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The involvement of oxidative stress in non-Hodgkin's lymphomas; a review of the literature

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ABSTRACT

Non-Hodgkin's malignant lymphomas are a heterogeneous group of hematological malignancies, characterized by a variety of clinical, morphological, histopathological, immuno-histochemical, molecular and evolutionary features. They represent a form of cancer that develops from the lymphatic tissue, as a result of the malignant transformation of B (85%) or T (15%) lymphocytes. Lymphomagenesis is described as a multi-stage process involving the mutation and proliferation of cell clones. Oxidative stress is defined as an imbalance of cellular redox status caused by the production of reactive oxygen species (ROS) and/ or by decreasing antioxidant systems that allows their accumulation in the cell. Small quantities of ROS are involved in physiological mechanisms such as cell growth and differentiation, cell signaling, antimicrobial defense, phagocytosis. Normally, cells are capable of defending themselves against ROS damage through various scavenger systems. On the other hand, excessive ROS contribute to various diseases such as carcinogenesis, ischemia, atherosclerosis, neurodegenerative diseases. Oxidative stress exerts noxious effects on the cell structures by inducing structural changes in membranes, lipids, proteins or DNA. The present review summarizes the latest findings in understanding the ROS-linked signaling pathways in the initiation of lymphomagenesis, disease progression, metastasis, as well as in the pharmacodynamics of specific treatments for this malignancy.

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Introduction

Non-Hodgkin's lymphoma (NHL) is the most frequent hematological malignancy [1]. The American Cancer Society has estimated 74,200 new cases of NHL for 2019 [2]. The incidence has doubled in the last 50 years, resulting from improved diagnostic techniques and access to medical care. Various classification systems have been developed, but three of them are most commonly used: the National Cancer Institute's Working Formulation (IWF), the Revised European-American Classification of Lymphoid Neoplasms (REAL) and the World Health Organization (WHO) classification [3-5]. The WHO modification of the REAL classification of NHL is based on cell lineage and morphology. In 2016, the World Health Organization's classification of lymphoid, histiocytic and dendritic neoplasms comprises B-line, T-line or Natural Killer (NK) malignancies, post-transplant lymphoproliferations and histiocytic and dendritic neoplasms, with two sub-divisions: precursor neoplasms and mature differentiated neoplasms [5]. Diagnostic and treatment methods have improved with this revised classification, bringing in the forefront the current cytogenetic and molecular biology data necessary for the most targeted therapeutic management. The natural history of these tumors shows considerable variation. From a clinical-evolutionary point of view, NHL are sorted into three classes: indolent (diffuse lymphocytic B-cell lymphoma, lymphoplasmacytic lymphoma, marginal zone lymphoma, grade I and II follicular lymphoma, Mycosis fungoid), aggressive (B-cell lymphomas: mantle cell lymphoma, grade III follicular lymphoma, large diffuse B-cell lymphoma, primitive mediastinal lymphoma and T-cell lymphomas: angioimmunoblastic, angiocentric, peripheral T-cell, intestinal T-cell, anaplastic with large cells) and very aggressive (lymphoma with B/T precursors,

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Burkitt lymphoma and other peripheral T-cell lymphomas). In their evolution, indolent lymphomas can progress to aggressive lymphomas. However, there is a paradox, as aggressive lymphomas have a better prognosis than indolent lymphomas [6,7].

Prognosis mainly depends on individual factors (such as age, comorbidities), lymphoma subtype and extent of lymph node involvement. For a better prediction of the outcome and management, the International Prognostic Index (IPI) and its variant were developed [8,9]. In addition to these factors, recent studies emphasize the importance of cytogenetic markers in the prognosis, as well as in the therapeutic strategies of NHL [10].

Discussion

Lymphomagenesis is a complex process resulting from the interactions between genetic and environmental factors. It involves a complex, multi-step process, characterized by a progressive clonal expansion of B-cells or T-cells and/or NK-cells. In the first stage, the proliferation is polyclonal under the action of certain risk factors (Table 1).

