

Review Article

Hypoxia-Inducible Histone Lysine Demethylases: Impact on the Aging Process and Age-Related Diseases

Antero Salminen^{1,*}, Kai Kaarniranta^{2,3}, Anu Kauppinen^{3,4}

¹Department of Neurology, ²Department of Ophthalmology, Institute of Clinical Medicine, University of Eastern Finland, Kuopio, Finland

³Department of Ophthalmology, Kuopio University Hospital, Finland

⁴School of Pharmacy, Faculty of Health Sciences, University of Eastern Finland, Kuopio, Finland

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ABSTRACT: Hypoxia is an environmental stress at high altitude and underground conditions but it is also present in many chronic age-related diseases, where blood flow into tissues is impaired. The oxygen-sensing system stimulates gene expression protecting tissues against hypoxic insults. Hypoxia stabilizes the expression of hypoxia-inducible transcription factor-1 α (HIF-1 α), which controls the expression of hundreds of survival genes related to e.g. enhanced energy metabolism and autophagy. Moreover, many stress-related signaling mechanisms, such as oxidative stress and energy metabolic disturbances, as well as the signaling cascades via ceramide, mTOR, NF- κ B, and TGF- β pathways, can also induce the expression of HIF-1 α protein to facilitate cell survival in normoxia. Hypoxia is linked to prominent epigenetic changes in chromatin landscape. Screening studies have indicated that the stabilization of HIF-1 α increases the expression of distinct histone lysine demethylases (KDM). HIF-1 α stimulates the expression of KDM3A, KDM4B, KDM4C, and KDM6B, which enhance gene transcription by demethylating H3K9 and H3K27 sites (repressive epigenetic marks). In addition, HIF-1 α induces the expression of KDM2B and KDM5B, which repress transcription by demethylating H3K4me_{2,3} sites (activating marks). Hypoxia-inducible KDMs support locally the gene transcription induced by HIF-1 α , although they can also control genome-wide chromatin landscape, especially KDMs which demethylate H3K9 and H3K27 sites. These epigenetic marks have important role in the control of heterochromatin segments and 3D folding of chromosomes, as well as the genetic loci regulating cell type commitment, proliferation, and cellular senescence, e.g. the INK4 box. A chronic stimulation of HIF-1 α can provoke tissue fibrosis and cellular senescence, which both are increasingly present with aging and age-related diseases. We will review the regulation of HIF-1 α -dependent induction of KDMs and clarify their role in pathological processes emphasizing that long-term stress-related insults can impair the maintenance of chromatin landscape and provoke cellular senescence and tissue fibrosis associated with aging and age-related diseases.

Key words: Aging, Chromatin, Epigenetic, Hypoxia, Pseudohypoxia, Senescence

Ever since the Cambrian period, oxygen availability has been in the center of energy metabolism and thus exposure to hypoxia or ischemia can jeopardize the maintenance of tissue homeostasis. During evolution, organisms have evolved mechanisms to survive in hypoxia by developing the oxygen-sensing systems, which can induce gene expression profiles protecting against hypoxia-induced injuries. In metazoans, the hypoxia response is induced by the oxygen-dependent control of prolyl 4-hydroxylases (PHD1-3), which regulate the cellular expression of

hypoxia-inducible transcription factors (HIF1-3) [1-3]. The PHD-HIF signaling is stimulated by the deficiency of oxygen, which inhibits the activity of PHDs preventing the hydroxylation of HIF factors and thus blocking their subsequent degradation, i.e. hypoxia stabilizes the cellular expression of HIF transcription factors. The HIF-induced hypoxia response involves the expression of hundreds of survival genes, e.g. enhancing energy metabolism and autophagy. Remarkably, hypoxia is not the only insult that can stabilize the expression of HIF factors. There are

*Correspondence should be addressed to: Dr. Antero Salminen, Department of Neurology, Institute of Clinical Medicine, University of Eastern Finland, P.O. Box 1627, FI-70211 Kuopio, Finland. E-mail: antero.salminen@uef.fi

several other signals, mostly related to stresses, which can increase the expression of HIF factors and thus improve cellular survival (see below) (Fig. 1). However, a chronic activation of HIF factors can have detrimental effects, e.g. stimulate cellular senescence and tissue fibrosis commonly enhanced in age-related diseases.

