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Crosstalk between hypoxia and inflammation in non-Hodgkin lymphoma

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Abstract

Tumor hypoxia is a well-known biological circumstance that has an impact on cancer growth and metastasis. This phenomenon is associated to poor patient outcomes, particularly in patients with non-Hodgkin Lymphoma. As the tumor mass grows, aggressive lymphoid malignancies necessitate a constant increase in perfusion which activate the hypoxia-inducible factor HIF-1 α . HIF-1 α is an important regulator that is widely discussed in various studies and pathological states which influence the expression of several genes through transcriptional regulation including metabolism/respiration, cell cycle, apoptosis, proliferation, angiogenesis, and others that may favor tumor growth. Tumor hypoxia also induces the expression of other important regulators such as microRNA-210 (miR-210) and Nuclear Factor Kappa B (NF- κ B) which propagate the tumorigenesis process. This article reviewed the molecular mechanisms of how HIF-1 α correlates with NF- κ B and other factors in non-Hodgkin Lymphoma patients.

Key words: non-Hodgkin Lymphoma, tumor hypoxia, HIF-1 α , miR-210, NF- κ B

Introduction

Non-Hodgkin's lymphoma (NHL) is a malignant disorder that arises from cells of the immune system and manifests primarily as lymphadenopathy or solid tumors. The classification system of non-Hodgkin's lymphoma is complex and continues to evolve, with more than 50 different subtypes listed in the most recent World Health Organization (WHO) classification. Over the past decade, there have been a number of changes in the knowledge pertaining to non-Hodgkin's lymphoma, including a new subtype classification that demonstrates a better understanding of the biology of diffuse large B-cell lymphoma (DLBCL). DLBCL itself, in addition to constituting the largest population of NHL, also comprises a heterogeneous group of aggressive lymphoid neoplasms originating from malignant B-cell transformation in the germinal center, which exhibits a distinct genetic, phenotypic, and clinical behavior [1-3].

The new WHO guideline recommends defining the molecular subset in the diagnosis of NHL, following an increased understanding of the impact of genomic changes on the biology and prognosis of the disease. In the revised WHO classification, the starting point for classifying aggressive B-cell lymphoma is using a pathological presentation with one of the following morphological descriptions: blastoid, Burkitt lymphoma (BL), DLBCL, or intermediate between DLBCL/BL. The second step is cytogenetic testing or fluorescence in situ hybridization (FISH) for MYC, BCL2, and BCL6 rearrangements. If the MYC is rearranged with BCL2 or BCL6 (or both), it is classified as High-Grade DLBCL with Double-Hit Lymphoma or Triple-Hit Lymphoma subtypes [1, 4].

The tumor microenvironment (TME) plays an important role in tumor properties. TME consists of blood vessels, lymphatic vessels, fibroblasts, immune cells, and extracellular materials. The function of and interaction between cancer cells and these aforementioned cells determine the tumor properties, seeing as how during tumor initiation and progression, both the tumor and its TME undergo a state of limited oxygen (hypoxia) and nutrients [5].

Tumor aggressiveness is determined by adaptation mechanisms and certain other mechanisms in hypoxic tissues, which are controlled by various transcription factors and other mediators. Lymphomas with indolent features and low proliferative activity rely solely on the circulation to maintain adequate blood supply. Meanwhile, more aggressive lymphoid tumors require continuously increasing perfusion as the tumor mass progressively increases. Large tumor mass and intra-tumoral pressure cause poor tissue perfusion. Significant oxygen depletion will result in hypoxic areas which will eventually turn into focal necrosis, which is commonly seen in DLBCL-type aggressive lymphoma. Whether the aggressive feature of lymphoid tumors is directly related to the hypoxic state remains to be further studied [6]. This hypoxic process then interacts with several other pathways, one of which is inflammation, and predisposes to hallmarks of cancers.

The Role of Hypoxia in tumor progression

In the 1950s, Tomlinson and Gray first discovered the hypoxic state in human tumor tissue [7]. By definition, tissue hypoxia is a state of low oxygen content in tissues below the physiological level (oxygen levels between 5–10 mm Hg) which may cause disturbances in the maintenance of

normal cell function. Generally, pO₂ levels below 10 mmHg will lead to activation of HIF-1 α and other adaptive molecule pathways to maintain cellular function [8].

Hypoxia might also occur in inflamed, infected, or damaged tissues. Hypoxia will arise if there is an imbalance between increased cell activity and decreased tissue perfusion [6]. The cell cycle itself will begin to be disrupted and slowed down at pO₂ < 1 mmHg, in which hypoxia will then induce transcriptional, post-transcriptional, and post-translational changes, thus affecting the cell's survival and apoptosis ability [9]. Hypoxia may also occur in tumors with rapid cell proliferation. Rapidly growing tumors demand more nutrients and oxygen supply from normal blood vessels, thus when the condition is not met, the tumor then becomes a hypoxic tissue. This hypoxic state will further promote regulation by increasing the production of angiogenic factors from the hypoxic tumor site [10].

Aggressive growth of cancer and stromal cells will lead to the development of an irregular, poorly-structured, leaky, and tortuous neovascularization. Temporary occlusion of these new abnormal blood vessels may result in impaired blood flow within the tumor tissue, resulting in an acute hypoxic state and impaired tissue perfusion. Tumor hypoxia also has a crucial impact on cancer growth and metastasis, as it causes cancer to develop resistance to chemo-radiotherapy – therefore tumor hypoxia has long been recognized as a major obstacle for cancer therapy [7].

When a tumor is hypoxic, it must adjust its metabolism to adapt to this oxygen-deprived microenvironment [12]. The abnormal structure and function of the tumor microvasculature will lead to an increase in fluid leaks to the tumor's extravascular space, thereby increasing blood flow and oxygenation resistance [13]. As a consequence of tumor hypoxia, at the cellular level,

the tumor will also adjust through metabolic adaptations through an important regulator, namely the activation of hypoxia-inducible factors (HIFs), which play an important role at the cellular level to divert oxygen phosphorylation in the form of anaerobic glycolysis [6, 14]. Cancer cells will also undergo other genetic alterations in adaptation to prevent hypoxia-induced cell death, which is favorable for the growth of malignant cells (fig. 1) [5, 7].

