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HIF-Regulated Leukemogenesis Through the Advances on Epigenetic Mechanism

Lei Dong and Yu Zhu

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Abstract

Hypoxia-inducible factor (HIF) is the central master regulator of adaptation to decreased oxygen availability in both physiological and pathological conditions. In leukemia, HIF regulates tumor cell metabolic regulation, metastasis, and other tumor-adaptive survival. However, the regulatory role of HIF in different types of leukemia, including myeloid leukemia, has been unclear. In this chapter, the focus throughout is on the aspects of roles of HIF in the tumor mitochondria metabolic change that are relevant to the assessment and treatment of myeloid leukemia. The connection of HIF with metabolic modification and anaerobic metabolism, along with epigenetic modification, contribute to abnormal biological and clinical behavior of myeloid leukemia, including response to treatment. We have also explored the metabolic requirements of tumor cell proliferation in an attempt to understand why tumor cells escape hypoxia-induced cell growth inhibition. We believe that a better understanding of the mechanistic links between HIF-regulated cellular metabolism, growth control, and epigenetic modifications could be useful for the indication of pharmaceutical agents in myeloid leukemia.

Keywords: myeloid leukemia, HIF, epigenetic modification, metabolism, treatment of myeloid leukemia

1. Introduction

Myeloid leukemia is the most prevalent leukemia in adults, including acute myeloid leukemia (AML) and chronic myeloid leukemia (CML). AML is an aggressive hematologic malignancy that results in the disruption of normal self-renewal, differentiation, and hematopoietic stem and progenitor cell expansion leading to increased proliferation and accumulation of immature nonfunctioning myeloid progenitors. In turn, myeloid progenitors were blocked to

further differentiate into mature myeloid cell to play its role in the hematopoietic system. In comparison, in CML, hematopoietic stem cell is preferred to differentiate myeloid cells (leukemia cells). CML is much milder due to these leukemia cells still partial functions to maintain homeostasis. However, the leukemia cells uncontrollably divide, build up in the bone marrow, and spill over into the blood. Over time, the cells settle in other parts of the body, especially in the spleen (causing splenomegaly), and it can also promote into a fast-growing AML. The American Cancer Society reports that incidence rates have increased over the past few decades, estimating that in 2015 about 20,830 new cases of AML and 14,620 new cases of CML were diagnosed, and 10,460 deaths from AML and 4650 deaths from CML would occur in the USA [1]. Currently, the majority of AML patients still have a poor prognosis, making the development of novel therapies a priority. Prognosis is influenced by a combination of cytogenetic and genetic characteristics of the disease, together with clinical features and the patient's age. In the albeit heterogeneous genetic landscape of myeloid leukemia, many myeloid leukemia patients exhibit recurrent mutations in genes encoding epigenetic regulators [2]. It is thus becoming increasingly clear that epigenetic dysfunction plays a key role in leukemogenesis of AML and CML [3]. More importantly, the epigenetic regulators CREB-binding protein (CBP) and p300 histone acetyltransferases (HATs), as important HIF co-transcriptional factors, facilitate leukemogenesis and represent therapeutic targets in AML [4]. Here, we have focused on the effect of dysregulated epigenetic programs in the development and maintenance of myeloid leukemia. In addition, we have discussed recent advances in therapies specifically targeting these key epigenetic mechanisms.

2. Hypoxia-inducible factor

Oxygen supply and consumption are tightly regulated and dynamically balanced in most normal tissues. However, supply and consumption of oxygen in tumor cells are usually decoupled due to the loss of physiological control and aberrant molecular signaling that provide malignant growth and survival advantages. Hypoxia appears in tumor cells when the metabolic demand for oxygen exceeds its extracellular availability. One of the main early cellular events responded upon hypoxia is activation of hypoxia-inducible factor 1 and 2 (HIF-1 and HIF-2), a critical heterodimeric transcription factor. HIF then in turn binds to hypoxia-responsive elements (HREs), with the minimal core sequence 5'-CGTG-3', and influences the expression of various genes involved in angiogenesis, metabolism, pH regulation, proliferation, metastasis, and a wide range of other signaling processes.

