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NATURAL KILLER CELLS A PRIMARY NATURAL DEFENCE AGAINST TUMOR SPREAD: CAN WE HELP WITH THE CHOICE OF ANESTHESIOLOGY TECHNIQUE?

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Abstract

Natural killer (NK) cells are a part of the innate immune system and were named after their ability to kill tumor cells without prior stimulation. They are presenting a frequency of around 5% in the blood, and even in such small numbers they are able to recognize and lyse virally infected cells and tumor cells. Morphologically, NK cells belong to the family of granular lymphocytes, while the phenotypic formula of these large cells is CD3−CD56+. CD16 is the most important surface receptor of the NK cells in the phase of the initiation of immune response and increased cell activity. Also, as a part of granular lymphocytes family, the NK cells contain multiple granular structures with either perforin or granzymes, that exhibit cytotoxic characteristics. The effect on different anesthetic techniques on the immune response to infection or the presence of tumor cells, is attracting increasing attention of the science. The results of some animal studies have identified some anesthetic techniques and/or anesthetic drugs that can reduce the incidence of metastasis during breast cancer surgery. Propofol and local anesthetics are the most emphasized in this manner. Regional anesthesia techniques are well known for their ability to attenuate the stress response to surgical trauma and to prevent negative effects on the immune function in the perioperative period. Fentanyl on the other hand has negative both short- and long-term effects on the activity of NK cells, while in some animal model's tramadol was shown to have protective effect with decreased incidence of metastasis during carcinoma surgery.

Key words: *Natural killer cells, tumor dissemination, anesthetic techniques.*

Introduction

The perioperative period is considered the critical period in cancer surgery because various factors can influence whether disseminated tumor cells will lead to metastases formation or they will be eliminated by the immune system. Several factors that can influence the perioperative immune function either in the direction of immunosuppression or preservation of innate immunity are of ongoing research interest. The association between the anesthetic technique and cancer recurrence was investigated in a population of patients with both breast and prostate cancer, but the results are still not conclusive enough. The results of some animal studies have identified some anesthetic techniques and/ or anesthetic drugs that reduce the incidence of

metastasis during breast cancer surgery. Propofol and local anesthetics are the most emphasized in this manner. As it is not yet clear what is the exact mechanism how these techniques are successfully preserving the innate immune function, the main hypothesis is that local anesthetic techniques have the effect of reducing the inflammatory reaction of the host to the stress caused by operative procedure (1).

When they were first discovered in 1960's it was believed that **the natural killer (NK) cells** are just an annoying artefact in the background activity of the cytotoxicity assays. These cells came into spotlight as the literature gained increasing knowledge of their role in the defensive actions against viral infections and malignant processes. Recently some clinical studies started to investigate the success of including the NK cells in immune based therapies in the treatment of malignancy. These lymphocytes are a part of the innate immune system and were named after their ability to kill tumor cells without prior stimulation, but they are also playing an important role in the immune defense against various threats. In terms of their vast potential to defend against different infections and against dissemination of tumor cells, NK cells are currently defined as founding members of innate lymphoid cell family (ILC) (2). They are presenting a frequency of around 5% in the blood, and even in such small numbers they are a part of the first line defense, able to recognize and lyse virally infected cells and tumor cells (3). Morphologically NK cells belong to the family of granular lymphocytes, while the phenotypic formula of these large cells is **CD3−CD56+**. NK cells can be subdivided into 2 groups: **CD16+CD56^{dim}** subgroup that consists of biggest number in circulation and the relatively immature **CD16−CD56^{bright}** subgroup. Mature NK cells have an array of known receptors that can trigger their effector functions when they are stimulated either alone or in combination (2). As with most of the immune active cells, the activity of NK cells and their potential is controlled by the interplay of signals provided by the receptors on their surface. The states of either full activation or the state of inhibition are both achieved by complex balance of signals on the cell surface. This is providing the necessary tight control in order to avoid self-induced damage by NK cells to normal cells (3). Using these immune receptors, NK cells can identify and attack enemy cells without previous memory, which is providing the first line defense against tumors and microbial agents. **CD16 is** the most important receptor of NK cells in the phase of the initiation of immune response and increased cell activity**. NKG2D** is another well-studied and important receptor, with numerous referrals in the literature. The presence of abnormal cells is momentarily triggering the NK cells effector functions, including cytotoxicity, cytokine production and proliferation. Contrary to other immune cells that require time for the activation and initiation of cytolysis, the response of NK cells is prompt and quick. This is offering new perspective in the area of development of new modalities of immune therapy (4). As part of granular lymphocytes family, the NK cells contain multiple granular structures with either perforin or granzymes, that exhibit cytotoxic characteristics. Upon the contact with the target cell, NK cells are creating synapse like contact with the stressed cell by which the specific granules are excreted, and the final kill is achieved. Additionally, NK cells are able to kill tumor cells by using molecules in the tumor necrosis factor (TNF) family, whose main role is the creation of cell connections that will result in lysis of the target cell. Recently, the secretory function of NK cells has come to the attention of the researchers. The secretion of cytokines or other chemokines is part of the activation process of the NK cells and has the role of controlling

the further immune actions. NK cells are the best known for the secretion of IFN-γ and TNF, as well as for production of IL10 and other growth factors and chemokines. The main purpose of this secretory activity of NK cells is the deepening and enhancing of the immune response by proliferation of other immune cells and their aggravation on the site of inflammation (5). Tumor cells, on the other hand, have developed various adaptive mechanisms to disturb the actions of the NK cells and to escape elimination. Moreover, tumor cells have the ability to locally secrete various factors that are altering NK cells and can decrease their cytotoxic potential.