Hypoxia and HIF

Hypoxia-inducible factor (HIF) is an important regulator that is widely discussed in various studies and pathological states. In recent years, significant advances have been made in our understanding of the molecular changes that occur in adaptation to hypoxia and the discovery of HIF as a central element of this process [15]. The HIF transcription factor family consists of HIF-1, HIF-2, and HIF-3. All of these factors contain an oxygen-sensitive alpha subunit (HIF1- α , HIF2- α , or HIF3- α) and are stable in the presence of sufficient oxygen. Hypoxia-inducible factor-1 alpha (HIF-1 α) is a transcription factor that is continuously expressed by cells but will be degraded in a way that depends on oxygen availability, where its function is to influence the expression of several genes through transcriptional regulation [16].

HIF-1 α is expressed and detected in immune cell populations such as macrophages, neutrophils, dendritic cells, T-cell lymphocytes, B-cell lymphocytes, and immune lymphoid cells (ILC1, ILC2, and ILC3). HIF-1 α is the most standout HIF and the most common HIF expressed in all tissues, whereas HIF-2 α is expressed especially in the heart, lungs, kidneys, and placentas. Under normal tissue oxygenation, HIF-1 α or HIF-2 α will be hydroxylated by the prolyl hydroxylases (PHD) and bound to von Hippel-Lindau protein (vHL) which will be degraded to

ubiquitin-proteasomal molecules. When the PHD is not active, VHL will fail to bound to HIF-1 α because PHD will be interrupted in mediating HIF-1 α hydroxylation. Another factor that plays a role in this process is the HIF-1 inhibiting factor (FIH1) [5–7]. Age also affects the stabilization of HIF-1 α concentration through the activation of SIRT1 pathway, a member of the sirtuin group that declines with age. In the nucleus, this decline of SIRT1 concentration triggers the stabilization of HIF-1 α concentration, resulting in its activation [5, 6, 15, 17].

During hypoxia, HIF-1 α is not hydroxylated, but transformed into a more stable form and bound to abundant gene promoters called Hypoxia Response Element (HRE). As a consequence, the transcription processes that are HIF-1 α -dependent will affect the vast cell adaptation processes, including metabolism/respiration, cell cycle, apoptosis, proliferation, angiogenesis, and others that may favor tumor growth [16, 18, 19]. It is specifically mentioned that there are 4 hydroxylation enzymes, which are prolyl-hydroxylases (PHD)-1, PHD-2, PHD-3, and *asparagine-hydroxylase Inhibiting-factor* HIF (FIH) that contribute to the post-translational regulation of hypoxia and inflammation. These 4 enzymes also play a role in the stability of the α unit in-HIF. Both FIH and PHD need oxygen as a cofactor, thus in a hypoxic state, both enzymes will be inactivated, causing HIF to become stabilized (tab. I) [20].

HIF-1 α is the main regulator of gene transcription during cellular hypoxia and controls more than 200 gene expressions. Genes that are regulated by HIF-1 α affect various cellular processes including glucose transportation, cell metabolism, angiogenesis, erythropoiesis, vascular tone, cell proliferation, apoptosis, and extracellular matrix metabolism. Clinically, the increase of HIF-1 α protein is correlated with a poor prognosis in most of the studies conducted

on solid tumors [23]. This is very interesting as there are a vast amount of research conducted to overcome tumor hypoxia, especially on drugs with an ability to inhibit HIF [24].

With the number of genes known to be the target of HIF-1 α , attention is focused on protein products as endogenous markers of tumor hypoxia. Research on the contribution of hypoxia to treatment resistance has also been extensively conducted in the field of radiation oncology, where adequate oxygen levels in tumors are needed to create maximum cytotoxic effects. Indirectly, hypoxia-induced gene and proteomic changes can have an important impact on radiation resistance by altering proliferation kinetics, and cell cycle position, inhibiting apoptosis, angiogenesis regulation, and altering cellular metabolism by increasing anaerobic glycolysis [25].

Another important thing that occurs in hypoxia in addition to the activation of the hypoxia pathway is, as shown by some recent studies, an increase in communication between tumor cells and TME through extracellular vesicles (EV) secreted by tumor cells. In recent times, studies of EVs, especially exosomes (one of the smallest types of extracellular vesicles) have demonstrated an increase in exosomes during hypoxic state. These exosomes contain several proteins, RNA, and DNA that serve as messengers for cell communication, both locally and environmentally-distant. *Non-coding* RNA contained in these exosomes will be delivered to the recipient cell to regulate several genes that include tumor growth, invasion, or metastases [26].

Exosomes are extracellular vesicles derived from the endosome, measuring 30–100 nm, and are an invagination of the cell membrane, resulting in lipid bilayer cell walls. Tumor cells secrete more exosomes than normal cells. The presence of various genetic materials such as

DNA, mRNA, miRNA, other NC-RNA, proteins, growth factors, and others carried by these exosomes, makes them an important tool used by cells to communicate between cells and with surrounding tissues. Exosomes are secreted by both normal and pathological cells and can be found in all bodily fluids; making the liquid biopsy approach a new breakthrough in diagnosis and prognosis. Additionally, this explains the various pathogenesis mechanisms, including cancer resistance [26].

A breast cancer study by Wang showed that the hypoxic state causes an increase in HIF-1 α and leads to an increase in the number of microvesicles, as well an increase in invasion and metastasis in breast cancer [27]. A study conducted by King showed that breast cancer cells that experience hypoxia have increased exosomes and miR-210 as the target of HIF-1 α [28]. An *in vitro* study by Tadokoro et al. in leukemia cells with hypoxia demonstrated an increase in the angiogenesis process in the umbilical venous cells (HUVECs) through an increase in miR-210. The study showed that miR-210 expression is higher in exosomes than in cells, and is consistent in all leukemia cell pathways [29]. Lawrie's study on DLBCL patients showed increased blood miR-210 compared to normal individuals. This increase is also accompanied by an increase in miR-155 and mirR-21 [30].

