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Perspective

Innovative Strategies for Enhancing Natural Killer Cell Function against Leukemia

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DESCRIPTION

Leukemias, a diverse group of hematological malignancies, continue to challenge clinicians due to their complex pathophysiology and the limited efficacy of conventional treatments. While therapies like chemotherapy and stem cell transplantation have made significant strides in improving patient outcomes, relapses and resistance remain significant hurdles. A potential area of investigation involves the role of non-Major Histocompatibility Complex (non-MHC)-restricted cytotoxic cells in the immune response to leukemia. These cells, including Natural Killer (NK) cells and γδ T cells, do not rely on MHC molecules for recognizing and killing abnormal or infected cells, positioning them as key players in immune surveillance and cancer immunotherapy.

Non-MHC-restricted cytotoxic cells, primarily NK cells and γδ T cells, have gained increasing attention due to their ability to target and eliminate malignant cells without the need for the highly specific antigen presentation required by conventional T cells. This characteristic makes them ideal candidates for targeting leukemia cells, which often employ mechanisms to evade MHC-mediated immune recognition.

NK cells are innate immune cells that can directly kill a broad range of abnormal cells, including tumor and virally infected cells, through a process known as cytotoxicity. Unlike T cells, which rely on antigen-specific receptors (TCRs) and MHC molecules to identify infected or malignant cells, NK cells use a balance of activating and inhibitory receptors to detect stressed, infected, or transformed cells. They are able to identify and respond to changes in the expression of surface molecules, such as the downregulation of MHC class I molecules (a common feature of cancer cells) or the upregulation of stress-induced ligands (like MICA/B or ULBPs).

In leukemia, abnormal hematopoietic cells often exhibit reduced expression of MHC class I, making them prime targets for NK cell-mediated killing. NK cells can also recognize and respond to tumor-associated antigens, such as CD19 in B-cell leukemias, and surface markers that are aberrantly expressed in leukemic cells. This ability to recognize and kill leukemia cells without the need for prior sensitization makes NK cells an attractive therapeutic option in the treatment of these malignancies.

The clinical potential of NK cells is becoming evident through advancements in NK cell-based therapies. Efforts to enhance the function of NK cells either by expanding them *ex vivo* or genetically modifying them have shown intriguing in preclinical studies and early-phase clinical trials. For instance, the use of cytokines such as IL-2 or IL-15 has been explored to boost NK cell proliferation and cytotoxic activity. Moreover, strategies to overcome the immunosuppressive tumor microenvironment, which often limits NK cell function, are under active investigation. Such approaches could lead to more effective therapies for leukemia and other hematologic malignancies.

γδ T cells, another subset of non-MHC-restricted cytotoxic cells, represent a less understood but equally potential component of the immune system. These T cells, which express TCRs composed of γ and δ chains, differ from conventional αβ T cells in that they do not require peptide-MHC complexes for activation. Instead, γδ T cells recognize a wide range of tumor-associated antigens, including phosphoantigens and stress-induced molecules, which are often present on the surface of malignant cells.

In the context of leukemia, γδ T cells have shown potential in directly targeting leukemic blasts. One of the key features of γδ T cells is their ability to recognize and kill tumor cells through the engagement of various activating receptors, such as NKG2D, which binds to stress ligands upregulated in leukemia. In addition, γδ T cells can produce cytokines such as Interferon-Gamma (IFN-γ), which can enhance the anti-leukemic immune response by recruiting other immune cells, including macrophages and dendritic cells.

Importantly, γδ T cells are less likely to be suppressed by the tumor microenvironment compared to other immune cells, providing a potential advantage in treating leukemia. Clinical

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studies have shown that adoptive transfer of γδ T cells can effectively reduce leukemic burden in both in vitro and animal models. Furthermore, the ability of γδ T cells to recognize stress ligands on malignant cells may allow for a broader and more flexible immune response, even against genetically diverse leukemias.

Despite their potential role in leukemia control, the use of non-MHC-restricted cytotoxic cells in therapy faces several challenges. One of the major obstacles is the heterogeneous nature of leukemia, which can complicate the development of universal immunotherapies. Leukemia cells can alter their surface markers or downregulate stress-induced ligands in response to immune pressure, potentially escaping NK cell or γδ T cell recognition.

To address these challenges, innovative strategies are being explored. For example, the combination of NK cells or γδ T cells with immune checkpoint inhibitors (e.g., anti-PD-1 or anti-CTLA-4) may help overcome the immune suppressive environment commonly found in leukemia. Additionally, genetic modifications, such as Chimeric Antigen Receptors (CARs) or TCRs targeting leukemia-specific antigens could further enhance the specificity and efficacy of these immune cells.

Another intriguing approach is the use of cytokine therapy or small molecules to stimulate the expansion and activation of NK cells or γδ T cells *in vivo*. These strategies could not only increase the number of cytotoxic cells available to target leukemia but also improve their persistence and functional activity.

CONCLUSION

Non-MHC-restricted cytotoxic cells, such as NK cells and γδ T cells represent a potential frontier in the treatment of leukemia. Their ability to recognize and eliminate tumor cells without the need for MHC-mediated antigen presentation offers a distinct advantage over traditional immunotherapies. With ongoing advances in cell-based therapies, immune modulation, and targeted treatments, these cells hold the potential to become powerful tools in the fight against leukemia, offering new hope for patients, particularly those with relapsed or refractory disease.