A substantial literature indicates that hypoxia is linked to the epigenetic modification of chromatin landscape. Interestingly, the stabilization of HIF-1 α increases the expression of several histone lysine demethylases (KDM), which are crucial enzymes in the control of gene expression in hypoxia but in collaboration with other chromatin modifiers they can also affect

heterochromatin structures, genome stability, and reprogramming of cellular senescence loci (see below). Increase in cellular senescence is associated with the aging process and many age-related diseases. We will review the molecular aspects of the HIF-1 α -induced expression of KDMs and clarify their role in the epigenetic modifications associated with the aging process and the appearance of age-related diseases. We propose that a chronic induction of HIF-1 α , especially through stress-related signals, can impair the regulation of chromatin landscape and thus provoke cellular senescence and aggravate age-related diseases.

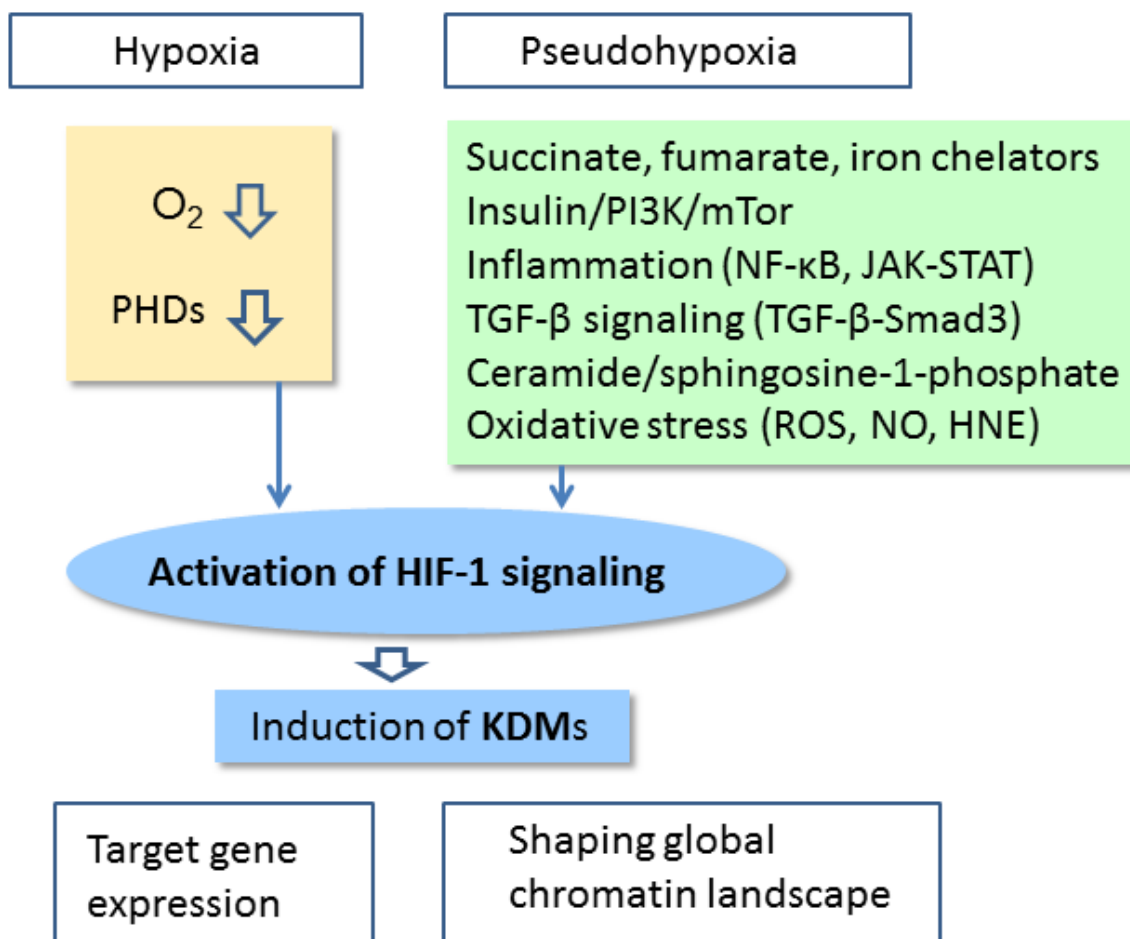


Figure 1. Induction of KDM expression by HIF-1 α signaling. HIF-1 α signaling can be activated by hypoxia and several stress-related signaling pathways, commonly called pseudohypoxia since they activate HIF-1 α signaling in normoxia. KDMs induced by HIF-1 α control the transcription of HIF-1 α target genes but in addition, they can modify the global chromatin landscape provoking pathological changes linked to the aging process and age-related diseases. Abbreviations: HIF-1 α , hypoxia-inducible factor-1 α ; HNE, 4-hydroxynonenal; JAK, Janus kinase; KDM, histone lysine demethylase; mTor, mammalian target of rapamycin; NF- κ B, nuclear factor- κ B; NO, nitric oxide; PI3K, phosphoinositide 3-kinase; ROS, reactive oxygen species; Smad3, SMAD family member 3; STAT, signal transducer and activator of transcription; TGF- β , transforming growth factor- β .

Hypoxia stimulates HIF-1 α signaling

Hypoxia, i.e. a decline in the oxygen partial pressure, is an environmental stress but hypoxia is also commonly present in many pathological conditions in which blood flow into tissues is impaired, e.g. in ischemia/stroke, arteriosclerosis, and inflammatory disorders. Organisms effectively respond to hypoxia, e.g. switching their energy production from oxidative to glycolytic