The composition of exosomes is currently widely researched, along with research on the roles of exosomes in cancer progression. The most widely discussed molecule among the many molecular compositions of exosomes is miRNA. There are a lot of classes of small endogenous molecules of RNA, such as small transfer RNA (tRNA), ribosomal RNA (rRNA), small nucleolar RNA (snoRNA), small interfering RNA (siRNA), and microRNA (miRNA). MiRNAs play an

important role in the regulation of gene expression that controls various cellular processes and metabolic pathways [31, 32].

Hypoxia and microRNA-210

Hypoxia, which often occurs in microenvironmental tumors (TME), may induce a certain amount of miRNAs expression. microRNA-210 (miR-210) is one of the miRNAs regulated by hypoxia and has been widely studied in cancer, where an increase in miR-210 is found in plasma in various types of cancer or other systemic diseases [33]. Oncogenes and tumor suppressor genes are also associated with proteins regulated by miRNAs. Oncogenic miRNAs will regulate the expression of mRNA of suppressor tumors and miRNA genes. Disruptions in the regulation of miRNA expression have been widely studied in various neoplasms [15, 34].

There are more than 50 microRNAs regulated or caused by hypoxia (called hypoxamir), including miR-210 (referred to as the "master hypoxamir"), which is consistently shown to be increased during hypoxic states not just in specific cells but also in all types of cells in the human body. Some hypoxamirs, such as the miR-210, have functional HRE in the promoter region and have been directly identified as targets of the HIF [15]. Although there are differences among some of the hypoxamir identified by various research groups, the increased expression of miR-210 implies miR-210's important role in the adaptation of hypoxia-undergoing cells. In tumor tissues such as breast cancer and head-and-neck cancer, the level of miR-210 expression has been proven to correlate with the hypoxia gene, which may describe a direct connection between miR-210 expression and hypoxia (fig. 2) [33]. Observation showed that the increase in miR-210 levels depends on the decrease in the tumor's oxygen concentration; therefore it is

suspected that miR-210 directly depends on the concentration of oxygen. In addition, processes that mimic hypoxia (low PH, oxidative stress, decreased growth factor, stress osmosis) do not affect the expression of miR-210 [37, 38].

Further miRNA examination showed that in addition to miR-210, there are also miR-21, 23, 24, 26, 103/107, 181, 213, and 373, which are also induced in hypoxia conditions [15, 39]. Among the hypoxamirs, miR-210 is the only miRNA agreed upon by all studies, and its levels are increased in various types of cells in response to hypoxia. In addition, miR-210 appears to be a specific target of HIF-1. In cancer, *in vivo* miR-210 correlates with a sign of a hypoxia gene expression, called hypoxia metagene. Based on this data, the expression of miR-210 appears to be an accurate picture of HIF activity *in vivo*, thus opening the door to the use of miRNAs as markers of tumor hypoxia [39].

Because hypoxia in tumors has a strong relationship with the incidence of angiogenesis, some pro-angiogenic factors increase in cells as a response to hypoxia in the microenvironment, with an increase in vascular endothelial growth factor (VEGF) [40]. The majority of studies have focused on the regulation of VEGF which is a pro-angiogenic factor to supports the growth of endothelial cells, but recent research has also shown the role of miR-210 in the angiogenesis process due to the occurrence of hypoxia [41].

Hypoxia-induced miR-210 plays an important role in this event, where the direct involvement of miRNA in this process is indicated by the inhibition of microcapillary formation and cell migration by VEGF after miR-210 blockade [35]. Interestingly, the expression of miR-210 appears to be closely related to the expression of VEGF, hypoxia, and angiogenesis in breast

cancer patients. This suggests the possible role of miR-210 on the formation of tumor angiogenesis and tumor growth [15, 40].

NF- κ B and hypoxia

Another very important encryption factor is Nuclear Factor Kappa B (NF- κ B), an important part of a system that may cause a cell to adapt and react to environmental changes. There are many external stimuli that trigger the activation of NF- κ B and the genes that are expressed. NF- κ B regulation plays an important role in immune response and stress. The activation of NF- κ B can be triggered by infection, physical triggers (UV or gamma radiation), physiological triggers (ischemic and hyperosmotic shock), as well as hypoxia, and oxidative stress [42, 44].

NF- κ B is a family of inducible transcription factors, which regulate a large range of genes that play a role in immune and inflammatory responses. The NF- κ B family consists of 5 related proteins, which are p50 and its precursors p105 (NF- κ B1), p52 and its precursors p100 (NF- κ B2), p65 (RelA), RelB, and c-Rel, which all play a role in the transcription of gene targets by attaching to specific elements (κ B enhancers) as hetero- or homo-dimers. These five NF- κ B proteins have 300 long amino acid chains of N-terminal Rel homology domain (RHD) that are responsible for dimerized proses, nuclear translocation, and DNA binding [45–47].

In unstimulated cells, the NF- κ B dimer is stored in an inactivated form in the cytoplasm through its interaction with the inhibitor Kappa B (I κ B) protein. Degradation of these inhibitor proteins through phosphorylation by the I κ B kinase (IKK) complex causes nucleic translocations of NF- κ B and transcription induction of the target gene. Although NF- κ B activity can be

triggered in most cells, NF- κ B can be detected in mature B cells, macrophages, neurons, vascular smooth muscle cells, and tumor cells as a result of the continuous activation of transcription of this gene [42].

The inflammatory response is described as the structured activation of various signaling pathways that regulate the expression of both pro-and anti-inflammatory mediators in tissue cells and leukocytes. At the moment, the inflammatory signaling pathways that are often discussed include IL-1, a family of tumor necrosis factors, and toll-like microbial pattern recognition receptors (TLRs), which are part of the IL-1R family [48]. Activation of NF- κ B consists of two major signaling pathways, namely the canonical and non-canonical (alternative) pathways [42, 45, 46, 48].

NF- κ B is the main regulator that plays a role in mediating inflammation and cancer through various stages. In tumor tissues with increased NF- κ B activity, the accumulation of pro-inflammatory cytokines at tumor sites has a direct effect on the "pro-tumorigenic" state of its microenvironment. Through epigenetic mechanisms, inflammatory signals can affect the tumor suppressor microRNA pathway and modulate IL-6/STAT3 signaling, which then triggers positive feedback and ends in cell proliferation and cancer initiation. In general, NF- κ B activity in cancer can be inferred into the following four mechanisms:

- stimulation of cell proliferation and prevention of apoptosis,
- regulation of tumor angiogenesis,
- promotion of tumor metastases,

- regulation of tumor metabolism [49].