Originally when they were first discovered, it was thought that NK cells were solely effector cells without memory. Current knowledge gained from clinical studies, on the other hand, implies that NK cells during the process of maturation can undergo some form of training in order to establish certain memory and to further increase their cytotoxicity (4). The data from in-vitro studies are showing that after the initial reaction to infection or tumor, NK cells are able to produce prolonged immune function simultaneously with the adaptive part of the immune system. The improved functional capacity of mature NK cells is the "consequence" of their initial process of initiation and activation. The term "immune training" in the case of NK cells refers to the acquisition of memory like properties after being sensitized with cytokines. Additionally, NK cells are enhancing their production of interferon (IFN-γ) upon restimulation, resulting in increased cytotoxicity towards target tumor cells. This is the base for development of specific cancer immunotherapy that is currently in phase 2 clinical trials for the treatment of leukemias, but also some solid malignant tumors (4).

This is also mirrored during acute virus infection, when naive NK cells undergo rapid metabolic reprogramming into potent effector NK cells (3). Several cytokines, including **IL-2, -10, -12, -15, -18 and -21 and type I IFNs,** are involved in the enhanced NK cell proliferation and effector functions during infection and inflammation. After being released by phagocytic cells and B lymphocytes, Il12 plays an important role in enhanced cascade production of other cytokines, in the first place the release of IFN-γ and TNF by NK cells. When released early during inflammation, IL12 is the activator of NK cells but also of the other T lymphocytes with the effect of increasing their activity and proliferation (6). The enhanced production of IFN-γ has central role in the differentiation of Th1 lymphocytes that will be vital in the defense against the dissemination of tumor cells. The initial reports regarding the role of NK cells in tumor elimination were in the context of the cellular infiltration and exerting direct cytotoxicity of primary tumors. However, the later reports showed that this action comprises only a minor population, raising questions about their true importance. Also, the results from some in-vitro studies have shown that NK cells are mostly present in the circulation and in smaller numbers within solid tumors, which can indicate that they are more important in the elimination of the misplaced tumor cells and the prevention of the development of metastasis (2). NK cells were first implicated in **tumor immunosurveillance** in the 1980s, when a higher incidence of cancers was reported in human population with defective NK cell function caused by certain genetic disorders (2). Some authors reported that in patients with malignancy the measurements showed reduced activity and smaller number of the NK cells compared to healthy population (3).

The effect of different **anesthetic techniques** on the immune response to infection, inflammation or the presence of tumor cells, is attracting increasing attention of the science. Considering that surgery is “golden standard” in the treatment of the early-stage malignant disease, anesthesiology techniques are coming into spotlight regarding their potential to shape immune defense against tumor cells dissemination. Opioids are the most used analgetic agents during surgery, but with conflicting effects on the immunomodulation. Fentanyl has negative both short- and long-term effects on the activity of NK cells, while on the other hand, in animal models tramadol showed protective effect with decreased incidence of metastasis during carcinoma surgery. However, we need to emphasize that inadequate perioperative pain treatment strategy results in a stress reaction in the host’s environment which suppresses cell-mediated immunity (1). Other anesthetic drugs were proven to have negative impact on the activity of NK cells in the perioperative period during breast cancer surgery which can result in dissemination of the malignancy. Ketamine and volatile anesthetics are in this group of anesthetics. Propofol is the most popular anesthetic agent in cancer surgery, mostly due to its positive pharmacodynamic properties, but also because of the reports that doesn’t produce negative impact on the activity of NK cells. In a mouse model, the administration of propofol caused reduced spread of the tumor and increased defensive role of the T lymphocytes. Another positive effect is the decreased levels of PGE2 which is of clinical significance if we know that prostaglandins have receptor mediated effect of down regulation of NK cells activity. Regional anesthesia techniques are well known for their ability to attenuate the stress response to surgical trauma, and to prevent negative effects on the immune function in the perioperative period. The main benefit of spinal anesthesia and the regional nerve blocking techniques is the avoidance of the volatile anesthetic and either elimination or significant decrease in the required dose of fentanyl. Indirectly we can expect a positive effect on the Th1/Th2 ratio and an increase in the NK cells cytotoxicity. In-vitro studies confirmed that regional regimen of anesthesia treatment results in significant decrease in the incidence of metastasis after operation due to malignancy (1).

Conclusion

At the end, we need to emphasize the importance of the immune defense against spread of the tumor cells in the perioperative settings. The role of NK cells in the direct elimination of the displaced tumor cells is confirmed, however the signaling pathways and the factors that are either enhancing or disturbing NK cells cytotoxicity are yet to be investigated and understood. The influence of different anesthetic techniques on the balance of the immune system during operation offers new fields of interest for clinical studies and investigation.

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