pathway [4, 5]. Moreover, animals can adapt to hypoxic conditions by generating hypoxia resistance [6, 7]. Early 1990, Gregg Semenza and his collaborators discovered that hypoxia induced a nuclear accumulation of DNA-binding factor, which was *de novo* synthesized in several cell lines [8-11]. They called that protein hypoxia-inducible factor-1 (HIF-1). HIF-1 protein was able to bind to the promoter of human *Erythropoietin* (EPO) gene, which is a well-known hypoxia-inducible gene. They also observed that the binding of HIF-1 protein induced the transactivation of *EPO* gene in hypoxia. Subsequently, they cloned the *HIF-1 α* gene and identified the HIF-1 α protein [11]. At the same time, Peter Ratcliffe and his team clarified the oxygen-regulated, cis-acting enhancer sequences in target genes, such as *EPO* and *LDH-A* genes [12-14]. HIF-1 α protein can bind to a specific DNA sequence as a heterodimer with HIF-1 β protein, also known as *Aryl hydrocarbon receptor nuclear translocator* (ARNT). This binding site was termed the hypoxia response element (HRE), present at the promoters of hypoxia-inducible genes. Wang et al. [11] observed that HIF-1 α protein was post-translationally modified in hypoxia and its post-hypoxic decay was very rapid indicating that HIF-1 α protein is unstable in normoxia. In 2001, several studies demonstrated that HIF-1 α was hydroxylated by specific prolyl-4-hydroxylases (PHDs) and subsequently ubiquitinated by von Hippel-Lindau E3 ligase (pVHL) [15-17]. This ubiquitination directed HIF-1 α protein to proteasomal degradation. Interestingly, the PHD1-3 enzymes, also called EGLN1-3, are 2-oxoglutarate-dependent dioxygenases (2-OGDOs), which require O₂ for a substrate and thus they are inactive in hypoxia [5, 17, 18]. This dependency on oxygen prevents the hydroxylation of HIF-1 α protein in hypoxia and thus enhances its stabilization and subsequent transactivation of target genes. The 2-OGDO enzymes are not only sensors for oxygen availability but also for the presence of 2-oxoglutarate, a Krebs cycle intermediate, and iron homeostasis [19, 20]. In addition to PHD1-3, the 2-OGDO family includes both DNA and histone demethylases [21, 22], as discussed later. We have recently reviewed the potential role of 2-OGDO enzymes in the control of aging process [23].

