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COULD COLD STRESS IMPROVE THE FUNCTION OF NATURAL KILLER CELLS OF THE IMMUNE SYSTEM?

¿PODRÍA EL ESTRÉS FRÍO MEJORAR EL FUNCIONAMIENTO DE LAS CÉLULAS ASESINAS NATURALES DEL SISTEMA INMUNE?

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ABSTRACT

Natural killer (NK) cells are a crucial component of the innate immune system, with a well-known immunosurveillance function that includes the recognition and elimination of virally infected and cancerous cells. Certain pathological and physiological situations alter the function of natural killer cells, rendering our body to infection and cancer development. Therefore, it is relevant to identify pathways to improve natural killer cell activity. In this article, one alternative using cold stress to promote natural killer cell function is presented.

Keywords: cold stress, natural killer cells, immune system, immunosurveillance

RESUMEN

Las células asesinas naturales (NK) son un componente crucial del sistema inmunitario innato, con una función de inmunovigilancia bien conocida que incluye el reconocimiento y la eliminación de células cancerosas e infectadas por virus. Ciertas situaciones patológicas y fisiológicas alteran la función de las células asesinas naturales, sometiendo nuestro cuerpo a infecciones y desarrollo de cáncer. Por lo tanto, es relevante identificar vías para mejorar la actividad de las células asesinas naturales. En este artículo, se presenta una alternativa que utiliza el estrés por frío para promover la función de estas células de nuestro sistema inmune.

Palabras clave: estrés frio, células asesinas naturales, sistema inmune, inmunovigilancia

INTRODUCTION

The human immune system is a complex network of cells and organs that protects the body from harmful pathogens and foreign substances. The immune system is composed of two main branches: the innate and the adaptive immune system (Nicholson, 2016).

The innate immune system is in charge of the defense against pathogens and is composed of physical barriers (such as the skin and gut epithelia), as well as cells such as neutrophils, macrophages, and natural killer (NK) cells. These cells are able to recognize and quickly respond to invading pathogens, triggering an inflammatory response, and recruiting other immune cells to the site of infection (Riera et al., 2016).

The adaptive immune system is a more specific and targeted response that develops over time as the body is exposed to different pathogens. This system involves the activation and proliferation of lymphocytes, including T cells and B cells (Catania, 2022).

The immune system is also regulated by various signaling molecules, including cytokines, chemokines, and growth factors, which help to coordinate and modulate the immune response (Kany et al., 2019)

In this article, the functions of NK cells will be briefly described and the possible beneficial effect of low temperature on NK cell activity is postulated.

FUNCTION OF NATURAL KILLER CELLS

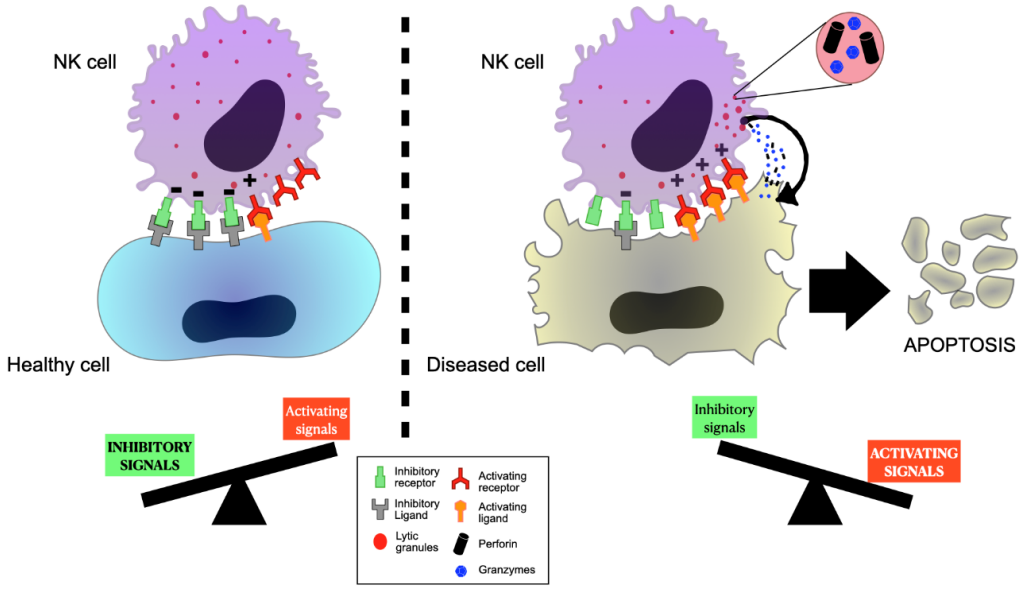
Natural killer (NK) cells belong to the lymphocyte family of cells with cytotoxic activity that form part of the innate immune system. Unlike T and B cells, NK cells do not require prior activation for their immune response (Abel et al., 2018). NK cells were first reported in 1970 while studying the interaction of lymphoid cells from the blood of patients with Hodgkin's disease against neoplastic cells (Sinkovics et al., 1970). Since then, a variety of receptors and ligands involved in NK cell recognition and activation have been discovered (Mace & Orange, 2019), as well as the mechanisms regulating their cytotoxic activity.