Table 1. Risk factors for NHL

➢ **Viral infections**
• Epstein-Barr virus is related with the endemic variant of BL [11];
• HTLV-1 causes adult T-cell lymphomas [12];
• Human Herpes virus-8 is associated with Kaposi sarcoma [13];
• Hepatitis B and C - DLBCL and splenic marginal zone lymphoma are the most frequent subtypes due to the infection with the hepatitis C virus [14];
➢ **Bacterial infections**
• *Helicobacter pylori* (HP) untreated and persistent infection has an increased risk of developing a primary gastrointestinal lymphoma [15];
• *Chlamydia psittaci* is responsible for ocular adnexal MALT lymphomas [16];
• *Borrelia burgdorferi* was reported in marginal lymphomas of the skin [17];
• *Campylobacter jejuni* in intestinal lymphomas [18];
➢ **Congenital immunodeficiency conditions**
• Ataxia-telangiectasia;
• Wiskott-Aldrich syndrome;
• Severe combined immunodeficiency disease;
➢ **Acquired immunodeficiency conditions**
• Chronic immunosuppressive treatment (cytostatic drugs, radiotherapy);
• Patients with Human Immunodeficiency Virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) can develop primary central nervous system lymphomas [19];
➢ **Autoimmune diseases**
• Rheumatoid arthritis;
• Sjogren's syndrome;
• Systemic lupus erythematosus;
• Hashimoto's thyroiditis is associated with primary thyroid lymphomas [20];
➢ **Occupational factors**: benzene, dyes, herbicides, pesticides [21-24];
➢ **Family history** of malignant hematological diseases and nutritional factors [25].

Later on, the mutant clone appears as a result of the lesions that affect proto-oncogenes or tumor suppressor genes. The activation of certain oncogenes offers the advantage of autonomous growth and expansion. These oncogenes can be activated by chromosomal translocations or suppressor tumor loci can be inactivated by chromosomal deletions or mutations. Specific chromosomal alterations are associated with significant changes in gene expression. Translocation (14;18)(q32; q21) produces the overexpression of BCL-2 protein which promotes lymphocyte expansion by inhibiting apoptosis. It is associated with follicular lymphoma (FL), but it has also been described in 30-40% cases of diffuse large B-cell lymphoma germinal center B-cell (GCB-DLBCL) [26,27].

The t(8;14)(q24;q32) involving the MYC oncogene which promotes cell proliferation and development is the most common chromosomal abnormality in Burkitt lymphoma (BL) [28]. The t(2;5)(p23;q35) affects the nucleophosmin (NPM) gene and the anaplastic cell lymphoma kinase (ALK) gene which are described in large cell anaplastic lymphomas occurring in 10-20% cases of pediatric lymphomas and in young adults under 30 years of age [29]. The t(11;14)(q13;q32) is present in most cases of mantle cell lymphoma (MCL) with mutant implications in the BCL-1 gene, leading to rapid cell proliferation [30]. Other mechanisms that involve the inactivation of tumor suppressor genes are linked to lymphomagenesis. It is well-known that the tumor protein p53 encoded by the TP53 gene represents a vital tumor suppressor. This activity is fulfilled through DNA repair, apoptosis, senescence, autophagy via transcription-dependent activity (TA) and transcription-independent activity (TIA) in the nucleus and cytoplasm [31]. Normal functions of these pathways are crucial for tumor suppression. Altered lymphocytes undergo p53-dependent apoptosis. Genomic instability caused by the dysfunction of this gene, along with other chromosomal alterations, allows B lymphocytes to escape immune surveillance, having a polyclonal evolution. Therefore, studies have demonstrated that TP53 mutations initiate and maintain the progression of lymphoproliferative disorders [32]. Moreover, TP53 mutations represent an independent prognostic marker of poor survival in DLBCL patients [33].

