Review: Myeloid-derived suppressor cells (MDSCs) – Will it become a therapeutic target for Non-Hodgkin Lymphoma?

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Abstract: **Non-Hodgkin's lymphoma (NHL) is a varied set of lymphoproliferative disorders initiatingfrom B, T, or natural killer (NK) lymphocytes. Common treatments of NHL include chemotherapy regimens, radiotherapy, rituximab administration, transfusion of blood products and Peripheral blood stem cell transplantation. Recently, several targeted therapies have been approved or are in the later phase of clinical trials and molecular targeted therapy is considered as a key aspect of NHL. Successful treatment of lymphoma may result from the induction of specific antitumor immunity. Myeloid-derived suppressor cells (MDSC) are being investigated as a possible target in solid tumors and most of blood cancers to improve the effects of commonly used undergoing treatment. The anti-tumor immune response of a diseased person is inhibited by MDSC expansion, which restricts, cytokine secretion, T cell proliferation and the activation of regulatory T cells. In order to identify immunological therapeutic targets, it is critical to identify tumor-promoting factors. Since this environment is focus to low selective pressure for mutations, targeting the Tumor Microenvironment (TME) is a promising therapeutic option for Non-Hodgkin lymphoma. The features, distribution, roles, cellular reactions, and aiming MDSCs in Non-Hodgkin lymphoma are discussed in this review.**

Key Words; **Non-Hodgkin lymphoma, Myeloid-derived suppressor cells, Target therapy, TEM**

I. INTRODUCTION

A. What is Non-Hodgkin Lymphoma

The word Non- Hodgkin's Lymphoma (NHL) addresses a number of lymphoproliferative diseasescaused by B, T, or natural killer (NK) lymphocytes (Zelenetz et al., 2011)andmore NHLs are originated from B lymphocytes (Bowzyk Al-Naeebet al.,2018). NHL is divided into more than 40 subtypes, ranging from low-grade indolent cancers to high-grade chronic cancers (Warawita et al., 2014, Bowzyk Al-Naeebet al.,2018).They are composed primarily of lymphocytes in different stages of development. As a result, the characteristics of each lymphoma subtype are determined by the cell that gave rise to them(Shankland et al., 2012).

Enlarged lymph nodes or tumor mass in NHLs trigger to express the symptomsof patients (Bowzyk Al-Naeeb et al.,2018). B symptoms, which are systemic signs and symptoms, determined by the site of involvement, history of the lymphoma subtype, and the fever of uncertain origin (38°C), unexplained weight loss (10 percent over 6 months), night sweats, physical discomfort, and lethargy. Furthermore, two-thirds of patients experience non-painful lymph node enlargement that lasts longer than two weeks, which is more common than in Hodgkin's lymphoma. These results are more common in advanced disease stages and are linked to a poor prognosis (Anderson et al., 1982).Furthermore, 20% of patients with mediastinal lymphadenopathy may experience a heavy cough, chest pain, or fluid accumulation in pleural cavity, or they may not have any symptoms and be diagnosed mainly by imaging techniques(Filly et al., 1976).In abdominal and pelvic lymphadenopathy compulsive overeating, dizziness, vomiting, pain, and weight loss are common symptoms. While distinct hepatic masses are common in indolent disease, diffuse hepatosplenomegaly is more common in chronic NHL(Goffinet et al.,1973; Rsdall et al., 1979).

The gastrointestinal (GI) tract, skin, testes (in men), kidneys, and bone are the primary extranodal locations, accounting for 10% to 35% of NHL incidents (Anderson et al., 1982).Most NHLs show the involvement of both nodal and extranodal sites (Singh et al.,2020). After squamous cell carcinoma, NHL is the second most common oropharyngeal malignancy despite the fact that oral manifestations are uncommon(DePena et al., 1990; Epstein et al., 2001). Increased calcium iron levels, superior or inferior vena cava obstruction, increased blood viscosity, significant hepatic dysfunction, and venous thromboembolism are all symptoms of NHL(Ottinger et al., 1995; Mohren et al., 2005).Anemia, thrombocytopenia, leukopenia and elevated creatinine are all major laboratory findings that could be of prognostic significance(Conlan et al., 1992; Josting et al., 2000, Bowzyk Al-Naeebet al.,2018).