Hypoxia and inflammation

Hypoxia and inflammation have been associated with a variety of pathological conditions.

Hypoxia is an activator of both HIF and NF- κ B through the dependent IKK-transforming growth factor β -activated kinase 1 (TAK1) pathway. There is currently a new theory on the negative feedback mechanism by which HIF can regulate IKK-TAK1 and dependent cell division protein kinase 6 (CDK6). NF- κ B can also function as a direct modulator of HIF expression in inflammation and hypoxia [43].

In 1994 it was first reported that hypoxia may activate NF- κ B, a mechanism thought to be an independent induction of IKK [51]. The exact mechanism of this activation remains not fully understood. Activation of NF- κ B due to hypoxia through the IKK and TAK1 pathways can occur without the role of oxygen sensor molecules, namely PHD1-3, HIF-1 α , or TRAF2 and TRAF6 adapter molecules [44, 52]. According to the study, TAK1 and IKK can be activated through a mechanism involving the release of Ca²⁺ and CaMK2 ions which is then followed by the SUMOylation process of I κ B α by SUMO-2/3 resulting in the activation of NF- κ B. Hypoxia can trigger NF- κ B activation very quickly, ranging from 5 to 30 minutes [44, 52]. Conversely, NF- κ B is also known to directly trigger the HIF expression in inflammation and hypoxia [43].

Nevertheless, NF- κ B activation induced by hypoxia can also be mediated by prolyl hydroxylases (PHD), which is the center of the oxygen-sensing pathway that triggers activation of HIF-1 α and FIH. As explained earlier, activation of HIF requires activated oxygen sensors such as PHD and FIH in a state of decreased oxygen availability (fig. 2) [53].

HIF-1 is involved in the intrinsic and extrinsic activation of tumor-associated inflammatory signaling. As explained above, the rapid growth of solid tumors induces hypoxia that may also cause necrosis of tumor cells. The hypoxia state and necrotic area of the tumor then produce pro-inflammatory mediators that later attract more immune cells. This chronic inflammation then activates the transcription factor NF- κ B. Both NF- κ B and HIF-1 then activate various gene promoters such as BCL-2, CXCR1, and CXCR2 which are pro-survival genes [11, 54].

Several proteins have been known to be associated with the modulation of the HIF and NF- κ B pathways, for example, tumor necrosis factor-associated receptor factor 6 (TRAF6), which is an important signaling mediator involved in the regulation of several physiological processes such as innate and adaptive immunity, tissue formation and differentiation, and bone metabolism. TRAF6 is an E3-ligase for K63-linked polyubiquitination that, together with the E2 enzyme complex (UBC13 and UEV1A), performs ubiquitination and activates NF- κ B through the TAK1 kinase pathway. The activated TAK1 kinase then phosphorylates IKK β and triggers activation of the IKK. TRAF6 can also regulate the expression of HIF-1 α independently from NF- κ B [55].

One of the interaction points between HIF and NF- κ B is through F-box and WD repeat domain-containing 7 (FBW7). FBW7 is a component of the SCF box ubiquitin ligase responsible for apoptosis, growth, and proliferation of various related proteins such as cyclin E, c-Myc, and NOTCH. FBW7 can degrade HIF-1 α during hypoxic state through a mechanism involving phosphorylation of HIF by glycogen synthase kinase 3 β (GSK3 β), which is then followed by the process of ubiquitination and proteasomal degradation. FBW7 is physically linked to HIF-1 α and

results in the degradation of HIF-1 α during hypoxic state. FBW7 can also interact directly with p100 through the phosphorylation-dependent process by GSK3 β . This interaction then degrades p100 and also affects the complex between the active forms of p100, p52, and RelB [55].

The interaction between HIF and NF- κ B pathways plays an extensive and intensive role. These interactions are functional and physical to a wide variety of stimuli, with various regulators overlapping on HIF and NF- κ B, so it is not surprising that we can find functional involvement of HIF where NF- κ B also plays a role, as in infectious and inflammatory processes. This interaction can induce a new outlook in therapeutic interventions in various diseases such as cancer, stroke, and inflammatory diseases [55].

In tumor cells, oncogenes and inflammatory signals (which can be mediated through toll-like receptors) and hypoxia can activate NF- κ B and HIF-1 α which later further activate each other. These interactions also resulted in tumor cell invasion, metastasis, epithelial-to-mesenchymal transition (EMT), survival, proliferation, and re-metabolic programming. In leukocytes, hypoxia also activates NF- κ B and HIF-1 α , endogenous ligands, as well as toll-like receptor (TLR) pathways via NF- κ B and HIF-1 α . Tumor blood vessels with prolyl hydroxylase domain 2 (PHD2) have abnormal hypoperfused endothelium, and cause tumor hypoxia and further enhancing the invasive and metastatic properties of tumors. Conversely, in tumor blood vessels with no PHD2, there is an increase in regulation of factors that are the opposite of abnormal tumor endothelial formation resulting in increased tumor perfusion and lowered incidence of metastasis [56].

HIF-1 α and NF- κ B in lymphoma

Many studies regarding the incidence of hypoxia were conducted on solid tumors, but hematological malignancy of aggressive lymphoid tissue with a clinical appearance resembling that of solid tumors (lymphomas) still has much to be disclosed. Compared to most healthy tissues, the bone marrow (BM) environment is characterized by low oxygen availability. Relatively low oxygen levels are indeed the characteristic of bone marrow progenitor cells, and hypoxia induces the secretion of several growth factors and cytokines such as SDF-1/CXCL12 (stroma cell derivative factor), VEGF (blood-scavenging endothelial growth factor) and interleukin-6 involved in hematopoietic stem cell (HSC) preservation [19]. It is reported that stabilization of HIF-1 α and HIF-2 α occurs in many non-Hodgkin lymphoma cell pathways, as well as among most patients with DLBCL and follicular lymphoma (FL), implicating the potential role of HIF activation in non-Hodgkin's lymphoma. A study conducted by Evens observed an activation of HIF levels that influence the poor prognosis in lymphoma in cases of DLBCL lymphoma and FL [57]. The presence of relative hypoxia and the occurrence of acidosis in lymphoma causes a diversion mechanism in the form of cell adaptation as occurs in non-hematological solid tumors malignancy. Histological research and *in vitro* studies attempt to reveal the role of HIF-1 on reprogramming and angiogenesis processes as one way for cells to adapt to hypoxic events [6].