The purpose of the latest research includes a better understanding of the signaling pathways involved in lymphomagenesis. In the medical practice, most NHLs are of B-line. Proteins that play a key role in these signaling pathways are affected by the chromosomal changes. Recently, two types of aberrant Signal Transducer and Activator of Transcription (STAT) 3 and 5 have been described, as important effectors of cellular transformation and their connection with hematopoietic cancers [34]. Among NHLs, DLBCL is associated with high-level STAT3 expression and activation, especially the activated B-cell like (ABC-DLBCL). Studies have indicated that different subtypes of peripheral T cell lymphomas (PTCL) and NK lymphomas are linked by activating the mutations of STAT 3 and STAT 5B and increased phosphorylated STAT3 and STAT5B proteins which give growth advantage to transduced cell lines or normal NK cells [35]. STAT 5BN642H mutations has been reported in adult T cell-leukemia/lymphoma and γδ-T cell lymphomas, like hepato-splenic TCL, primary cutaneous TCL, monomorphic epitheliotropic intestinal TCL, while STAT 3 domain Y640 F and D661Y/V/H/N mutations have been found in T-large granular lymphocyte leukemia, NK, NK/T and adult T cell leukemia/ lymphoma [36].

What is known about the B cell receptor (BCR) signaling pathways in normal B-lymphocytes?

BCR is a signaling complex expressed by the most normal and malignant B lymphocytes. It is a transmembrane signaling complex involved in the proliferation, differentiation, adhesion or apoptosis of these cells [37,38]. Initially, it was considered that an inducible loss of murine BCR causes the death of peripheral B-cells. Subsequently, it was concluded that both ligand-independent activation in the absence of the receptor and the activation sustained by its presence are important in normal B-cell survival. It is thought that the chronic activation of the BCR pathways is responsible for various B-cell malignancies. Studies on B-line lymphomas, such as DLBCL, FL, MCL, and BL have shown major importance in the survival and proliferation of lymphocytes through BCR [39]. Receptor activation is dependent on nuclear factor Kappa-B (NF-kB) and PI3K mediated signaling pathways. Normally, NF-kB is involved in several stages of growth and differentiation of B and T lymphocytes, having a protective role on lymphocyte precursors, ensuring an anti-apoptotic role against tumor necrotic factors (TNF-α) [40]. Constitutional mutations of BCR at immunoglobulins α and β levels have been identified in primary DLBCL, especially in ABC-DLBCL expressing high levels of NF-kB activity and associated with a poor outcome [41]. These mutations are not the only ones which increase the cellular response to BCR activation. Studies demonstrate the existence of additional mutations, such as CARD11 mutation which ensures the activation and potentiates NF-kB activity [42,43].

Many studies have evaluated the role of Wnt signaling pathways in carcinogenesis [44,45]. Normally, this signaling pathway is involved in cell proliferation, differentiation, survival and apoptosis, as well as, angiogenesis. The Wnt signaling pathway is characterized as canonical and non-canonical, B-catenin-dependent and B-catenin-independent. In the absence of the ligand, B-catenin is destroyed by a complex. It binds to receptor-transmembrane frizzled proteins (Fz proteins) and low-density lipoprotein receptor-related protein 5/6 (LRP 5/6) and reaches the nucleus. Through T-cell factor and lymphoid-enhancing factor (Tcf/Lef), transcription factors produce cellular changes. Several studies have documented its involvement in carcinogenesis, leukemogenesis, as well as in lymphomagenesis (DLBCL, BL, and MCL) [46-48].

For a better understanding of the molecular mechanisms underlying the pathogenesis of lymphomas, the researchers studied how signaling pathways potentiate one other. MiR-101 is associated with proliferation, migration, invasion and cell apoptosis [49,50]. Its role in carcinogenesis was demonstrated by various studies [51,52]. Recently, Huang et al. developed a theory

according to which miR-101 expression is down-regulated in DLBCL [53]. Therefore, low levels of miR-101 in patients with DLBCL are correlated with tumor progression by targeting KDM1a pathway.

