Classical HLA Class I molecules as ligands for inhibitory- and activating NK cell receptors.

Masayuki Fujino*

Department of Immunology, Juntendo University School of Medicine, Tokyo, Japan.

Introduction

The immune system functions like a symphony orchestra, where each component plays a specific role in maintaining harmony. Among the various immune cells, NK cells are akin to the vigilant conductors of this orchestra. They are crucial for defending the body against infections and cancer. To accomplish this, NK cells have evolved a unique mechanism to recognize aberrant cells.

One of the central elements in NK cell recognition is the interaction between NK cell receptors and HLA Class I molecules. HLA (Human Leukocyte Antigen) molecules are proteins present on the surface of most nucleated cells in the human body. They play a pivotal role in presenting antigenic peptides to T cells, which is crucial for adaptive immune responses. However, they also have an essential role in regulating NK cell activity. NK cells possess an array of receptors, with some acting as "inhibitory" and others as "activating" receptors. The balance between signals from these receptors dictates the fate of a target cell when encountered by an NK cell. Inhibitory NK cell receptors: These receptors primarily recognize HLA Class I molecules, especially classical HLA Class I molecules (HLA-A, HLA-B, and HLA-C), which are expressed on healthy cells. When an inhibitory receptor on an NK cell binds to its cognate HLA Class I ligand on a target cell, it sends a signal that prevents the NK cell from initiating an attack. This inhibitory signal is essential for maintaining self-tolerance and preventing NK cells from mistakenly attacking healthy cells. Activating NK cell receptors: Unlike inhibitory receptors, activating receptors recognize various ligands expressed on the surface of infected or stressed cells. When an activating receptor binds to its ligand, it sends a signal that stimulates the NK cell to initiate cytotoxic activities, such as releasing toxic granules or producing cytokines to eliminate the target cell. This activation is a critical response to infections or cellular stress, allowing NK cells to swiftly eliminate threats. The interaction between NK cell receptors and HLA Class I molecules forms a dynamic equilibrium that determines the outcome of an NK cell encounter with a target cell. If a target cell expresses normal levels of classical HLA Class I molecules, inhibitory receptors prevail, and the NK cell remains quiescent, avoiding unnecessary harm to healthy cells. However, if a target cell downregulates or lacks HLA Class I expression, activating receptors gain dominance, and the NK cell becomes activated, poised to eliminate the threat. This balance is essential for immune surveillance. It allows NK cells to target cells that have lost or downregulated HLA Class I molecules due to viral infections or cellular transformation (e.g., cancer cells) while sparing healthy cells expressing intact HLA Class I molecules.

The clinical relevance

Understanding the intricate relationship between classical HLA Class I molecules and NK cell receptors has significant clinical implications.

Cancer Immunotherapy: Exploiting the NK cell receptor-HLA interaction is a promising avenue for cancer immunotherapy. Some therapies aim to enhance NK cell activity by blocking inhibitory signals, allowing NK cells to attack cancer cells more effectively. Conversely, therapies that promote HLA Class I expression on cancer cells can make them less susceptible to NK cell-mediated killing, a strategy used to evade immune surveillance.

Viral Infections: Viruses often target HLA Class I expression to evade immune detection. Understanding how viruses manipulate this pathway can inform the development of antiviral therapies. Additionally, therapies that boost NK cell activity may help in controlling viral infections.

Autoimmune Diseases: Dysregulation of NK cell activity and HLA Class I expression can contribute to autoimmune diseases. Modulating the NK cell-HLA Class I interaction is a potential therapeutic approach for managing such conditions.

Transplantation: In the context of organ transplantation, HLA matching is essential to prevent rejection. Understanding the intricacies of HLA Class I recognition by NK cells can improve transplantation outcomes by minimizing graft rejection.

Conclusion

The interaction between classical HLA Class I molecules and NK cell receptors is a finely tuned mechanism that allows NK cells to distinguish between healthy and aberrant cells. This dynamic balance between inhibition and activation is essential for immune surveillance, protecting the body from infections and cancer while maintaining self-tolerance. As our understanding of this intricate dance between NK cells and HLA Class I molecules deepens, we are better equipped

***Correspondence to:** Masayuki Fujino, Department of Immunology, Juntendo University School of Medicine, Tokyo, Japan, E-mail: Masayukifujino@gmail.com

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to harness this knowledge for therapeutic purposes. Cancer immunotherapy, antiviral strategies, autoimmune disease management, and transplantation medicine all stand to benefit from our growing insights into this fundamental aspect of the immune system. The symphony of immunity plays on, and with every discovery, we become better conductors of this magnificent orchestra.

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