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LESSONS FROM NATURAL KILLER DEFICIENT PATIENTS – IMPLICATION IN EXERCISE IMMUNOLOGY

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KEY WORDS: natural killer cell deficiency, herpes family virus, trafficking

Natural killer cell was found as large granular lymphocyte, a distinct subset of lymphocytes exhibiting antigen independent killing of leukemia cells and virus infected cells. NK cells had long time been one of the main focuses of research in exercise immunology because intensity or duration exercise largely influence the number and the function of NK cells in the blood sample, and because the cytotoxicity was not restricted to a specific antigen. The early findings lead to the assumption of the well-known open window theory. The efforts, however, of elucidating the mechanism of NK cell recognition of target cells reached to the conclusion that the recognition is indeed highly specific but antigen independent. Both altered-self theory and missing-self theory were successful in defining the molecular mechanism of target condition principally regulated by the modulation of class I major histocompatibility antigen (MHC-I) expression on the target. The cytotoxicity of NK cell is further determined by corresponding NK cell receptors, some of which inhibit the killing response (killer inhibiting receptor: KIR) and some activating the killing process (killer activating receptor: KAR), and the consequence seems to be determined by the balance between target bound KARs and KIRs.

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CLINICAL FINDINGS OF NATURAL KILLER DEFICIENT PATIENTS

The progress in elucidating the mechanisms of NK cells enabled clinical scientists to better characterize immunodeficiency syndromes. A NK cell deficient patient within a family was reported in 1989 by Biron et.al.⁽¹⁾ Several types of NKD have been characterized;

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NKD lacking NK cells at all or NKD lacking functional molecules. A common feature among various NKD patients is that they all are susceptible to infection of herpes virus including varicella zoster virus (VZV), Herpes simplex virus (HSV) I and II, Epstein Barr virus (EBV), and cytomegalovirus (CMV) and occasionally papilloma virus often leading to severe to fatal outcome⁽²⁾. This fact clearly demonstrates that NK cells have distinct role in the protection of herpes viruses exhibiting lower cytotoxicity in the initial phase of infection. The most effective therapeutic approach for these patients lacking NK cells is considered as bone marrow transplantation to reconstitute their NK cell defense system.

Another relevant study to understand the role of NK cells is a 11-year cohort study with setting cancer incidence among 3625 community-dwelling adults over the age of 40 by Imai et al⁽³⁾. They found a significant association between baseline NK cell activity grouped in tertiles and cancer incidence and mortality over 11 years among 3625 community-dwelling adults over the age of 40. There was no significant difference in cancer incidence or mortality between the highest NK cell activity tertile and the mid tertile groups. The lowest tertile group, however, had a significantly higher mortality rate of cancer. The study is the first population study suggesting the role of NK cells in tumor surveillance, and suggests there is a distinct population who have lower NK cell activity with higher risk of cancer.

IMPLICATION IN EXERCISE IMMUNOLOGY

Considering the protective role of NK cells in herpes family viruses, question arises whether herpes gladiatorum, a common skin infection among wrestlers⁽⁴⁾, or EB virus reactivation among elite swimmers⁽⁵⁾ involve transiently impaired NK function due to strenuous training. Similar to other types of strenuous exercise, wrestling training resulted in a marked increase in the circulating number of NK cells. This altered trafficking of NK cells during strenuous exercise may largely depend upon catecholamine released during exercise. Both marked increase during exercise and marked decrease after exercise in the circulating number of NK cells may reflect altered trafficking without modifying the total pool of NK cells⁽⁶⁾. Whether this altered distribution, previously considered as an open window, has a role in the high prevalence of skin infection among the wrestlers or EB reactivation in elite swimmers is unknown.

Changes in the distribution of NK cell subtypes (mature and immature) during and after exercise are reported, but the length of changes required for altered susceptibility or severity of herpes family virus infection is unknown. Examination of herpes family virus infected cells for the expression of KAR (most commonly NKG2D) ligands such as MICA, MICB and ULBPs, which trigger NK cell activation upon binding to KARs and trigger inhibition upon binding to inhibitory KIRs may give a clue to the presence of open window during and after strenuous exercise. It must be noted that herpes family virus infection is known to epige-

netically modulate the expressions of KARs and KIRs ligands of the infected cells suggesting the strategy of viruses to escape from the human immune system⁽⁷⁾. Whether hormonal changes or changes in sympathetic activity confer expression patterns of KARs and KIRs on herpes family virus infected cells is still unknown.

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