, these results suggest potential treatment strategies for certain subclasses of patients, for example those with immune deficiencies induced by disease, drugs, or age. Such an approach might be valuable in cancer patients who, like the mice in these authors' previous studies, are undergoing surgical debulking of various tumors. Clearly, additional studies are required, but the present report suggests that the untoward effects of anesthetics on at least NK cell function may be circumvented by prior boosting with IFN-α/β, with perhaps some sort of maintenance regimen through the postoperative period.

Like any good scientific study, the present paper raises a number of interesting questions for future investigation. Among the obvious ones are whether other cytokines have similar benefits for NK cell function or for other immune compartments. One also would like
to see the present study extended to other classes of anesthetics. A rather intriguing finding that bears further investigation is the basis for the prolonged inhibitory effect of anesthesia on NK function. Depression of IFN-inducible NK cytotoxicity is apparent for up to 11 days after exposure to anesthesia. Why this should be so is not immediately obvious; effects of anesthetics on membranes would be expected to reverse more quickly. Do unstimulated NK cells die as a result of exposure to anesthesia? Are they permanently energized? The kinetics of recovery of NK function certainly are more consistent with a need to regenerate a substantial portion of the NK compartment, but our present knowledge does not allow us to draw conclusions. Further investigations along this line would be of interest to both immunologists and anesthesiologists.

At any rate, we look forward to further progress by these authors and hope their new findings will stimulate others to pursue a similar course toward application of basic immunologic research to the practice of anesthesiology.

**References**

3. Markovic SN, Knight PR, Murasko DM: Inhibition of interferon stimulation of natural killer cell activity in mice anesthetized with halothane or isoflurane. *Anesthesiology* 78:700–706, 1993

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