2.1. Structure of hypoxia-inducible factor and domain structure of α subunits

The structure of HIF was identified as a dimer protein composed of HIF-1β and HIF-1α subunits. HIF-1β, the aryl hydrocarbon receptor nuclear translocator (ARNT), and its highly homologous protein ARNT2 and ARNT3, is constitutively expressed. All the three HIF-β subunits have the potential in forming dimers with various HIF-α subunits [5]. In normoxic conditions, HIF-1α is expressed ubiquitously at low closely balanced levels in all organs and has six different

splice variants [6]. HIF-2α is most abundantly expressed in the lung, followed by the heart, brain, liver, and various other organs. Despite their similarities in mediating transcriptional responses to hypoxia, HIF-1α and HIF-2α have distinct, nonredundant functions (reviewed in Semenza [2004] [7]). HIF-3α is the least-studied member of the family and has multiple splice variants [5]. The functional domains of HIF include DNA-binding region basic helix-loop-helix (bHLH), HIF dimerization-binding region PER-ARNT-SIM (PAS), oxygen tension modulated N-terminal transactivation domain (N-TAD), and C-terminal transactivation domain (C-TAD). HIF-α subunit also contains oxygen-dependent degradation domain (ODDD).

2.2. Oxygen-dependent hypoxia-inducible factor regulation

The regulation of HIF by the extent of oxygen pressure is dependent on the intermediator that affects HIF-α protein stability and/or its ability to bind cofactors essential for transcriptional activity. In normoxia, HIF-α is strictly controlled by two types of oxygen sensors. First, 2-oxoglutarate (2-OG)-dependent prolyl hydroxylase domain (PHD) proteins could hydroxylate two prolyl residues (Pro[402] and/or Pro[564]) in the N-TAD of HIF-1α ODDD regions (**Figure 1**) [8, 9]. Currently, three functional 2-OG-dependent PHD have been identified—PHD1, PHD2, and PHD3,—and all three require oxygen, Fe^{2+}, and 2-OG as cofactors. This modification of HIF-α promotes its destruction by the proteasomal system through interaction with von Hippel-Lindau (VHL) protein, a component of an E3 ubiquitin ligase complex [10]. A second
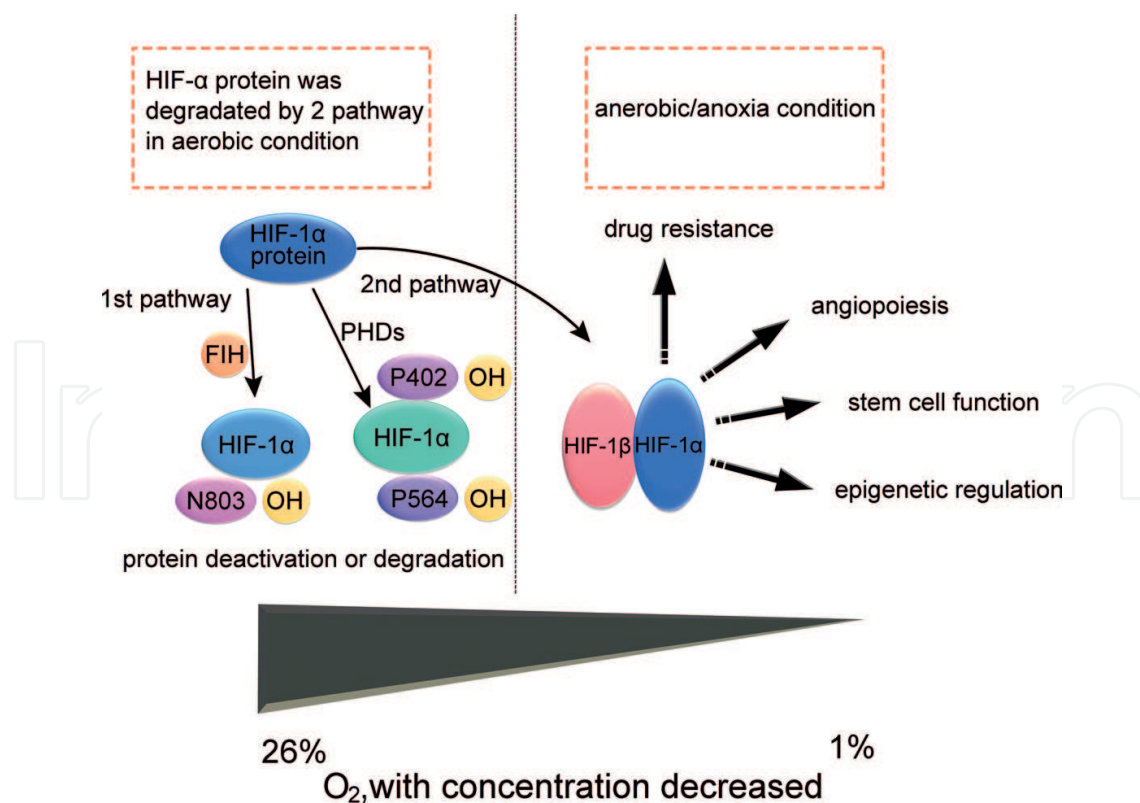