The main function of NK cells is to detect and eliminate diseased cells. In order to do so, NK cells recognize specific molecules on the surface of target cells, stress-induced ligands, through natural cytotoxic receptors (Arno et al., 2006). These ligands are upregulated in response to cellular stress, caused by infection or malignancy (Parsons et al., 2010; Upshaw et al., 2006). In addition, NK cells express membrane receptors to detect the level of expression of major histocompatibility complex (MHC) class I molecules on their surface.

MHC class I molecules are present on all healthy cells and are essential for presenting self-antigens to T cells (Kumar, 2018). If NK cells recognize the surface presence of stress-induced ligands with low expression of MHC class I, NK cells become activated and begin the release of cytotoxic molecules, such as perforin and granzyme, to induce apoptosis in the target cell (Abel et al., 2018) (Fig.1). On the other hand, high levels of MHC class I inhibit the NK cytotoxic response. The balance between activating and inhibitory signals determines whether the NK cell induces apoptosis or spares the target cell.

FIGURE 1

Regulation of NK cells cytotoxic activity



Note: When encountering a healthy cell, NK cells block the cytotoxic response due to the interaction of NK inhibitory receptors binding to the inhibitory ligands of healthy cells. These healthy cells also present low levels of activating ligands (Left panel). In several diseased cells (viral infection or cancer development), there is a decrease of inhibitory signals and an up-regulation of activating ligands that promote the activation of NK cytotoxic activity. This activity involves the secretion of perforin and granzymes that trigger the apoptosis of the diseased cell (Right panel).

In addition to their cytotoxic activity, NK cells collaborate with the adaptive immune response. NK cells produce cytokines, such as interferon gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), to promote the functions of T cells and B cells (Gyurova et al., 2020; Vivier et al., 2008) and activate a more effective immune response of the antigen-presenting dendritic cells (Goldszmid et al., 2012).

NK cells play a critical role in the immune response to a variety of diseases, including infectious diseases, cancer, and autoimmune diseases (Kucuksezer et al., 2021; Yu &Caligiuri, 2023). In infectious diseases, NK cells are activated in response to the presence of viral, bacterial, and parasitic pathogens. Thus, NK cells are responsible for eliminating cells infected with hepatitis B and C (Ebihara et al., 2008; Wang et al., 2022). In addition, NK cells are activated upon the presence of *Mycobacterium tuberculosis* (Ota et al., 1990) and *Plasmodium* spp. (Mavoungou et al., 2003), pathogens that cause tuberculosis and malaria, respectively. Furthermore, to enhance the immune response, NK secrete a variety of cytokines (Abel et al., 2018).

In cancer, NK cells play an important role in immune surveillance, recognizing and eliminating cancerous cells. However, cancer cells can evade NK cell-mediated killing by downregulating the ligands that are recognized by NK cell receptors, or by producing immunosuppressive factors that inhibit NK cell function (Zhang et al., 2022). Strategies that enhance

NK cell function, such as the use of monoclonal antibodies or cytokines, are being developed as potential cancer therapies.

Interestingly, cancer cells and certain viruses have evolved strategies to downregulate MHC class I expression in order to evade recognition by T cells (Griffin et al., 2021; Kshersagar et al., 2022).

In autoimmune diseases, NK cells have been implicated in the pathogenesis of diseases such as multiple sclerosis (Beliën et al., 2022) and rheumatoid arthritis (Ahern & Brennan, 2011). NK cells may contribute to disease by producing pro-inflammatory cytokines and promoting the activation of autoreactive T cells (Liu et al., 2021).

Recent studies have shown that NK cells are a heterogeneous population, with different functions. Thus, some NK cell subsets are specialized in producing cytokines, while others are more efficient at killing cancerous cells (Phan et al., 2017). Understanding the functional diversity of NK cells may be important for developing more targeted therapies for cancer and infectious diseases.

