A review on the Role of FLT3/FL System in Non- Hodgkin's Lymphoma

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Abstract

Non-Hodgkin's lymphoma (NHL), a cluster of hematological cancers originating from lymphoid tissues is more frequent in developed countries than in the developing world. It is the 10th leading cancer type in Sri Lanka and according to the recent Globacan cancer statistics in Sri Lanka, it has shown 2.9% mortality rate. In such a situation, early diagnosis, and effective monitoring of treatment used in NHL ought to be a huge task to increase the recovery of patients and to reduce mortality rate among them. The absence of a well-recognized system which governs the cell proliferation and survival in NHL baskets developing therapeutic targets. FMS like tyrosine kinase 3 (FLT3)/ligand (FL) system is responsible for the hematopoietic cell proliferation, cell survival and certain intracellular activities that takes place in the normal condition, especially for lymphoid cells. In this review, we study the presence of FLT3 (CD 135) on lymphoid cells in NHL to investigate the possibility of using FLT3/FL system for novel drug targets for NHL.

***Key Words*:** Non-Hodgkin Lymphoma, FLT3 receptor, FLT3 ligand, Prognosis

1. Introduction

1.1 What is Non-Hodgkin Lymphoma

Lymphomas are originating from lymphoid tissues and are mainly categorized into two groups as Non-Hodgkin's Lymphoma (NHL) and Hodgkin lymphoma (HL). A high percentage (~85%) of lymphomas is NHL occurring due to chromosomal translocations, infections, chronic inflammations, and another various factors since the exact etiology is unknown yet (Campo *et al*.,2011). Non-Hodgkin Lymphomas are graded as lower, intermediate, and high-grade depending on the aggressiveness of abnormal lymphoid cells (Canadian Cancer Society,2021). Although, most of the NHL cases are B cell origin while T cells and Natural killer (NK cells) cells also causing for some percentage of NHLs (Medscape,2021). Most common subtypes of B cell origin lymphomas are Diffuse Large B-cell lymphoma (DLBCL) and follicular lymphoma, and the common symptoms of NHL are the presence of swollen lymph nodes in groin/neck areas, fatigue, chest pain, abdominal pain/swelling, fever and weight loss. (Mayoclinic,2021).

1.2 Epidemiological survey on NHL

As stated in the lymphoma classification by World Health Organization (WHO), NHL is currently classified into more than 36 subtypes (>20 of B cell origin and > 15 of T cell origin) (Swerdlow *et al*.,2018). In the developed world, NHL is more common with high prevalence (e.g., USA, Australia, Europe) and the prevalence is low in most of Asian countries. The age standardized incidence of NHL was high in USA, Canada (14 per 100 000 person-years), Denmark and Sweden (10 per 100 000), while it is low in South Central Asia (3 per 100 000) around the year 2000. Usually, T cell neoplasms are rarer than B cell neoplasms, but it is reported as common in Asian countries than in other regions. Worldwide, NHL has got the tenth place from all type of diagnosed malignancies, whereas it ranks seven in the developed world (Boffetta, 2011). It was reported that the incidence of NHL is highest in Africa too (Globacan graphs, 2021).

According to 2010 statistics, lymphoma is a leading cancer type in Sri Lanka (The National Cancer Control Programme, 2021). It is mentioned that 5% of males and 3% of females have lymphoma. The age group 15-34 is highly affected by lymphoma (male -19.7%, female -7.3%). It revealed that the aging is a one possibility for lymphoma since most lymphoma cases were identified in 60 years' age (American Cancer Society, 2021). To our knowledge, the only published research paper on lymphoma in Sri Lanka reveals that their study group contained 87 B cell lymphoma, 26 follicular lymphoma and 25 peripheral T cell lymphoma patients out of 192 Non-Hodgkin lymphoma patients (Warawita *et al*., 2015).

1.3 Diagnosis of NHL

Currently, Non-Hodgkin lymphomas are diagnosed by physical examination of patient for swollen lymph nodes, imaging tests, investigating lymph node and bone marrow biopsies. X ray, computerized tomography (CT), Magnetic resonance imaging (MRI), and positron emission tomography (PET) are used as imaging techniques (Mayoclinic,2021). Different laboratory investigations performed as light microscopy, immunohistochemistry for biopsy samples and flowcytometric analysis for bone marrow and peripheral blood (The Royal College of Pathologists of Australia, 2021). Examination of biopsy is the only technique available to confirm NHL.

Excisional, incisional, needle and bone marrow biopsies and fine needle aspirations are used for histopathological studies to detect NHL. Advanced testing like chromosome studies (cytogenetics, fluorescent in situ hybridization, polymerase chain reaction) can be used for further diagnosis (American cancer society,2021).