In hematological malignancies, including lymphoma, bone marrow involvement is something that can occur in the course of the disease [58]. Among microarrays tumor (TMA) specimens, HIF- α expression was found to be significantly higher among DLBCL cases compared to FL. It is possible that these observations are related to the more aggressive nature of DLBCL.

The results showed that HIF- α and Thioredoxin were expressed in lymphoma cells and among primary samples of the patient's lymph nodes [59].

In a study of 153 DLBCL lymphoma patients conducted by Evens, HIF-1 α expression was shown to be a good prognosis factor for the survival of DLBCL patients receiving R-CHOP therapy. Good response with increased progression-free survival (PFS) and overall survival (OS) with the administration of R-CHOP is thought to be caused by an increase in angiogenesis that correlates with an increase in CD20, rendering a good response to anti-CD-20 therapy [23]. Results from Vacca's study showed that high-grade non-Hodgkin's lymphoma does have a greater number of micro blood vessels compared to low-grade lymphoma or reactive lymphoid tissue.⁶⁰ Salven's research suggests that high serum concentrations of vascular endothelial growth factor (S-VEGF) and basic fibroblast growth factor (S-bFGF) are associated with poor prognosis in non-Hodgkin's lymphoma [61].

The role of NF- κ B in the maturation and differentiation of B cells has also been identified for a long time. In general, 90% of lymphoma cases arises from B cells at various stages of differentiation, with some coming from T-cell lymphocyte [62]. The NF- κ B signaling pathway in lymphoid/ lymphoma malignancy can be activated by the tumor microenvironment or as a result of genetic changes in the components of the NF- κ B pathway. Genetic changes in the components of the NF- κ B pathway have recently been studied further due to the availability of next-generation sequencing examinations that can provide a clear pattern of genetic changes that cause chaotic NF- κ B activity [63].

It has long been proven that lymphoma and plasma cell malignancy arises from the malignant transformation of B cells and plasma cells at various stages of cellular differentiation. The heterogeneity of the lymphoma subtype seems to be reflected by the heterogeneity of the germinal center (GC) B cell subtype. For example, Burkitt lymphoma is a malignancy derived from dark zone B cells. Follicular lymphoma and GC DLBCL type (GCB-DLBCL) are derived from light zone B cell transformation and activated B-cell DLBCL (ABC-DLBCL) is derived from the final stages of the GC B cells differentiation, before transforming to plasma cells. Mantle cell lymphoma is derived from oncogenic transformation to antigen-activated pre-GC B cells, while multiple myeloma is a malignancy derived from plasma cells. Marginal zone lymphoma (MZL) is derived from the post-GC zone/memory B cells, while CLL is derived from the IgV gene that may or may not be mutated. The finding that canonical and alternative pathways of the NF- κ B subunit have a clear function of B cell differentiation and maturation has prompted researchers to conduct studies regarding the possibility of specific therapies for disorders of NF- κ B activity [63].

These various subtypes of lymphoma cells depend on the NF- κ B pathway to survive. This may be possible due to the passive role of NF- κ B in the maturation and activation of normal B cells. The genetic deletion of the NF- κ B subunit in B cells inhibits the differentiation of B cells. The alternative NF- κ B-activated pathway is a response to B cell exposure to BAFF, a member of the tumor necrosis factor (TNF) family formed by myeloid cells of the secondary lymphoid organ. Cells from BAFF are essential in the development and maturation of follicular B cells of transitional B cells. NF- κ B is also needed in the maintenance of entire mature B cells, due to conditional deletion of the IKK β subunit or IKK γ which causes B cells to disappear from the

follicular compartment. During the antigenic process, the classic NF- κ B pathway is activated by the B cell signaling process, through the formation of the "CBM" signaling complex which includes CARD11, MALT1, and BCL10. This CBM pathway is usually pathologically disrupted in certain lymphoma subtypes. Significant differences between these DLBCL subgroups include the continuous activity of the NF- κ B lines in the ABC and PMBL subgroups but not in the GCB DLBCL, which usually has a better outcome. ABC and PMBL have higher expression of NF- κ B gene targets than GCB [62, 64].

More than 80% of ABC subtypes of DLBCL cases have a genetic disorder that triggers distorted NF- κ B activation. Genetic mutations can be identified in BCR regulators (CARD11, CD79A, CD79B) and Toll-like receptor signaling pathways (MYD88), leading to downstream activation of NF- κ B and negative regulators of NF- κ B (TNFAIP3, encoding A20) to be dysregulated. BCR oncogenic supercomplex (MYD88-TLR9-BCR) has been identified on ABC-DLBCL to activate NF- κ B pathways. This complex facilitates signaling and interaction between BCR, CD79A, CD79B, MYD88, and related proteins, including IKK, in the endolysosome membrane to create efficient downstream signaling through NF- κ B. Lymphomas with MYD88-TLR9-BCR supercomplex have good sensitivity to BCR signaling pathway inhibition by ibrutinib [63].

A study conducted by Compagno et al. showed that >50% of ABC subtype of DLBCL and a part of GCB patients carry somatic mutations of various regulatory genes from NF- κ B that are negative (TNF AIP3/A20) and positive (CARD11, TRAF2, TRAF5, MAP3K7/TAK1, and TNFRSF11A/RANK). Of these genes, the negative mutation of the A20 gene that codes for the

ubiquitin-modifying enzyme that functions in the termination response of the NF- κ B is the most commonly encountered. Furthermore, mutations in the TRAF2 and CARD11 genes, which serves in coding the production of molecules that significantly increased NF- κ B activation ability, were also found. Compagno *et al.* concluded that activation of NF- κ B in DLBCL is due to genetic lesions in multiple genes that can trigger lymphomagenesis and prolonged NF- κ B response. From 168 DLBCL samples, Compagno *et al.* conducted immunohistochemical examinations to detect NF- κ B1/p50 nuclei (classical/canonical pathways) and NF- κ B2/p52 (alternative/non-canonical pathways). Nuclear localization of NF- κ B is found in 61% of ABC DLBCL cases and 30% of GCB DLBCL, and some in unclassified cases [65].