Several factors influence NK cell function, including age, infection, and cancer. It has been reported that aging is associated with a decline in NK cell function, allowing an increase in the susceptibility to infection and cancer in older individuals (Al-Attar et al., 2016; Gounder et al., 2018). In fact, a recent study highlights the changes in expression of miRNAs in NK cells due to aging (Lu et al., 2021). Hence, there is an interest in the biomedical community to determine ways to stimulate NK cell immunosurveillance function.

IMPACT OF COLD EXPOSURE ON NK CELLS

Cold stress exposure activates internal mechanisms to maintain the body's core temperature. These responses are controlled by the sympathetic nervous system that triggers the release of the hormones adrenaline (or epinephrine) and noradrenaline (or norepinephrine) by the adrenal gland (Kozyreva et al., 1999) and involve the increase of heartbeats and blood pressure, shivering and mobilization of glucose from hepatic storage (Lamotte et al., 2021; Sellers et al., 2021; Zhang et al., 2014).

There is evidence that exposure to extreme low temperatures affects the function of the immune system. It has been established that prolonged or extreme exposure to cold temperatures can have negative effects on the immune system. Thus, intraoperative moderate hypothermia diminished cytokine production and suppressed *in vitro* concavalin A-stimulated proliferation of peripheral blood mononuclear cells (Beilin et al., 1998).

However, studies performed in Antarctica showed no impact of low temperatures on the human immune system for an increased susceptibility to infection risk (Allen, 1973). On that matter, it was reported that the acute exposure of young adult men to 14 °C water increased the total count of white blood cells (Janský et al., 1996). This implies that the type of cold exposure may affect the response of immune cells.

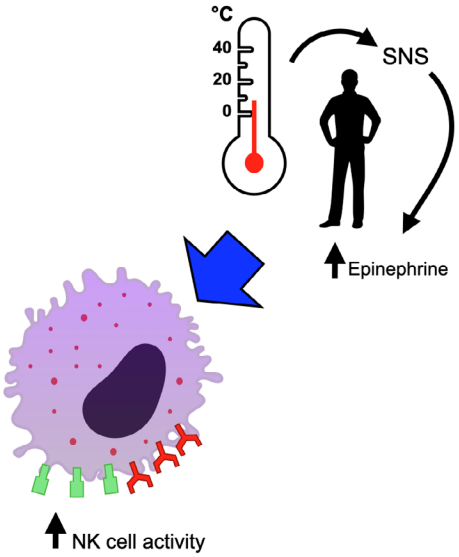
There are studies showing that NK cells may be influenced by cold exposure. It was observed that NK cell activity increased in men exposed to 30 min to 4 °C (Lackovic et al., 1988). Similarly, repetitive cold exposure (14 °C for 1 h) increased NK cell count and activity in young men possibly due to the increased metabolic rate stimulated by the elevated blood concentrations of catecholamines (Janský et al., 1996). Noteworthy, a gender-specific neuroendocrine and immune responses to cold exposure has been described. While studying the effect of cold temperatures on men and women, it was observed that men showed a larger increase in blood epinephrine and tumor necrosis factor-α than women (Solianik et al., 2014).

As aforementioned, catecholamines are the main

regulators of the response of the body to cold stress (Kozyreva et al., 1999). Among them, epinephrine was shown to be voluntarily increased in a group of healthy males exposed to cold temperatures and trained for breathing techniques (Kox et al., 2014; Zwaag et al., 2022). Since epinephrine administration to healthy volunteers is able to increase the NK activity (Kappel et al., 1991) and its blood concentration increases upon cold stress (Janský et al., 1996; Kox et al., 2014), it could be postulated that moderate cold exposure increases the epinephrine blood level which stimulates the activity of NK cells (Fig. 2).

FIGURE 2

Postulated effect of cold stress on NK cell activity



Note: Exposure of the body to low temperatures stimulates the sympathetic nervous system (SNS) to release epinephrine to the bloodstream. This catecholamine may stimulate then the activity of NK cells.

CONCLUSION

Overall, the impact of cold stress on NK cell activity appears to be complex and may depend on the severity and duration of the stress, as well as individual differences in susceptibility. Available studies point to an advantageous effect of repetitive exposure to low temperatures in order to improve NK cell activities. More research is still required to fully understand the mechanisms underlying the effects of cold stress on NK cells.

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