The involvement of oxidative stress in NHL

Involvement of oxidative stress in lymphomagenesis has been the main aim of several studies [54-57]. Oxygen participates in energy production, a process that takes place in the mitochondria. Following this process, intermediate forms of reactive oxygen (ROS) and nitrogen species (RNS) appear into the body within the basal cell metabolism, but also as a result of the exposure to exogenous factors such as pollution, cigarette smoke or hyperoxia [58]. Numerous enzymes participate in the process of producing free radicals (FR), including nicotinamide-adenine-dinucleotide phosphate (NADPH), succinate dehydrogenase (SDH), cytochrome c reductase, cytochrome b5, monoamine oxidases (MAO-A and MAO-B), pyruvate dehydrogenase complex (PGDH). A variable number of endogenous antioxidant defense systems have the ability of neutralizing ROS. These antioxidant systems include enzymes and non-enzymatic systems [59-61]. Oxidative stress is a biochemical imbalance of cellular redox status caused by the production of reactive oxygen species and/or by decreasing the antioxidant systems that allow their accumulation in the cell [62]. Small quantities of ROS intervene in the physiological mechanisms, such as cell growth and differentiation, cell signaling, antimicrobial defense, phagocytosis. In exchange, large quantities produce pathological processes such as inflammation, carcinogenesis, ischemia, atherosclerosis, neurodegenerative diseases and allergies [63-66].

It is considered that inflammation is a protective mechanism of the body against cell destruction, but there is a correlation between NHL, inflammation and oxidative stress. Sustained antigenic stimulation promotes the clonal proliferation of lymphocytes by inhibiting apoptosis and the activation of NF-kB by pro-inflammatory cytokines and growth factors [67]. Clonal proliferation is also supported by elevated levels of B lymphocyte growth factor (BAFF/BlyS) as shown in some autoimmune disorders, but also in FL [68]. Oxidative stress can activate a variety of transcription factors that lead to the expression of the genes involved in chronic inflammation, increase the level of pro-inflammatory cytokines (mainly interleukin-1), stimulate and activate B lymphocytes to produce antibodies and alter cellular DNA [69]. Recent studies have shown that genetic variations of pro-inflammatory cytokines (TNF-α, interleukin-10) double the risk of DLBCL, a subtype particularly associated with autoimmune diseases, as demonstrated by other studies [70]. Genomic instability in B lymphocytes, as well as the activation of a transcription factor, NF-kB, give an advantage of autonomous growth and expansion to mutant lymphocytes [71]. Therefore, chronic infection disrupts cell growth and survival [72].

Genes controlling the redox homeostasis are important 'actors' in lymphomagenesis, therefore in a multi-center study, performed on 1,172 cases of NHL, ten oxidative stress genes (AKR1A1, AKR1C1, GPX, MPO, NOS2A, NOS3, OGG1, PPARG, SOD2, CYBA) were analyzed and it was established that the genetic variations of these genes lead to a high status of ROS, thus increasing the risk of NHL, especially DLBCL, one of the most common and aggressive subtypes of NHL [73]. Based on this idea, subsequent studies conducted on the Korean population group highlighted the link between the gene polymorphism involved in the DNA repair and the risk of NHL, as follows: four gene genotypes (XRCC1 399 GA, OGG1 326 GG, BRCA1 871 TT and WRN 787 TT) have a low risk of NHL, while MGMT 115 CT genotype is associated with an increased risk. Regarding the MDR1 gene (multidrug resistance 1), genotype 1236 CC is associated with a low risk, while genotypes 3435 CT and TT have an increased risk of NHL [74].

Oxidative stress defined as an imbalance between oxidants and antioxidants, in favor of the oxidants, destroys nuclear and mitochondrial DNA [75] and favors the appearance of specific markers such as 8-hydroxy-2-deoxyguanosine (8-OHdG) [76], protein carbonyl groups as a marker of protein oxidation [77], malondialdehyde (MDA) and F2-isoprostanes as markers of lipid peroxidation [78,79]. Mezayen et al. evaluated the activity of oxidant/antioxidant status in patients with NHL, before and one month after the specific cytotoxic regimen and concluded that there was an increase in MDA and a reduction in SOD levels, thus suggesting that chemotherapy destroys the balance [80]. High-levels of 8-OHdG in tumors, blood samples and urine represent a promising marker for predicting the prognosis of cancers [81-84]. Similarly, other scientists have shown a correlation between elevated 8-OHdG levels and an increased risk of developing malignant hematological diseases [85] and highlighted that elevated urinary levels of 8-OHdG are associated with a poor prognosis in patients with FL [86]. Guanosine hydroxylation is the result of normal metabolism processes and environmental factors, such as exposure to cigarette smoke, asbestos, heavy metals or polycyclic aromatic hydrocarbons. For this purpose, a study conducted by Fenga et al. in 2017 demonstrated that 8-OHdG can be used as a non-invasive marker of early genotoxic DNA damage following the exposure to low doses of benzene [87]. The conclusion was that benzene metabolism (through cytochrome P450) induces FR that affect the oxidant/antioxidant balance, increases the level of ROS and produces increased toxicity, affecting cell proliferation, differentiation and apoptosis (through p38-MAPK signaling pathways, SAPK/JNK, STAT3).

