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Mini Review

Exploring the Role of Natural Killer Cell Receptors and HLA Ligands in Diffuse Large B-Cell Lymphoma Treatment: Potential Targets for Novel Therapies

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ABSTRACT

Natural Killer (NK) cells play a crucial role in the response to treatment of patients with Diffuse Large B-Cell Lymphoma (DLBCL). The Killer-Cell Immunoglobulin-Like Receptors (KIR) expressed on the surface of NK cells and their respective Human Leukocyte Antigen (HLA) ligands expressed on the surface of target cells, command the main signaling pathways of NK cells. Understanding the binding profile of KIR receptors and their HLA ligands is of utmost importance in defining new strategies for therapies and treatment for DLBCL patients.

Keywords: New therapies; Diffuse large B cell lymphoma; KIR polymorphisms; Human leukocyte antigen ligands

INTRODUCTION

Non-Hodgkin lymphoma is the most common hematologic neoplasm worldwide. Diffuse Large B-Cell Lymphoma is the most aggressive subtype of NHL, with a diffuse growth pattern and high rates of relapse after first-line treatment (around 20%-50% of patients within a 5-year period) [1-2].

The most common first-line treatment for Diffuse Large B Cell Lymphoma (DLBCL) is Rituximab-Cyclophosphamide-Hydroxydaunorubicin-Oncovin-Prednisone (R-CHOP), which is a combination of cyclophosphamide, doxorubicin, vincristine, and the anti-CD20 monoclonal antibody known as rituximab. The introduction of rituximab to combined therapy with CHOP has improved Overall Survival (OS) and Progression-Free Survival (PFS) for patients with B-cell derived hematologic diseases. However, many DLBCL patients do not respond to R-CHOP, and in these cases, treatment options become increasingly limited [3].

Despite recent studies showing promising alternative treatments for DLBCL patients, such as cell therapy with T cells genetically modified with Chimeric Antigen Receptors (CAR-T), for the vast majority of centers, R-CHOP will remain the first available line of treatment for many years to come [4].

The main mechanism of action of rituximab is the activation of Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC). In this case, the Fc portion of the anti-CD20 Monoclonal Antibody (mAb) is recognized by a receptor expressed on the surface of an effector cell that opsonizes these cells, promoting the binding of anti-CD20 to CD20 expressed on the surface of B cells (normal and modified), leading to the destruction of these lymphocytes through the activation of effector cell cytotoxicity [1].

LITERATURE REVIEW

Natural Killer (NK) cells are considered the main effector cells involved in the activation of ADCC by rituximab. Therefore, it is important to thoroughly study the profile of NK cells in relation to their surface inhibitory and activating receptors, along with their respective ligands, as well as the characteristics of these interactions. Additionally, in the last decade, the number of studies related to the antitumor role of NK cells has shown that these cells are promising in the scenario of Hematopoietic Stem Cell Transplantation (HSCT), allogeneic and haplo identical, as well as in the adoptive transfer of these cells as therapy for some hematological diseases [5-7].

Therefore, the aim of this mini-review is to present the most recent findings related to the role and importance of NK cells,

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mainly of Killer-Cell Immunoglobulin-Like Receptors (KIR) and their HLA ligands, in the context of treatment, development, and progression of patients with DLBCL.

NK cells are a subset of lymphocytes that express CD56 but not CD3 and play a vital role in the immune system, including involvement in autoimmunity and recognition of tumor cells. In the context of HSCT, donor-derived NK cells can recognize and kill residual leukemia cells and cure malignant patients [8].

The function of NK cells is regulated by many types of expressed receptors. The most important group of them can be represented by KIR receptors (Killer-Cell Immunoglobulin-Like Receptors) that recognize and bind to specific class I HLA molecules expressed on target cells, signaling for the activation/inhibition pathways and licensing/education of NK cells. Evolutionarily, class I HLA molecules are functionally selected in close correlation with the specificity of KIR genes [9].

Recent evidence suggests that the KIR/HLA interaction may play a role in both the development and progression of DLBCL. Makanga et al. evaluated the impact of KIR genotypes, HLA class I, and CD16 on rituximab-dependent NK cell responses in an in vitro cellular model of healthy blood donors and ex vivo rituximab-treated Non-Hodgkin Lymphoma (NHL). The study describes, for the first time, the triggering effect of the *KIR2DS1*-C2 interaction on rituximab-dependent NK cell degranulation. Although the triggering effect of *KIR2DS1* on the total rituximab-dependent NK cell response is limited due to the low frequency of *KIR2DS1*+ NK cells, selecting *KIR2DS1*+C2- NK cells may be advantageous with the overall goal of obtaining a more efficient CD16 lineage for promoting ADCC [10].