B. Pathophysiology & Molecular Pathology of NHL

Lymphoma pathogenesis is a complex process that is caused by genetic alterations or certain infections/organ transplantation led to compromise the immunity (Bowzyk Al-Naeebet al.,2018, Singh et al.,2020).Mainly a collection of gene mutations affects proto-oncogenes and tumor suppressor genes, in the same way as other malignancies. Certain NHL subtypes have a genetic susceptibility to progress (familial chronic lymphocytic leukemia/small lymphocytic lymphoma

[CLL/SLL]) (Coupland, 2011).During normal B-cell maturation, cells emerge from the central lymphoid tissues (bone marrow and thymus), where recombination of gene sections leads to the accumulation of immunoglobulin heavy and light chain genes, which is assisted by enzymes that trigger double-stranded DNA breaks (George and Staudt, 2010).In lymphoma, these strand breaks may trigger chromosome translocations, but DNA repair processes are triggered in normal cells (Jung et al., 2006). Proto-oncogene activation is usually the product of such translocations. B lymphocytes (matured) migrate into the lymphoid tissues of the peripheral circulation (blood, spleen, lymph node, and mucosa-associated). In normal conditions, when B-cells receive signals from T lymphocytes, they activate in the germinal center of lymph nodes, where B cell maturation takes place. Many forms of lymphoma, including diffuse large B-cell lymphoma, follicular lymphoma, and Burkitt's lymphoma, are caused by the germinal center(George and Staudt, 2010; Allen et al., 2007).

During germinal center reaction, cells undergo two remarkable DNA remodeling processes: class-switch recombination, where the heavy chain class of immunoglobulin may change from IgM to IgG, IgA, or IgE; and somatic hyper mutation, in which the variable immunoglobulin (IgV) light chain mutates, which aids in changing the affinity of B cell populations for an antigen(George and Staudt, 2010). During these common genetic modification pathways, DNA damage may provide a path to lymphoma, allowing non-Hodgkin lymphomas to be divided into non-Hodgkin lymphomas with and without IgV mutations. Non-Hodgkin lymphomas without IgV mutations are called pre germinal center-derived non-Hodgkin lymphomas (eg, most cases of mantle-cell lymphoma). Other tumors derived from B cells, however, have not undergone somatic hyper mutation although being derived from the germinal center (B-cell chronic lymphocytic leukemia or small lymphocytic lymphoma). Burkitt's lymphoma, follicular lymphoma, lymphoplasmacytic lymphoma, mucosa-associated lymphoid tissue lymphoma, and diffuse massive B-cell lymphoma are among the NHLs with IgV mutations originating from the germinal center or post germinal center (Küppers et al., 2010).

WHO classification, Ann Arbor classification are recently used for the staging of NHL (Bowzyk Al-Naeebet al.,2018, Singh et al.,2020). During several stages of NHL,genotype of malignant cellsremains relatively stable (Gamberi et al., 1997). On a molecular level, the genetic lesions found in lymphomas so far include oncogene activation caused by chromosomal deletion or mutation (Quesada et al., 2011). The deletion of the long arm of chromosome 6 (6q) is the most common genetic modification in NHL and is linked to a poor prognosis (Giadono et al., 1992; Offit et al., 1991).

C. Diagnosis and Treatment of NHL

NHL was diagnosed mainly by using biopsies for immune histochemistry(Warawita et al., 2014,Bowzyk Al-Naeebet al.,2018). Lowgrade Non-Hodgkin lymphoma patients can show the symptoms as enlargement of spleen and liver. Intermediate and high-grade NHL symptoms are advanced than the low-grade symptoms. Also, skin lesions are associated with cutaneous lymphomatypes(Medscape,2021). Gold standard method to diagnose NHL is excisional tissue biopsies which help to identify tissue microarchitecture. Various laboratory techniques (Ex: immunohistochemistry, flow cytometry) are being used to investigate tissue samples (Ninkovic and Lambert, 2017).