Oxidative stress is involved in various stages of the cell cycle, by activating cell signaling pathways, including tumor cell proliferation, migration and increased tumor cell pro-angiogenic factors. DNA-oxidative damage via moderate levels of ROS lead to several repercussions: it causes genomic instability, favors BCR and oncogenic kinase signaling, promotes B-cell survival and facilitates tumor progression [88]. On the contrary, high levels of ROS produce cell death. Eliminating cellular mechanisms that maintain efficient ROS levels might turn the balance of protumorigenic ROS activity toward cancer cell death. The role of antioxidant systems in carcinogenesis has been debated over the years. However, it has now been established that exaggerated antioxidant responses, regulated by specific signaling pathways, have an important impact in lymphomas. For example, various studies demonstrated that there is a correlation between rs1001179 polymorphisms and lower catalase activity which interferes with the response to oxidative stress and enhances tumorigenesis [89,90]. Catalase is an important endogenous antioxidant system that decomposes H_2O_2 into oxygen and water. In 2017, Wang et al. conducted a meta-analysis which studied the correlation between GPX-1 and cancer risk [91]. Their conclusion was that there are specific polymorphisms of this enzyme family, especially for patients with TT/CT genotype who have an increased risk of bladder cancer and brain tumors, but no evidence was found between these polymorphisms and NHL.

It is known that uric acid is the final product of purine metabolism, important components of nucleic acids and coenzymes that can be synthesized in the body or can be obtained by eating certain foods. Over the years, arguments have been brought to support the role of uric acid as an antioxidant [92,93]. This fundamental idea is supported by another study which has suggested that uric acid improves indomethacin-induced enteropathy in mice through its antioxidant effect [94]. A study conducted in 2015 assigned the link between p53 and a uric acid transporter – SLC2A9 or GLUT9 – which functions as an antioxidant, capable of protecting cells against ROS [95].

Increased ROS levels in certain tumor cells due to metabolic changes or classical chemotherapeutic use, rely on targeting specific antioxidant pathways. Thioredoxin (Trx) and GSH represent two antioxidant systems with an important role in the regulation of cellular redox homeostasis. The researchers have tried to utilize the pharmacological inhibition of antioxidant enzymes or other ROS-inducing molecules to describe the specific antioxidant defense, but with limited efficacy in monotherapy regimens. Trx family members represent a major antioxidant system, containing Trx 1 protein, thioredoxin reductase (TrxR) and NADPH. For instance, in BL cell line models two specific compounds were utilized, i.e. SK053 and adenanthin, with specific targets on Trx, TrxR and periredoxins (Prx) 1 and 2, two H_2O_2-scavenging enzymes [96,97]. These molecules trigger ROS-induced extracellular signal-regulated kinase ½ (ERK1/2) activation and induce apoptosis. Auranofin, a gold complex, is the inhibitor of TrxR with antitumor activity in the preclinical models of chronic lymphocytic leukemia [98] and classical Hodgkin lymphoma [99]. Regarding GSH, elevated levels are associated with different types of cancer and chemoresistance [100]. Therefore, pharmacologists paid attention to a GSH-depleting agent, buthionine sulfoximine against cancer progression and chemoresistance, which is more effective in combinations with other therapeutic drugs [101].