Figure 1. HIF-1α regulation and HIF-1α dependent gene expression under hypoxia.

oxygen sensor called factor-inhibiting HIF-1 (FIH-1) involves hydroxylation of an asparagine residue (Asn[803]) in the C-TAD of HIF-1α, which also utilizes oxygen as a substrate [11]. The hydroxyl modification of Asn[803] blocks the binding of the cofactor proteins) CREB-binding protein (CBP) and p300 thus inhibit HIF transcriptional activity. In hypoxia, HIF-α is regulated through "bicephalous" transcriptional nature in an FIH-dependent or FIH-independent manner [12]. In short, PHD has a lower affinity for oxygen than HIF and therefore is more rapidly inhibited. Consequently, genes require only the N-TAD to be induced. As oxygen decreases further, the inhibition of C-TAD is released and HIF-1α retains full transcription activity.

2.3. Metabolic-dependent HIF regulation

The metabolic intermediates are also the key regulators disrupting the hemostasis of HIF activates. As mentioned earlier, PHDs are 2-OG-dependent dioxygenases, catalyzing the conversion of a prolyl residue, molecular oxygen, 2-OG to hydroxyprolyl, carbon dioxide, and succinate using ferrous iron as cofactor. In addition, succinate also intermediates in the tricarboxylic acid (TCA) cycle catalyzed by succinate dehydrogenase (SDH) to fumarate in mitochondria. SDH dysfunction in cells raises the levels of succinate, which accumulates and leaks out to cytosol [13]. The increased level of succinate also inhibits PHDs activity due to accumulation succinate feedback, leading to the stabilization of HIF-α and activation of HIF complex. Similarly, deficiency of fumarate hydratase (FH) leads to accumulation of fumarate in the cytosol. Due to chemical similarity of fumarate to succinate, FH-deficient cells could also inhibit PHDs [14]. Other metabolic changes, such as diseases related to iron homeostasis, also crosstalk with HIF regulation. Hepcidin, a small polypeptide, plays a central role in regulating iron uptake. Iron demand in bone marrow increases when erythropoiesis is stimulated by hypoxia via increased erythropoietin (EPO) synthesis. Iron overload disease like hemochromatosis and iron decrease in anemia, feedback hepcidin production through VHL-HIF regulation [15].

3. HIF regulation in mitochondria metabolic change

HIF is the central master regulator of adaptation to decreased oxygen availability in both physiological and pathological conditions. It is evolutionary pressure to reestablish metabolic balance to allow normal tissue and/or even tumor to survive. Physiologically, in the wound-healing area, damaged tissue leads to hypoxia and facilitates vascular growth. However, pathologically, in the solid tumor region, oxygen demand is in continuous increase due to the uncontrollable growth of the cancer cell. Hypoxia also represents the unifying feature of the microenvironment of solid tumors. The adaptive changes of tumor survival pattern referred to as "hypoxia tumor phenotype" are greatly noticed.

3.1. HIF regulation of metabolic change

HIF upregulation in tumors plays a central role in metabolic switch from aerobic metabolism to anaerobic metabolism. In turn, all the enzymes (e.g., aldolase A and C, enolase 1, hexokinase 1 and 2, pyruvate kinase M (PKM), phosphofructokinase) and glucose transporters (GLUT1, GLUT3) involved in glycolytic pathway are upregulated [16]. Moreover,

conversion of pyruvate to acetyl-CoA, TCA cycle, and mitochondrial biogenesis are inhibited through downregulation of pyruvate dehydrogenase kinase (PDK) 1 and 3 [17, 18]. Even though the glycolysis produces far less energy than TCA cycle per glucose molecule, it has a significant higher throughout. In addition, the accumulated by-products could be used as sources of carbon to produce nucleotides and lipids for proliferating cells [19]. The classic view of metabolism is that of a self-correction of homeostasis responding to microenvironment. In this model, for cancer to arise, tumor hypoxia selects cells depending on anaerobic metabolism [20]. Secondary mutations are needed to give cells the ability to transform the capability to alter existing cell metabolism in a way that supports cell growth. One example is that of mouse embryonic fibroblasts that reduce oxygen consumption when switching from 20% O_2 to 1% O_2, and continued low oxygen consumption when returning to 20% O_2, suggesting HIF stable modified metabolic reprogramming [21].