High grade NHLs need quick treatment than low grade because of the speedy growth of cancer (Bowzyk Al-Naeebet al.,2018). Common treatments of NHL include chemotherapy regimens, radiotherapy, rituximab administration, transfusion of blood products and peripheral blood stem cell transplantation(PBSCT).Cytotoxic agents, histone deacetylase inhibitors, monoclonal antibodies, immunomodulators and colony-stimulating growth factors are used as medications in patient management. For the treatment of NHL, CHOP (Cyclophosphamide, Doxorubicin, Prednisone, Vincristine) is themost common chemotherapy combination is being used(Cancer net,2021). Surgeries also applicable for indolent Non-Hodgkin lymphomas.Side effects as short term (hair loss, loss of appetite, fatigue, etc.) and long-term (peripheral neuropathy, cardiomyopathy, etc.) can occur in NHL patients after chemotherapy (Bowzyk Al-Naeebet al.,2018). Adverse effects such as dehydration after diarrhea, vomiting and severe infections due to severe neutropenia also occurs (National cancer control programme, 2021). Although not commonly considered treatable, indolent B cell NHLs, such as follicular lymphoma (FL), can be treated for many years with a favorable prognosis. A proportion of indolent B cell NHLs, on the other hand, can undergo histologic transition into more aggressive B cell NHLs (Hill et al., 2019).

Though some popular treatment schedules are recently available for NHL, those are not 100% effective since some cases are showing relapsing and resistance to the chemotherapy (Johnston et al., 2010).Growing and dividing of cancer cells are blocked by chemotherapy. Radiotherapy which uses high energy X rays, also destroy cancer cells.These therapies have short term and long-term adverse side effects (National cancer control programme,2021).According to the review of Hill. L et al (2019) T cells that have been genetically modified with chimeric antigen receptors, have shown a remarkable ability to generate complete and long-lasting clinical responses in patients with chemotherapy-resistant lymphomas in recent years. The U.S Food and Drug Administration (FDA) has approved two autologous CD19-directed chimeric antigen receptors (CAR) modified T cell products for the treatment of patients with relapsed or refractory diffuse large B cell lymphoma, primary mediastinal B cell lymphoma, and transformed FL, and a several of other CART cell targets are being investigated in ongoing clinical trials. Finding of new therapies which shows the long-termpersistence and less toxicity for the patient are an urgent

medical need (Johnston et al., 2010).Immunotherapy and targeted therapy are more popular in these days which target cancer specific markers and tumor environment(Cancer net,2021).

D. What is the "Targeted Therapy "

The current trend of medicine is to detect biomarkers for a particular disease or disease states. Those markers are quantifiable indicators which can be used to detect a special disease or the staging of a disease. It is commonly being used for the specific therapies and to monitor the treatments. Therefore, biomarkers specific diseases look likely to become one of the major driving forces in the pharmaceutical research and drug development (Workman et al., 2006; Peng et al., 2009).

II. MYELOID DERIVED SUPPRESSOR CELLS (MDSCs)

A.Tumor Environment and MDSCs

In tumor environment, cancer cells interact with non-malignant cells and create an immune suppressive microenvironment by impairment of tumor associated immune cells. Soluble factors secreted by tumor cellular constituents, maintain this microenvironment. TGF-β, IL 13 like factors released by tumor result in increasing the population of Myeloid-derived suppressor cells (MDSCs) (Upadhyay et al., 2015; Draghiciu et al., 2015; Gabrilovich et al., 2009).

MDSCs are a diversegroup cells derived from the bone marrow environment including myeloid progenitors, macrophages, granulocytes, dendritic cells, and immature myeloid cells (Zhang et al., 2015). Recent Studies have discovered that during tumor growthMDSCs multiply intenselyand evade host's immune response in many types of tumors (Zhang et al., 2015; Draghiciu et al., 2015).There was a significant correlation between population of MDSCs and the clinical stage of cancer (Montero et al., 2009). Rather than using cytokine induced cell (CIK) therapy alone to limit the efficacy of MDSCs, combination of CIK therapy and chemotherapy increased the survival period of some cancer patients (Wang et al., 2015). Depletion of MDSCs or blockade of immunosuppressive factors in tumor environment will help to inhibit the tumor growth (Gabrilovich et al., 2009; Upadhyay et al., 2015; Ding et al., 2014).