1.4 Grading of NHL

A grading system that was introduced to NHL defines how aggressive or slow growing the malignant cells is likely to be (Cancer Net,2021). Patients with low-grade NHL may show the swelling of the lymph nodes, enlarged spleen, and liver. Patients with Intermediate and high-grade NHL may show the rapid growing and massive swelling of lymph nodes, enlarged spleen and liver and large abdominal masses (e.g., Burkitt lymphoma). Skin lesions are usually associated with sub types of T-cell lymphoma (Medscape,2021). Even though NHL is a fatal disease, some subgroups have shown good prognosis (Swerdlow *et al*., 2018). Early diagnosis of any cancer is more important to begin reliable treatments and to reduce morbidity and to increase the survival rate (World Health Organization,2021).

1.5 Treatment for NHL

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 immune modulators and colony-stimulating growth factors are used as medications in patient management. The combination of drugs named as CHOP; Cyclophosphamide, Doxorubicin, Prednisone, Vincristine is the most common chemotherapy combination treatment for aggressive NHL (Cancer Net,2021). However, the existing treatments for NHL are not impeccably effective, with degeneration of tumors, resistance to chemotherapy treatments and the possibility of occurring secondary malignancies are an unending concern (Johnston *et al*., 2010). Growing and dividing of cancer cells are blocked by chemotherapy. Radiotherapy that utilizes high energy X rays, also decimate cancer cells. These therapies have short term and long-term adverse side effects (Cancer Net, 2021). Finding of new treatments with prolong survival and less toxicity is a crucial medical need (Johnston *et al.,* 2010). Nowadays immunotherapy and targeted therapy are in demand which target cancer markers and tissue environment those contribute to the cancer growth (Cancer Net, 2021).

2. The use of bio markers

2.1 The role of biomarkers in the diagnosis of hematological malignancies

The current trend of medicine is to detect biomarkers (Eg. peptide, protein, glycoprotein, lipid, nucleic acid) for a particular disease or disease states (Mayeux *et al*., 2004). Biomarkers could be detected in the blood, other body fluids and tissues. It could provide an immediate assessment of a disease and response to treatment (Workman *et al*., 2006; Peng *et al*., 2009). Since the biomarkers can express during the whole range of disease or some stages of the disease (Mayeux *et al*., 2004) it is widely being used for early diagnosis, classification and grading of diseases to decide on patients for targeted treatments, to observe treatment response, and to spot disease reappearance. (Workman *et al*., 2006; Peng *et al*., 2009; Goossens *et al*.,2015; Mayeux *et al*., 2004)

Genetic biomarkers are available for most of the hematological malignancies. Philadelphia gene for chronic myeloid leukemia, JAK 2 mutation (*V617F*) for Polycythemia vera /granulocytic leukemia and HER2 receptor

for breast cancers are few of them (Hussaini ,2015). Bairy *et al*. (2003) has proposed that CA 125 is a well-known ovarian cancer marker as a prognostic factor for non-Hodgkin lymphoma. However, there is a nonexistence or non-detectable lymphoma specific immune biomarkers since lymphoid malignancies are a diverse group of tumors which shows different performances (Rimsza *et al*.,2016; Disanto *et al*.,2016). In such situations, it is inevitably a challenging task to find out specific biomarkers for lymphoma or for its subtypes.

2.2 CD antigens and hematological malignancies

Cell surface antigens are popular membrane markers recently used as biomarkers for most leukemias specially in myeloid lineage (Ding *et al*., 2017). Flowcytometry is the gold standard method used to identify cell surface antigens (Belov *et al*.,2001). Cluster of differentiation or CD antigen distribution patterns associate with sub types of leukemia and other diseases. They were categorized according to the expression as myeloid cells; CD13, CD15, CD33 and Stem cells; CD34, CD117 (Barber *et al*.,2019). Demonstrating cluster differentiation (CD) antigen on hemopoietic cells is a well recommended method to identify their type (Shahni *et al*., 2018; Naeim,2009). It has been investigated the presence of abnormal CD antigens on bone marrow cells of patients with acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL) and chronic lymphocytic leukemia (CLL). For example, aberrantly expression of antigens was detected in 32% of AML patients: CD5, CD7, CD64dim, CD10, CD117, CD25, TdT, 25% of ALL patients; CD3, CD13, CD33, HLA-DR, 36% of B CLL patients; CD11c, CD3 and CD10 (Shahni *et al*., 2018). Promyelocytic leukemia a subtype of AML has expressed CD9 and CD117 (Paietta *et al*., 2004).