A study by Baochun *et al.* showed that activation of canonical and non-canonical pathways can occur in DLBCL. Genetic lesions associated with the NF- κ B alternative pathway were found in about 15% of all DLBCL patients (characterized by positive nuclear staining for p52), while activation of both pathways (characterized by positive nuclear staining for p50 and p52) was found in about 20% of all DLBCL patients examined. Baochun *et al.* also concluded that mutations/ deletion of the TRAF3 gene (a negative regulator of the NF- κ B pathway) occurred in about 15% of DLBCL patients and were often found in conjunction with BCL6 translocations that inhibit terminal B cell differentiation [66].

Chemotherapy is an important treatment in a variety of cancer stages, especially in hematologic malignancy. However, the results of chemotherapy treatment have not been encouraging. One of the contributing factors to treatment failure is resistance to certain drugs or multi-drug resistance (MDR), referring to the ability of cancer cells to become resistant to

various chemotherapy drugs. This is a complex phenomenon, and one of the causes of MDR is the pump system conducted by P-glycoprotein (P-gp), a transmembrane protein that reduces intracellular concentrations of chemotherapy drugs. Hypoxia affects the expression of the multidrug resistance (MDR1) gene that encodes the P-gp protein. Increased P-gp expression is also correlated with hypoxia-induced HIF-1 expression in different types of cancer cells. In addition, suppression of apoptosis processes induced by HIF-1 through modulation of the tumor suppressor gene p53 also contributes to chemotherapy resistance. Hypoxia also increases the activity of enzymes that are able to repair the cancer cells' DNA, thus protecting tumor cells from DNA-damaging chemotherapy. Another challenge is that cancer cells that experience hypoxia are often located far away (50–250 μm) from nearby blood vessels, thus – administration of good medication that can reach these cancer cells needs to be considered [7].

Conclusions

Based on the theories outlined above, it can be concluded that hypoxia is one of the factors that affect the malignancy of a cell. HIF-1 α and NF- κ B are transcription factors that are activated through various stimuli, two of which are hypoxia and inflammation. Activation and interaction of each transcription factor will trigger the expression of genes that ultimately benefit tumor growth. Since the 1980s, direct tumor oxygenation measurements have generally used polarographic needle electrode methods. Another possible alternative method is the use of exogenous and endogenous hypoxia markers. Intravenous administration of the drug, the inability to study stored materials, and the high cost of exogenous hypoxia markers are the main inhibitory factors in widespread clinical application, so endogenous hypoxia markers are preferred.²⁵ The development of biomarkers using miRNA exosomes has the potential to be

used in the diagnosis, assessment, and possible development of malignancy treatments in the future [31].

Hypoxia is among the various causative factors for chemoresistant tumors, in addition to molecular mechanisms and cellular and extracellular involvement [67]. Hypoxia causes resistance to therapy through several pathways, including:

- direct effects due to the lack of O₂ required by some drugs and maximum cytotoxic radiation,
- indirect effects through altered cellular metabolism that decreases drug cytotoxicity, and,
- increased genetic instability that can lead to faster development of drug-resistant tumor cells [68].

Thus, it can be concluded that cancer management targeting tumor hypoxia is a potential target of cancer therapy in the future.

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Table I. Various genes activated by HIF-1 [21, 22]

Function	Gene(s)
cell proliferation	cyclin G2, IGF2, IGF-BP1, IGF-BP-2, IGF-BP-3, WAF-1, TGF-α, TGF-β3
cell survival	ADM, EPO, IGF-BP1, IGF-BP-2, IGF-BP-3, TGF- α, VEGF
apoptosis	NIP3, NIX, RTP801
motility	ANF/GPI, c-MET, LRP1, TGF-α
cytoskeletal structure	KRT14, KRT18, KRT19, VIM
cell adhesion	MIC2
erythropoiesis	EPO
angiogenesis	EG-VEGF, ENG, LEP, LRP1, TGF-β3, VEGF, VEGFR, ADM, ET1, α18 ⁻

	AR, HO1, NOS2
invasion and metastasis	KRT14, KRT18, KRT19, VIM, MIC2, CATHD, Collagen type V (α 1), FN1, MMP2, PAI1, prolyl-4-hydroxylase α (1), UPAR, AMF, c-MET, LRP1, TGF- α
vascular tone	α_{1B} -adrenergic receptor, ADM, ET1, haem oxygenase-1, NOS2
transcriptional regulator	DEC1, DEC2, ETS-1, NUR77
pH regulator	carbonic anhydrase 9
HIF-1 activity regulator	P35srj
epithelial homeostasis	intestinal trefoil factor
drug resistance	MDR1
nucleotide metabolism	adenylate kinase 3, Ecto-5'-nucleotidase
iron metabolism	ceruloplasmin, transferrin, transferrin receptor
glucose metabolism	HK1, HK2, AMF/GPI, ENO1, GLUT1, GLUT3, GAPDH, LDHA, PFKBF3, PFKL, PGK1, PKM, TPI, ALDA, ALDC, LEP
extracellular matrix	CATHD, collagen type V (α 1), FN1, MMP2, PAI1, Prolyl-4-
metabolism	hydroxylase α (1), UPAR
energy metabolism	LEP
amino acid metabolism	transglutaminase 2