The expansion of MDSCs and its connection with thedifferent levels of the disease were shown in solid cancers (Swerdlow et al., 2008).MDSCs increase the tumor growth and T cell proliferation by facilitating tumor metastasis. It can also inhibit host's anti-tumor immunity by suppressing T cells and Natural Killer cells (NK) function by accelerating the production of arginine, reactive oxygen species (ROS) and nitric oxide (NO). Treg cells and TGF-β secretion also mediate T cell suppression (Zhang et al., 2015; Draghiciu et al., 2015).MDSCs are described as a collection of various cells present in inflammatory diseases and in several tumors including multiple myeloma, chronic lymphocytic leukemia (CLL), and Diffuse Large B cell lymphoma(DLBCL) (Azzaoui et al,2016).These immature cells can inhibit the immune system of the body through a variety of mechanisms and play a role in the onset and progression of cancer (Betsch et al.,2018).

B. MDSC and Non-Hodgkin Lymphoma

Similar mechanisms mentioned previously have been shown in lymphoma as Lin et al. (2011) revealed that monocytes population in the blood circulation of patients with B-cell NHL have contributed to systemic immune suppression. Recently, the findings of Marini et al. (2016) suggested a previously unknown G-MDSC-mediated mechanism of immune-escape in lymphomas (Hodgkin and Non-Hodgkin), count on possible targets for therapeutic interventions. Early studies noted that the most common chemotherapy (CTX) given to lymphoma patients can induce cells with immune suppression activities and later the cells were identified as MDSCs (Angulo et al., 2000; Mikyskova et al., 2011).

It was found that a considerably lesser percentage of regulatory NK cells in B cell lymphoma patients compared with healthy blood and it was further mentioned that the granulocytic MDSCs were increased in whole lymphoma sample(Amini et al.,2019).In the study conducted by Azzaoui et al,2016have mentioned that the expansion of circulating monocytic MDSCs correlates with the clinical outcomes of diffuse large B cell lymphoma; major sub type of Non - Hodgkin lymphoma and they identified the myeloid suppressive signature by gene expression in peripheral blood samples of 66 DLBCLpatients. Higher amount of circulating Granulocytic -MDSCs and Monocytic-MDSCs was shown in that cohort of Non-Hodgkin lymphoma patients and specially the count of Monocytic-MDSCs was mentioned as a related parameter with the international prognostic index (Azzaoui et al.,2016).Tadmor et al,2013 also found the higher levels of Monocytic-MDSC in DLBCL compared to healthy controls and they have focused on the relationship between monocytosis and survival in (DLBCL) patients. It was mentioned that the efficacy of treatments for lymphoma patients can be reduced by the patients' immune system, more specifically by myeloid-derived suppressor cells (MDSC)(Betsch et al.,2018). Gabrilovich, 2017has stated that the MDSCs act on immune suppression in cancer, tumor angiogenesis, drug resistance, and tumor metastases. Because of the ability in drug resistance, MDSCs are limiting the effects of cancer immunotherapy. Therefore, targeting these cells can be a desirable therapeutic method (Gabrilovich, 2017).

III. CONCLUSION AND FUTURE DIRECTIONS

In summary, MDSCs play a vital role in promoting tumor progression, metastasis, and creating an immunosuppressive TME. In addition, their role in resistance against immunotherapy makes them a promising therapeutic target (Law et al., 2020). The understanding on the characterization

and clinical value of MDSC enhancesto emerge more selective anti-MDSC therapies. Currently, research has demonstrated the worth of targeting MDSC populations as a part of a mixture therapy to reinforce the potency of immune checkpoint inhibitors and other sorts of immunotherapy. This strategy was shown to be effective in reducing tumor burden and metastasis, to the extent of improving overall survival. Targeting these cells could also be the key to development of a next generation of immunotherapies with improved therapeutic outcomes.Since there is trivial understanding of the immune evasion strategies of MDSC utilized by lymphomas, it is questionable whether this system directly or indirectly contribute to a tumor microenvironment in NHL. In such grounds, better understanding of such mechanisms in the presence or absence of chemotherapy may lead to develop better prognostic markers as well as targeted therapeutics against NHL.

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