3. FMS like tyrosine kinase 3 (FLT3)/FLT3 ligand (FL) system

3.1 Introduction on FLT3 (CD135) and FL system

FMS like tyrosine kinase 3 (FLT3) is the receptor tyrosine kinase expressed by immature blood cells and is vital for the normal maturation of stem cells and the immune system (Gilliland and Griffin, 2002). Also, this receptor is known as CD135 (Graf *et al*.,2004) and it was found in cells of the hematopoietic bone marrow microenvironment, including the cells like bone marrow fibroblasts, as well as in hematopoietic cell lines of myeloid, and B and T cell lineages (Brasel *et al*., 1995; Lisovsky *et al*., 1996). FLT3 ligand (FL) is a type I transmembrane (TM) protein that can be proteolytically processed and released as a soluble protein (Wodnar Filipowicz, 2003). The tyrosine kinase activity of the FLT3 receptor can activate by both the membrane-bound and soluble forms of FL and stimulate growth of progenitor cells in the marrow and blood by strongly synergizing with other hematopoietic growth factors and interleukins (Lyman *et al*., 1995; Lyman *et al*., 1994).

In healthy state, the development of myeloid derived cells and maturation of macrophages or dendritic cells have been studied (Gabrilovich *et al*., 2009). FLT3/FL system plays a major role in differentiation and homeostasis of myeloid cells and activates the transcription factors in STAT3 pathway which stimulate the expansion and function of myeloid cells (Rosborough *et al*., 2014). It was revealed that human FLT3 signaling prevents stem cell and immature cells from natural apoptosis by up-regulating of Mcl-1; and known to be an important survival factor for hematopoiesis (Kikushige *et al*., 2008).

3.2 FLT3 (CD135)/FL system and hematological malignancies

It is stated that FLT3 (present in various types of cell lines) and ligand for FLT3 receptor (FLT3 ligand or FL) which are functioning as growth factors may have a possible role in leukemogenesis (Meierhoff *et al*., 1995). Abnormal expression of FLT3 found in hematological malignancies (Tsapogas *et al*.,2017). Stimulated mutation in FLT3 receptor was found in AML but clinical prognosis of mutation is very poor (Gilliland and Griffin,2002). The mutation is common in most AML cases and some percentage of myelodysplasia (MDS) and ALL patients also have exhibited the mutation in FLT3 gene (Annesly and Brown,2014). It was noted that the significant expression of CD135 is associated with monocytic subtypes of AML(M4/M5), undifferentiated leukemia (FAB M0/M1/M2) on bone marrow cells (Graf *et al*.,2004).

3.3 FLT3/FL system and Lymphoma

Human FLT3 is mainly found in early myeloid progenitors and as well as in lymphoid progenitors (Kikushige *et al*., 2008; Noronha *et al*., 2016; Wells *et al*., 1996). It was identified that the few cell lines containing mutation of FLT3 antigen has also developed lymphoid diseases in mouse models (Lee *et al*., 2005; Grundler *et al*.,2005). FL acts as a circulating biomarker be conductive of useful information about tumor response and toxicity in patients undergoing standard chemotherapy and has a probable value in the development of individualized treatment approaches in lymphoma (Greystoke *et al*., 2011). The role of FLT3 ligand (FL) and dendritic cells (DCs) had been studied using murine lymphoma and melanoma cells and found that with the administration of FLT3 ligand (FL) elicited a reversible gathering of functionally active DCs in both lymphoid and non-lymphoid tissues (Esche *et al*., 1999).

4. Future directions

The JAK-STAT pathway is one of the most important pathways for the functioning of hemopoiesis (Staerk and Constantinescu, 2012) using various cytokines and growth factors. It also accomplishes leading acute cellular events, such as lactation and development of the immune system and mammary glands. As signaling pathways take place by gene regulation, a clear understanding of them involved during hematopoiesis is essential (Seif *et al*.,2017). The function of JAK-STAT pathway and the production of diverse forms of hematopoietic cells have been reviewed and the possible mutations in the pathway that leads to hematological malignancies (Eg. Polycythemia vera) also studied (Cardama and Verstovsek, 2013; Hammaren *et al*.,2019). Understanding a mechanism of a particular pathway in normal and abnormal state is important as the targeted drugs could be developed against its abnormal behavior. Seif *et al*., (2017) revealed that dysregulation of the JAK-STAT pathway and their regulators may lead to various immune disorders such as T cell disorders as it affects the development of T helper cells, so, the targeted strategies as promising therapeutic approaches in the treatment of T cell associated immune disorders could introduce (Seif *et al*.,2017). Bose *et al*., (2020) studied the therapeutic effectiveness of phytoconstituents as inhibitors of JAK/STAT signaling against cancer cell growth.

Since FLT3/FL system has already used to develop inhibitors against AML, similarly, broadening the investigations of FLT3/FL in NHL would facilitate better understanding of the possible pathways and it could be used as therapeutic targets against NHL.

5. Conclusion

In this review an attempt has been made to summarize the role of FLT3/FL in NHL and the potentials of augmenting the cell proliferation with FLT3/FL system. This information should be of value for better understanding of current trends and future perspectives of research in lymphoma.

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