The main subtypes and their specific features related to oxidative stress

Diffuse large B-cell lymphoma is the most frequent aggressive B-cell NHL [102]. Flow-cytometry identifies typically B-cell antigens like CD19, CD20, CD22, CD79a and CD45. Molecular features have a prognostic impact. C-MYC is a proto-oncogene on the chromosome 8q24, which confers the advantage of proliferation and growth of malignant cells when deregulated. Translocation (14;18) is associated with the overexpression of BCL-2, an antiapoptotic factor, which along with c-MYC, characterizes double-expresser lymphoma (DEL), with intermediate prognosis. When the deregulation of BCL-6 oncogene is added, the DLBCL turns to aggressive triple-hit lymphoma [103]. Four distinct genetic subtypes of the disease with recurring mutation have been recently identified by Schmitz and colleagues: MCD, BN2, N1 and EZB [104]. The MCD subtype is characterized by the presence of MYD88 and CD79 mutations, the N1 has NOTCH1 mutations, the BN2 by BCL-6 and NOTCH2 mutations and the EZB subtype has EZH2 and BCL2 translocations. These facts have an important clinical outcome, the BN2 and EZB subtype have good prognoses. Genetic mutations are not the only ones responsible for malignant evolution. As demonstrated, oxidative stress can initiate lymphomagenesis, but also the progression of the disease. A study that evaluated oxidative stress in DLBCL patients via the Free Oxygen Radical Testing (FORT) for FR and via the Free Oxygen Radical Defense (FORD) for the antioxidant status has concluded that patients with advanced stage DLBCL have a higher level of FORT and a decreased level of FORD which demonstrates that ROS are involved in NHL pathogenesis [72]. Tumors in patients with advanced disease and poor prognosis have deregulated the expression of certain ROS-metabolizing enzymes and extended pro-oxidant phenotype. According with these findings, Kinowaki et al. demonstrated the link between the overexpression of GPX4 in DLBCL and worse prognosis [105]. GPX4 is an intracellular antioxidant enzyme which prevents ROS-induced cell death. Therefore, an antioxidant treatment of advanced tumors

may help patients manage oxidative stress conditions. The Trx system defends both normal and malignant cells against oxidative stress [106]. However, the overexpression of Trx-1 gives cancer cells the advantage of growth, proliferation, survival and it also correlates with drug resistance, as reported in DLBCL-derived cell lines when compared to normal B cells, using Western blotting and real-time PCR [107]. But, the latest studies have shown a new possible hope by using pro-oxidant therapies to urge cancer cells toward death with promising aspects in B-cell malignancies. Therefore, Wang and colleagues have established that the down-regulation of Trx-1 sensitized lymphoma cells to chemotherapy regimens [108]. According to this idea, cells lacking Trx are more sensitive to ROS due to reduced proapoptotic activity of Forkhead box protein O1 (FOXO1) [109]. Trx reduces the bonds between FOXO1 and p300, formed as a response to oxidative stress. The depletion of Trx facilitated p300-mediated acetylation of FOXO1 and mediated cell death. These findings underline the role of Trx in the pathogenesis of DLBCL and are a solid argument for therapeutic exploitation. Recent studies have evaluated the involvement of the second group members thioredoxin-domain-containing (TXNDC) proteins 2,3 and 6 in DLBCL and demonstrate that these proteins are all expressed in testicular and systemic lymphomas with clinical importance [110]. This study included a limited number of cases (28 de novo confirmed systemic DLBCL and 21 testicular DLBCL) so, further investigations are needed. An interesting drug-resistance mechanism involving antioxidant enzymes was reported in ABC-DLBCL, with chronic activation BCR signaling. In these DLBCLs, the activity of STAT3 led to the upregulation of antioxidant enzyme SOD2 mitochondrial and mediated doxorubicin resistance. The use of STAT3 inhibitor oppressed SOD2-dependent resistance mechanisms and restored doxorubicin sensitivity in preclinical models [111].

Grade I and II follicular lymphoma is an indolent B cell lymphoproliferative disorder of transformed follicular center B cells, while grade III is an aggressive NHL. In FL, 85% of the cases have t(14;18) which results in the overexpression of the BCL-2 protein. Recent studies have developed a theory according to which this translocation can also be identified in normal cells, so it is considered that additional mutations are needed to produce neoplasia, such as the methyl transferase H3K27 EZH2 mutation, recognized in 27% of FL [112]. There is a particular subtype of FL, the pediatric form, which does not describe the BCL-2 rearrangement and which, according to the 2016 WHO classification, has a high possibility of curability [113]. The involvement of oxidative stress in this subtype has recently been demonstrated [84]. Peroja and colleagues evaluated redox-state regulating enzymes Prx I-VI and Trx in untreated FL [114]. In a cohort of 76 histologically confirmed FLs, the expression of Prx I-VI, Trx and the oxidative stress marker, nitrotyrosine, were assessed. The immuno-histochemical results were correlated with clinical prognostic factors such as disease-specific survival, progression-free survival and overall survival. Their findings suggested that high Prx levels have a good disease-specific survival and overall survival which exhibit a protective role in FL patients.