The direct consequence of glycolysis is the production of lactic acid by hypoxic tumor cells leading to tumor acidosis. Intracellular acidosis poses a threat to cell survival. Readjusting intracellular pH (pHi) is a critical strategy to protect against apoptosis and cell death. HIF upregulated monocarboxylate transporter 4 (MCT4) and Na^+/H^+ exchanger (NHE1) facilitate exportation of H^+ [22, 23]. Moreover, two transmembrane carbonic anhydrases (CAs) catalyze CO_2 to be hydrated to HCO_3^- and H^+, CA IX, and XII overexpressed in tumors also regulated by HIF. This reaction facilitates proton generation in the extracellular space, which contributes to acidification in tumor microenvironment, while preventing acidification of intercellular milieu of cancer cell [24].

4. HIF regulation in epigenetic modification

Wadding first proposed the concept of epigenetics in 1915 and believed that the phenotypes generated from certain genotype within the scope of epigenetics. Meanwhile, he explained the expression of the genetic materials in the entire life process for the first time by using the concept of "Whole View" [25]. Holiday summarized with a more comprehensive explanation that "epigenetics refers to the changes of the gene expression manner with no difference and/or change of heritage DNA sequence" [26]. Epigenetics is involved in individual development and the gene expression regulation in the biological process, however, it could also lead to human diseases when it is interfered [27].

4.1. Histone acetylation

Histone acetylation, a process closely related to transcriptional activation is one of major epigenetic modifications. Histone acetylation occurs in the lysine residue located at the end of the histone N-terminal. Histone acetylation induces relaxed and/or higher-order structure of chromatins through transcriptional regulation [28]. In addition, the acetylated histone produces a signal that binds to the protein, producing intrinsic activities or capped-chromatin remodeling complexes, thereby promoting the transcriptional induction. Histone acetylation is mainly controlled by the inhibitory activities of histone acetyltransferases (HATs) and histone

deacetylases (HDACs), and the substrates of HDAC include non-histone proteins, some transcription factors, and cofactors [29]. As a consequence, histone deacetylases generally inhibit transcription. It is also interesting that they negatively regulate HIF-dependent transcriptions. Previous studies have shown that methylation of Reptin at lysine 67 in hypoxia condition by the methyltransferase G9a negatively regulates hypoxic responses [30]. Consequently, while in hypoxia condition, the chromatin remodeling factor HIF-1α Reptin binds to HDAC1, the target gene of HIF is involved in the supplementation of HDAC1, besides, HDAC4 and HDAC5 complement the expression of HIF target promoter in HIF-dependent transcription to become more active [31]. Moreover, histone deacetylase inhibitors could promote gene expression in the transcription of several HIF target promoters and induce inhibition of HIF-dependent angiogenesis.

The mechanisms of the HDAC-dependent gene activation are still not well defined. However, it becomes increasingly apparent that the HIF C-TAD-p300/CBP interactions are necessary. There are evidences suggesting the targets of deacetylated p300/CBP and HIF. In this concept, HIF, P300 and HDAC4, HDAC5, or HDAC7 have been reported to form multi-polyprotein complexes [31, 32]. This also shows that HDAC4 and HDAC5 could promote the binding between HIF-1 and p300, thereby enhancing the expression of HIF target genes. However, the gene expressions regulated by epigenetic mechanisms that are involved in the hypoxia response are different. It is generally separated into following steps: (1) HIF recruit co-activator enhancing the expression of HIF. (2) The interaction between HIF-p300 and CBP by the inhibition of hypoxia to induce HIF-1 expression. (3) HDAC4 and HDAC5 can promote the interactions between HIF-1α and p300. (4) HDAC4 and HDAC5 promote the interaction between HIF-1α and p300. (5) SWI/SNF complexes alter the chromatin structures in some HIF target promoters and enhancers to benefit their expression [33].