ADM – adrenomedullin; ALDA – aldolase A; ALDC – aldolase C; AMF – autocrine motility factor; CATHD – cathepsin D; EG-VEGF – endocrine gland-derived VEGF; ENG – endoglin; ET1 – endothelin-1; ENO1 – enolase 1; EPO – erythropoietin; FN1 – fibronectin 1; GLUT1 – glucose transporter 1; GLUT3 – glucose transporter 3; GAPDH – glyceraldehyde-3-P-dehydrogenase; HK1 – hexokinase 1; HK2 – hexokinase 2; IGF2 – insulin-like growth-factor 2; IGF-BP1 – IGF-factor-binding-protein 1; IGF-BP2 – IGF-factor-binding-protein 2; IGF-BP3 – IGF-factor-binding-protein 3; KRT14 – keratin 14; KRT18 – keratin 18; KRT19 – keratin 19; LDHA – lactate dehydrogenase A; LEP – leptin; LRP1 – LDL-receptor-related protein 1; MDR1 – multidrug resistance 1; MMP2 – matrix metalloproteinase 2; NOS2 – nitric oxide synthase 2; PFKBF3 – 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase-3; PFKL – phosphofructokinase L; PGK1 – phosphoglycerate kinase 1; PAI1 – plasminogen-activator inhibitor 1; PKM – pyruvate kinase M; TGF- α – transforming growth factor- α ; TGF- β 3 – transforming growth factor- β 3; TPI – triosephosphate isomerase; VEGF – vascular endothelial growth factor; UPAR – urokinase plasminogen activator receptor; VEGFR2 – VEGF receptor-2; VIM – vimentin

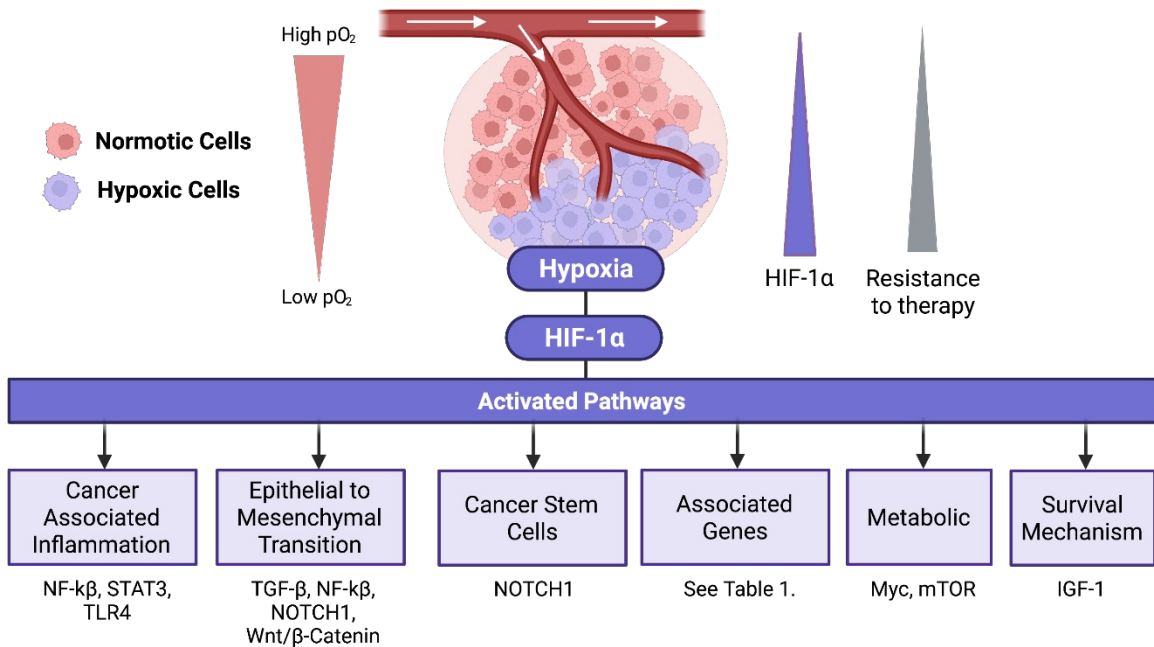


Figure 1. Tumor hypoxia and activation of the hypoxia-inducible transcription factors 1α (HIF-1α) pathway

Blood vessels can only reach the adjacent part of the tumor, while the distant part could not be reached; as a result, the cells became hypoxic. There is an increase in HIF-1α which causes resistance to cancer treatment. HIF-1α will activate several pathways, including the inflammatory pathway through the NF-κB pathway, and the metabolic pathway through the activation of Myc and mTOR. Created with BioRender.com. HIF - hypoxia-inducible factor; IGF-1 - Insulin-like growth factor 1; mTOR - mammalian target of rapamycin; NF-κB - nuclear factor κ B; STAT3 - signal transducer and activator of transcription 3; TGF-β - transforming growth factor β; TLR4 - toll-like receptor 4