Translocation (11;14) is present in most cases of *mantle cell lymphoma* with mutant implications in the BCL-1 gene. There are also forms in the absence of cyclin D1, but the overexpression of cyclin D2, with a better prognosis, is independent of the risk factors [115]. Zhang and colleagues correlated B-cell-specific transcription factor (BACH2), a tumor suppressor factor with hypoxic environment in MCL [116]. Their explanation lies in the fact that oxygen depletion produces an increased level of ROS and excessive heme, which are harmful to the body. Excess heme causes BACH2 degradation in B lymphocytes. Under hypoxic conditions, HIF-1α independently produces the downregulation of BACH2. Under these aspects, the survival of cancer cells in MCL is ensured by the downregulation of BACH [117].

Mucosa-associated lymphoid tissue lymphoma is an indolent, multifocal lymphoma. Between 4-20% are gastric MALT lymphomas, strongly associated with the HP infection. There is a loop between HP infection-chronic inflammation-ROS release and lymphomagenesis initiation [118]. The malignant transformation of B lymphocytes occurs as a result of t(11;18), (1;14), (14;18) during the HP infection, via the activation of NF-kB [119]. If the tumor's proliferation is limited to the mucosa and it is closely related to the infectious agent, sometimes it is sufficient to eradicate the infection by means of antibiotic therapy in order to stop lymphomatous proliferation. Studies have shown that t(11;18) is associated with antibiotic resistance and a worse prognosis [120].

Small lymphocytic lymphoma is a neoplasm of mature clonal B lymphocytes with a typical immunophenotype expression of CD5 and CD23 surface antigen and mutated variable regions of the immunoglobulin heavy-chain (IGHV) genes in 50-70% of the cases [121]. The genomic background provides specific chromosomal abnormalities with prognostic importance, such as: 17p or 11q deletion indicate poor prognosis, whereas 13q deletion represents a better prognosis [122]. The role of oxidative stress in the pathogenesis of this malignancy has been discussed in several studies that have shown correlations between the level of oxidative stress markers and cytogenetic changes [123,124]. Supporting this idea, some researchers discovered that high levels of MDA, protein carbonyl and decreased levels of antioxidants (SOD and catalase) were associated with 17p deletion and worse clinical presentation [125].