Specifically, hypoxia promotes the changes in the status of the hypoxia-induced gene promoter histone methylation: activation of hypoxia histone demethylase and inhibition of JMJD1A histone demethylase, which can cause H3K9me2 reduction and H3K4me2 increase, respectively, thus enhancing the gene expression [34, 35]. In addition, hypoxia could increase the expression of some HIF target promoters H3K27me3 and H3K4me3. Under hypoxia conditions, the interactions of HIF1-α and Reptin are enhanced, leading to some HDAC1 supplementation of the HIF target genes and negative regulation of transcription; the changes in the status of histone methylation and acetylation promote hypoxia-inhibited gene. Hypoxia could increase the levels of H3K9me2 and H3K4me3, and decrease the levels of H3K27me3 and H3K9ac.

4.2. Histone methylation

Histone methylation, as another main epigenetic modification, is a stringent regulatory process, which relies on the activities of histone methyltransferase and histone demethylase. Histone demethylase induces the dynamic equilibrium of the histone methylation during hypoxia. During hypoxia, histone demethylase can increase the expression of these enzymes, and the decreased enzyme activity can be regulated completely or partly by oxygen deficiency. Some histone lysine methylation can be specifically prevented under hypoxic conditions.

Hypoxia-induced histone methylation might be achieved by the partial inhibition of spherical JHDMS and the reduction of histone methylation of some hypoxia response promoters. Interestingly, Jumonji domain-containing protein 1A (JMJD1A) is the HIF target gene itself. Krieg and his colleagues suggested the regulation of feed-forward mechanism in which HIF might represent for the likely HIF-dependent gene expression of JMJD1A [36]. They suggested that JMJD1A maintained the apparent genetic pattern of the activities of the target promoters, thereby minimizing the required energy-supported expression. JMJD1A indicates that more consideration should be given to the induction of differential genes and other JHDMS involved in the activation of hypoxia-responsive genes. Further research is required to determine whether this is true.

Although there is a detailed study of hypoxia-induced conditions on JHDM, this kind of enzyme in hypoxia requires one or more RNA interference-silencing experiment targeting studies of JHDMS or multiple biological effects of JHDMS response. In the apparent regulation of hypoxia, histone modification and chromatin remodeling caused by relative enzymes also play a key role. Hypoxia-induced histone acetylation has become a highly suspected etiology of Alzheimer's disease and attention deficit hyperactivity disorder (ADHD) [37].

Evidence suggests that the increase of H3K9me2 is partly due to hypoxia-induced G9A methyltransferase. During hypoxia, H3K9me2 induces the increase of certain gene promoters as well. Further studies are required to assess the effects of hypoxia-induced epigenetic alterations on the organisms. To activate the gene transcription, a series of specific HIF-targeted genes promoter region is commonly regulated through histone methylation, acetylation, or alteration of chromatin structures. On the other hand, hypoxia could stimulate the inhibition of induced transcription, possibly by supporting the changes of the whole chromatin. Thus, it seems that hypoxia plays a dual role in the studies of epigenetic mechanisms of the genes as well as in controlling the induction and transcriptional downregulation of the HIF target gene.

HIF will be activated when hypoxia occurs in vivo. As a consequence, transcription of more than 100 genes, such as vascular endothelial growth factor (VEGF) and erythropoietin (EPO), can be induced. However, the activation of HIF could be accompanied with significant decline in the activity in many other transcription factors. However, hypoxia-induced gene modulation is not limited to HIF activation. In contrast, epigenetic modification can be involved in this process. The epigenetic mechanisms play dual roles in hypoxia, meaning that they not only upregulate the HIF-controlled target genes but also downregulate the general transcription factors. However, the specific mechanisms remain to be further explored.