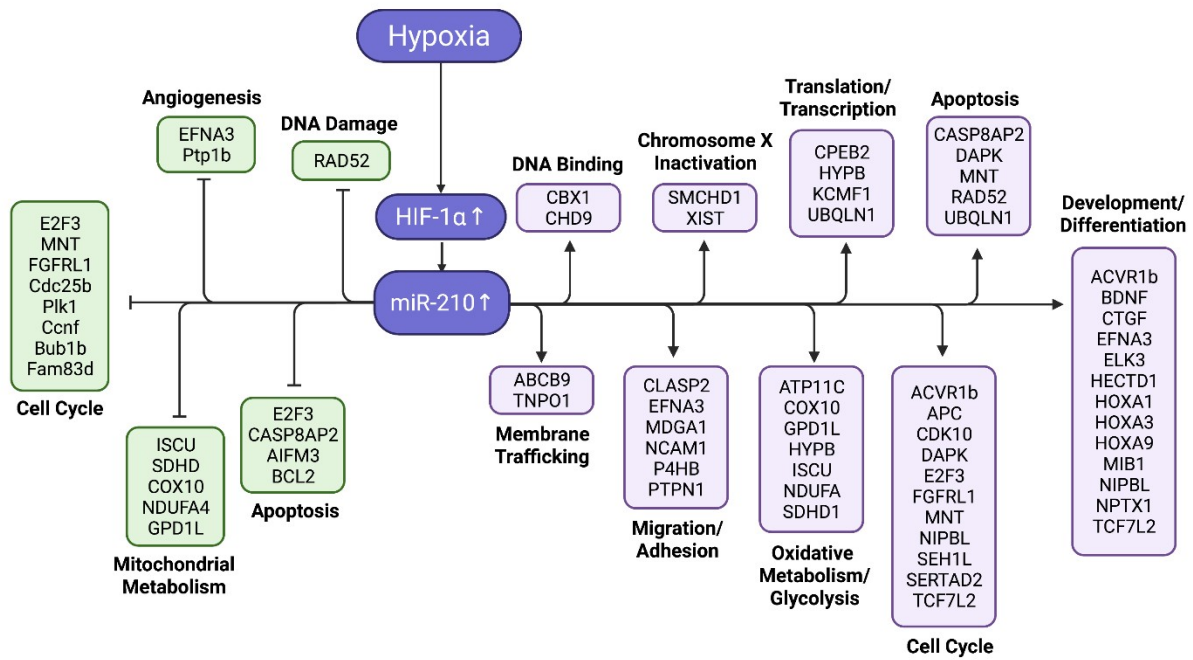


Figure 2. MicroRNA-210 regulation during a hypoxic state

Hypoxia affects various processes in the human body. MiR-210 plays various roles in DNA Repair, apoptosis, angiogenesis and inflammation. Hypoxia activates the HIF pathway which will further increase the expression of miRNA-210 to then activate some of the target genes. Created with BioRender.com. HIF – hypoxia-inducible factor; miR – microRNA

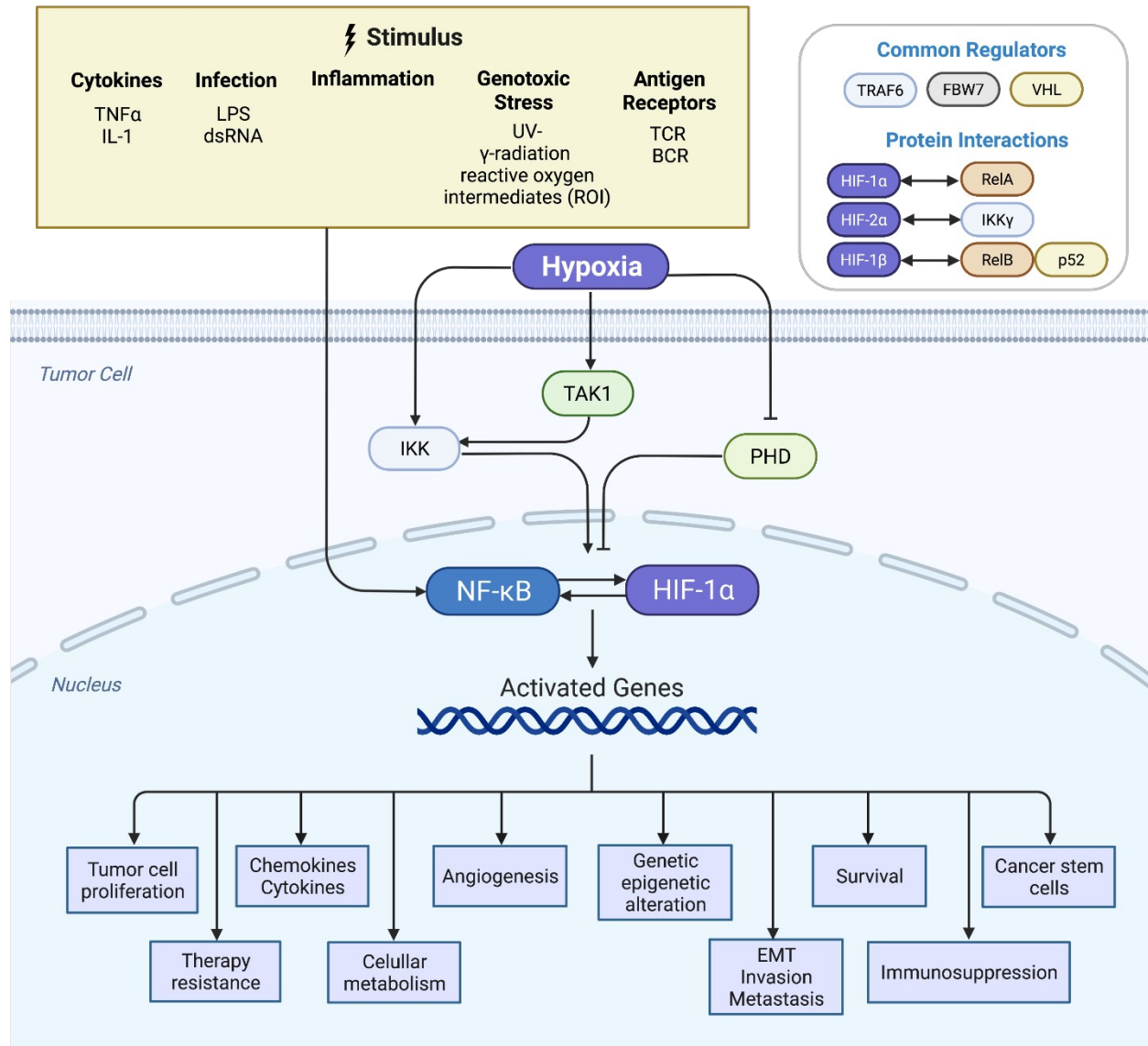


Figure 3. The crosstalk of NF- κ B and HIF-1 α in cancer [50]

Nuclear factor κ B (NF- κ B) can directly or indirectly crosstalk with HIF-1 α and control inflammation, proliferation, and survival of cancer cells, epithelial-to-mesenchymal transition (EMT), invasive traits, angiogenesis and metastasis, genetic and epigenetic changes, cancer stem cell formation, cellular metabolism, and therapeutic resistance. Activation of NF- κ B may also trigger immunosuppression through various mechanisms. Created with BioRender.com. BCR - B-cell receptor, LPS - lipopolysaccharides; TNF - tumor necrosis factor; HIF - hypoxia-inducible factor; NF- κ B - nuclear factor κ B; EMT - epithelial-to-mesenchymal transition; PHD - prolyl hydroxylase domain; TCR - T-cell receptor; IKK - I κ B kinase; IL-1 - interleukin-1; TAK1 - TGF β activated kinase 1; TRAF - TNF receptor-associated factors; FBW7 - F-box and WD repeat domain-containing 7; vHL - von Hippel-Lindau