DISCUSSION

In addition, the lack of class I HLA ligands for KIR receptors may favor ADCC responses of rituximab-dependent NK cells in patients with NHL. Therefore, class I HLA typing and the frequency of NK cells KIR+ in peripheral blood may be simple and useful markers for predicting response to rituximab [10].

Lisovsky and colleagues demonstrated the contribution of education to antibody-dependent NK cell activation and found that education through *KIR3DL1* and *KIR2DL1*, but not *KIR2DL3*, enhances antibody-mediated secretion of IFN-γ and CCL4, compared to uneducated cells [11].

Erbe et al. also demonstrated that patients who inherited *KIR2DL2* and its ligand (HLA-C1) together with *KIR3DL1* and its ligand (HLA-Bw4) had better outcomes compared to patients without this genotype. Furthermore, patients with *KIR2DL2* and HLA-C1 together with *KIR3DL1* and HLA-Bw4 also showed better duration of response and tumor reduction during maintenance period, while patients without this genotype did not show improvement when receiving maintenance [12].

Kaddu-Mulindwa and colleagues observed that DLBCL patients who were positive for *KIR2DS1* and homozygous for HLA-C2 did not benefit from the addition of rituximab to CHOP therapy, further demonstrating that defining KIR/HLA genotypes can be a useful marker for evaluation and decision-making regarding treatment [13] .

There is evidence suggesting that in the context of allogeneic Stem Cell Transplantation (SCT), for patients with NHL, the KIR B/x genotype of the donor provides the recipient with better rates of progression-free survival after HLA 10/10 unrelated SCT [14].

Indeed, the latest evidence confirms the importance of the role of KIR receptors and their HLA ligands in the context of treatment of patients with NHL, especially DLBCL, and highlights the importance of understanding the NK cell response to different receptor profiles, which could bring new treatment perspectives for these patients.

As an example, we can mention Chu and colleagues, who suggest that, just like Chimeric Antigen Receptor (CAR-T) cell therapy, NK cells can receive chimeric antigens with the goal of recognizing modified B cells and treating patients with DLBCL [15]. Phase I/II studies have already shown that CAR-NK therapy could be the future of treatment for patients with more aggressive subtypes of NHL such as DLBCL [16-19].

CONCLUSION

Therefore, we can conclude that the study of NK cells, their activating and inhibitory receptors, as well as their respective ligands can greatly contribute to the establishment of new lines of therapy for patients who do not respond to the treatments available for NHL, especially for DLBCL. Natural Killer (NK) cells are considered the main effector cells involved in the activation of ADCC by rituximab. Therefore, it is important to thoroughly study the profile of NK cells in relation to their surface inhibitory and activating receptors, along with their respective ligands, as well as the characteristics of these interactions. Additionally, in the last decade, the number of studies related to the antitumor role of NK cells has shown that these cells are promising in the scenario of Hematopoietic Stem Cell Transplantation (HSCT), allogeneic and haplo identical, as well as in the adoptive transfer of these cells as therapy for some hematological diseases. The most common first-line treatment for DLBCL is R-CHOP, which is a combination of cyclophosphamide, doxorubicin, vincristine, and the anti-CD20 monoclonal antibody known as rituximab. The introduction of rituximab to combined therapy with CHOP has improved Overall Survival (OS) and Progression-Free Survival (PFS) for patients with B-cell derived hematologic diseases. However, many DLBCL patients do not respond to R-CHOP, and in these cases, treatment options become increasingly limited. In addition, the lack of class I HLA ligands for KIR receptors may favor ADCC responses of rituximab-dependent NK cells in patients with NHL. Therefore, class I HLA typing and the frequency of NK cells KIR+ in peripheral blood may be simple and useful markers for predicting response to rituximab. Recent evidence suggests that the KIR/HLA interaction may play a role in both the development and progression of DLBCL. Makanga et al. evaluated the impact of KIR genotypes, HLA class I, and CD16 on rituximab-dependent NK cell responses in an in vitro cellular model of healthy blood donors and ex vivo rituximab-treated Non-Hodgkin Lymphoma (NHL). The study describes, for the first time, the triggering effect of the KIR2DS1-C2 interaction on rituximab-dependent NK cell degranulation.

Although the triggering effect of KIR2DS1 on the total rituximab-dependent NK cell response is limited due to the low frequency of KIR2DS1+ NK cells, selecting KIR2DS1+C2- NK cells may be advantageous with the overall goal of obtaining a more efficient CD16 lineage for promoting ADCC.

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DECLARATIONS OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHORS STATEMENT

Daniela Cardozo: Conceptualization, Methodology, Software, Reviewing and Editing; Amanda Marangon.: Data curation, Writing- Original draft preparation; Fernando Guimarães: Visualization, Investigation and Supervision; Carmino de Souza: Supervision and Project Administration; Jeane Visentainer: Writing- Reviewing and Editing.

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