In conclusion, hypoxia could induce extensive histone modifications that are usually associated with transcriptional repression or activation. Specifically, however, more research is needed to fully understand its biological functions and to identify the enzymes involved in signal transduction pathways. It provides holistic assessments regarding hypoxia on the epigenetic changes. Under hypoxia conditions, the following epigenetic changes were greatly noticed: (1) p300/CBP histone acetyltransferases interact with HIF and acetylate histones in HIF target promoters. HDAC4, HDAC5, or HDAC7 form a multi-protein complex with HIF-p300 increasing HIF transcriptional activity. HDAC4 and HDAC5 exert their effects by

promoting association between HIF and p300. (2) SWI/SNF are complementary gene promoters of HIF-1α, which is a requirement for the expression of HIF-1α mRNA. The regulation of SWI/SNF could also describe the profound effects of HIF-dependent responses on hypoxia. On the other hand, the SWI/SNF complex alters the chromatin structure in some HIF target promoters or enhancers, thereby favoring their expression. (3) Hypoxia activates JMJD1A which promote a decrease in H3K9me2. In the meantime, oxygen deprivation also inhibits JARID1A histones demethylases which provoke an increase in H3K4me2 levels at their target promoters, thus enhancing gene expression. In addition, hypoxia increases H3K4me3 and H3K27me3 levels in some HIF target promoters, and hypoxia-inductive H3K4me3 seems to depend on the inhibitory effects of histone demethylase [38]. The hypoxia-inducible gene promoter was also observed in EPO, HMOX1, and DAF [39, 40]. (4) The interaction between Reptin and HIF1-α is enhanced in hypoxia, leading to recruitment of HDAC1 to some HIF target genes, negatively regulating their transcription (**Figure 2**). However, more research is still needed to fully understand its biological functions and to identify the enzymes involved in signal transduction pathways. It provides holistic assessment regarding hypoxia on the epigenetic modifications.
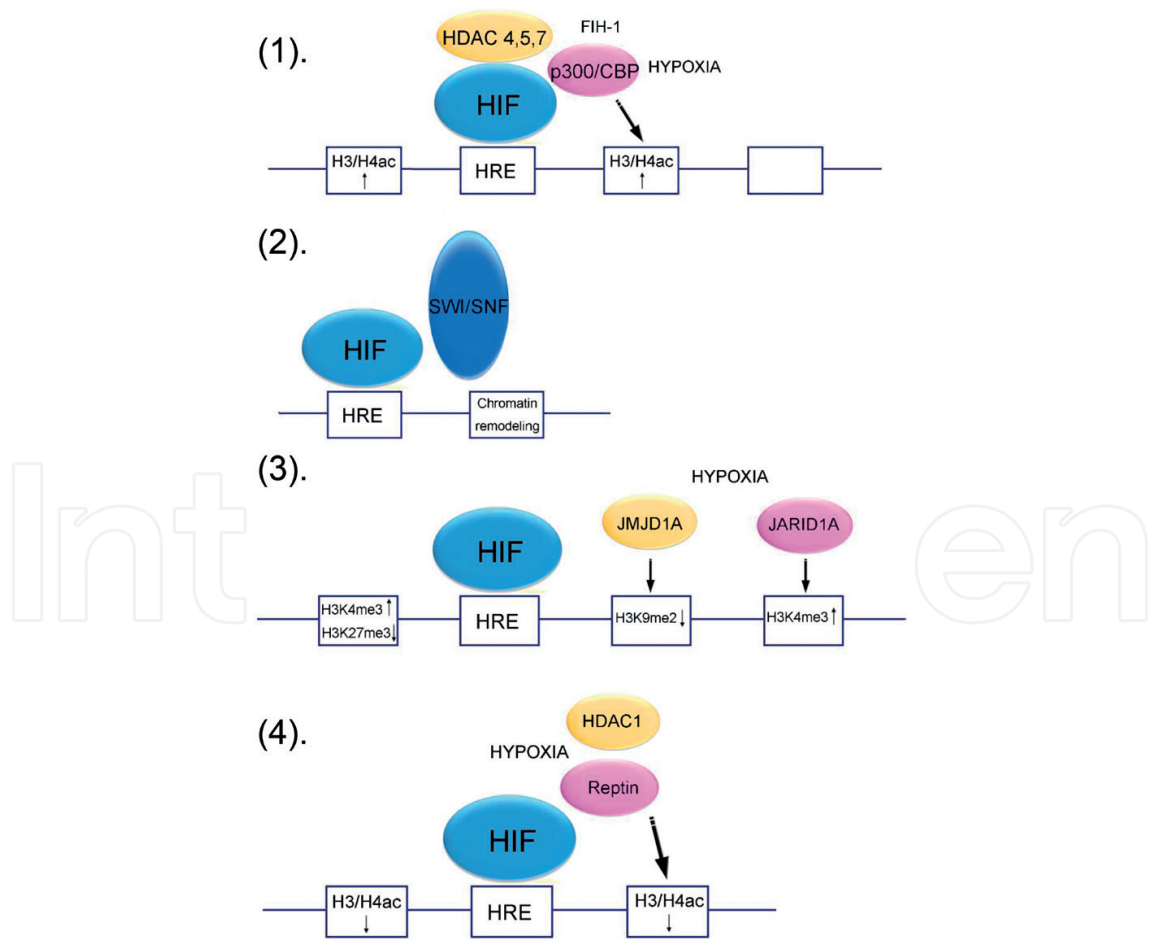