Oxidative stress and NHL management

The most important findings were pointed out on the involvement of oxidative stress in the initiation and progression of NHL, but it seems that it also intervenes in the mechanisms of action of some cytostatic agents. Chemotherapeutic regimens included drugs that destroy cancer cells through different mechanisms. One possible mechanism is related to the redox cellular status. The adjustment of oxidative stress is a relevant factor in both tumor development and the responses to anticancer therapies. As seen before, ROS can stimulate tumor formation by inducing DNA mutations and pro-oncogenic signaling pathways. On the other hand, high ROS levels are usually harmful to cells and may represent a barrier for tumorigenesis. A large number of chemotherapeutic drugs exert their activity through high levels of ROS by interfering with antioxidant systems or ROS inducing pathways [126]. Cyclophosphamide is an alkylating agent used in the treatment of various cancers [127] which generates cell death through its 2 metabolites, acrolein and phosporamide [128]. Acrolein is responsible for the decreased overall antioxidant capacity and the activation of the stress-signaling MAP-kinases JNK, p42/44 and p38 pathways with an increased production of ROS and subsequently oxidative stress causing DNA damage, lipid peroxidation, increased permeability of the mitochondrial membrane, release of cytochrome C, activation of caspase-3 and apoptotic cell death [129]. Studies have shown that doxorubicin causes cell death by increasing ROS levels via p53-dependent manner, but it also promotes the accumulation of a transcription factor, FOXO3, which activates two apoptotic genes (Noxa and BIM) with subsequent release of cytochrome C and ROS [130]. The anti-CD20 antibody, rituximab, has a proapoptotic effect by downregulating BCL-2 (an antiapoptotic factor) and inhibiting survival p38 MAPK signal pathways. Its cytotoxic effect is also due to a complement-dependent process that generates increased amounts of ROS [131]. Glucocorticoids have a considerable effect on oxidative stress which depends on the duration of the treatment. These hormones increase the metabolic rate, mitochondrial membrane potential and mitochondrial oxidation, which in turn increases the production of superoxide, H_2O_2 and hydroxyl radicals leading to a state of cellular oxidative stress which causes oxidative damage to the DNA, protein carbonyl formation and membrane lipid peroxidation [132]. The benefits of radiotherapy (RT) for lymphomas have been well documented for many years. The RT concept is based on the alteration of DNA cancer cells, which can be done directly and indirectly [133]. The appearance of ROS is incriminated for indirect DNA damage, both in cancer cells exposed to the area of irradiation and in healthy cells at a distance from it. The penetration of heavy particles of ionizing radiation in the body produces the breakdown of chemical bonds and, on the other hand, the water which represents half of the body weight, is split by ionizing radiation, these mechanisms favoring the assimilation of hydroxyl ROS. However, there is a thin line between the useful level and the harmful level of oxidative stress in cancer treatments. When pro-oxidant treatment is used, malignant cells generate DNA oxidation, proteins oxidation and lipid peroxidation being the cause of the increased tumor burden. Some of the antioxidants, such as vitamin C, can act both as antioxidants and pro-oxidants [134]. The pro-oxidant effect of vitamin C was observed at high doses, having an anticancer role. Ascorbate produces large amounts of H_2O_2 which activates proapoptotic signaling pathways, causes DNA damage and ultimately, cell death. Further evidence has been provided that targeting the antioxidant capacity of tumor cells can have a reliable therapeutic impact [135,136].

Nowadays, antioxidants are in the spotlight as an emerging solution to various disorders, such as cardio-metabolic disorders, solid and blood cancers via reducing the oxidative stress and the inflammation levels, e.g., increasing TAC and SOD and decreasing MDA, TNF-α and C-reactive protein concentrations, and pathogenic links between the antioxidant levels in the serum and the development of malignancies has been demonstrated [137-141]. To this regard, recent studies have focused on the effect of melatonin (MLT) in different diseases [142]. MLT is a natural hormone of the pineal gland. MLT activates MT1 and MT2 receptors and takes part in learning, memory and neuroprotection [143]. Besides its role in maintaining our wake-sleep cycle, melatonin may have anticancer activity through antiproliferative, antioxidant and immunostimulant effects via different pathways [144,145].

Yan et al. demonstrated anti-tumor activity in Hodgkin's lymphoma by inhibiting cell proliferation and by promoting apoptosis via the increased expression of LC3-II and the decreased p62 proteins [146]. Knowing its anti-inflammatory and anti-oxidant effects, it was concluded that this molecule may represent an adjuvant treatment in several types of cancer. The beneficial effect has been reflected both in the quality of life and control over the disease (growth, size, effectiveness of chemotherapies) [147,148]. The data coming from our research group which evaluated the involvement of oxidative stress in lymphoproliferative, e.g., chronic lymphocytic leukemia and DLBCL, and myeloproliferative neoplasms, e.g., essential thrombocythemia, pointed out that the aforementioned malignancies are associated with increased reactive oxygen species levels and reduced antioxidant capacity [149-152].

Highlights

- ✓ Lymphomagenesis is associated with increased oxidative stress levels.
- ✓ Oxidative stress can also be involved in the action of several chemotherapeutic drugs.
- ✓ The involvement of oxidative stress has been studied in DLBCL, FL, MCL, MALT and small lymphocytic lymphomas.

Conclusions

The current evidence suggests that oxidative stress is involved in lymphomagenesis, genetic instability, disease progression and NHL management. Further studies are therefore necessary to evaluate if and how oxidative stress-modulating therapies can influence these processes.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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