Figure 2. HIF regulated epigenetic changes in response to hypoxia.

5. HIF and epigenetic modification in myeloid leukemia

Metabolic flexibility relies on the rewiring of the existing metabolic pathways, which are closely controlled by "pathway switch proteins," to efficient rerouting of metabolites selected by cellular needs. As discussed earlier, HIF controls many aspects of tumor in terms of location, size, cell type, or local invasion. Other aspects, like state of differentiation and hierarchical nature, were also regulated by HIF. Most tumor-initiating mutations occur in stem cell or progenitor populations. The expansion of these mutant cells with a more differentiated phenotype that usually characterizes individual cancers are responsible for the cause of pathogenesis. This was first described in 1997 for acute myeloid leukemia and subsequently extended to solid tumors, including melanoma, Glioblastoma (GBM), and pancreatic cancer [41, 42].

Limited oxygen access is the common feature in solid tumor due to inadequate tissue perfusion, thus, cancer metabolism is heavily influenced by adaptation to highly hypoxic microenvironment. In many cases, HIF is involved as a master regulator. Recently, an increasing number of other proteins, regulated by HIF, are found to influence energy metabolism. In addition, a series of mutations in these proteins—for example, SDH, FH, isocitrate dehydrogenase (IDH), activation-induced cytosine deaminase (AID), or drive altered metabolism. These findings have supported the notion that HIF has a role to play in oncology, and affects diagnostic methods and drug discovery.

In hematological tumors, bone marrow and lymph nodes represent hypoxic environments. The quiescent hematopoietic stem cells (HSCs) in the bone marrow existing in the hypoxic niche utilization of predominantly glycolysis pathway are regulated by HIF-1α stabilization [21]. Hypoxia modulates mitochondrial respiration in an HIF-1α-dependent manner. HIF promoter, the expression of pyruvate dehydrogenase kinase-1 (PDK1), in turn, inhibits pyruvate dehydrogenase (PDH) [43]. In addition, PKD1 activation is also important in inducing pluripotent stem cell, as evidenced by four Yamanaka factors (OCT4, SOX2, KLF4, and c-MYC) sufficient to upregulate PDK1, and initiates a Warburg-like metabolic rewiring which is closely linked with conversion of pluripotency [44]. On the other hand, metabolic reprograming initially triggered by HIF stabilizes HIF expression independently of oxygen to gain tumor survival advantage. As an example, imatinib-resistant cell expresses high levels of HIF-1αs and induces BCR-ABL upregulation [45]. Recent study further suggests that HIF is the potential cause to trigger gene translocation through limiting activation-induced cytosine deaminase (AID) expression [46, 47]. In the therapeutic point of view, the stem cell nature of cancer is also reflected in removing differentiation block therapy. For example, all-*trans* retinoic acid combined with cytotoxic drug was used in the clinical practice for the treatment of acute promyelocytic leukemia (APL) [48]. Other promoting differentiation agent aurora kinase A inhibitors were shown effective in acute megakaryocytic leukemia [49].

Other feature of leukemia cell is attenuated metabolic pathway in glycolysis even in aerobic conditions [50]. Leukemic cells, other than solid tumors, have the advantage to access oxygen; however, levels of HIF-1α, GLUT1, GLUT3, and CA4 are still significantly enhanced compared to normal blood cells. Clinical evidence shows that higher glycolytic rate in leukemic cells

induces resistance to chemotherapeutics. Instead, inhibition of glycolysis using 2-deoxyglucose (2DG) promotes leukemic cell susceptibility to chemotherapeutic treatment, resulting in induction of leukemic cell death in normoxia [51].

Acknowledgements

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