The family of HIF factors contain three isoforms, of which HIF-1 α and HIF-2 α are activating factors and HIF-

3 α is an inhibitor lacking the C-terminal transactivation domain [24]. There seems to be another negative feedback system preventing the stabilization of HIF-1 α protein in hypoxia, since HIF-1 α increases the expression of PHD2/3 and thus can reduce the accumulation of HIF-1 α protein [25] (Fig. 1). HIF-1 α and HIF-2 α factors have distinct expression patterns in hypoxia as well as specific target genes although they both bind to the HRE elements [26, 27]. Moreover, they have various post-translational modifications, distinct interactions with other transcription factors, and thus they have clear functional differences. Gene expression profiling studies have indicated that HIF-1 α protein controls the expression of about 200-1000 genes, the most common target genes regulate angiogenesis, autophagy, glucose uptake, and glycolytic enzymes, i.e. those genes which increase adaptation to hypoxia [28, 29]. In addition, HIF-1 α factors control immune responses, embryonic development, and tumorigenesis [30, 31]. Hypoxia can also regulate gene expression via the generation of miRNAs, denoted hypoxamirs [32]. For instance, it has been observed that HIF-1 α induced the expression of miR-210, which subsequently affected mitochondrial metabolism, cell cycle progression, DNA repair, and cancer formation [33]. These examples indicate that HIF-1 α factor can stimulate a complex network of genes to facilitate the adaptation to hypoxia and enhance the survival of organisms.

Pseudohypoxia stimulates HIF-1 α signaling in normoxia

Reduced oxygen availability is not the only way to stimulate the HIF-1 α signaling. The activation of HIF-1 α and subsequent target gene expression under normal oxygen pressure is called pseudohypoxic response (Fig. 1). There are several mechanisms which can induce the HIF-1 α signaling in normoxia by e.g. (i) suppressing the activity of PHDs with mitochondrial metabolites, such as succinate and fumarate, as well as nitric oxide (NO) and iron chelators, (ii) inhibiting the VHL ligase-induced ubiquitination of HIF-1 α , (iii) stabilizing HIF-1 α expression through post-translational modifications, (iv) enhancing the transcription and transcriptional activity of HIF-1 α . In 2005, Selak et al. [34] observed that the inhibition of succinate dehydrogenase (SDH) in normoxia increased the accumulation of succinate, which consequently augmented the expression of HIF-1 α in human embryonic kidney cells. They demonstrated that succinate inhibited the activity of PHD *in vitro* and thus might have stabilized HIF-1 α protein. Consequently, Koivunen et al. [35] revealed that fumarate and succinate were potent inhibitors of all three PHDs and they also increased the expression of HIF-1 α and its target gene

VEGF in cultured cells. Pollard et al. [36] reported that the germline mutations of fumarate hydratase (*FH*) and *SDHB*, *-C*, and *-D* genes provoked the accumulation of fumarate and succinate into cultured cells and induced the over-expression of HIF-1 α , which promoted the appearance of different types of cancers. These studies clearly indicated that fumarate and succinate were competitive inhibitors of Fe²⁺/2-oxoglutarate-dependent PHDs and thus stabilized HIF-1 α expression in normoxia. Moreover, several studies have revealed that iron chelators are potent inducers of HIF-1 α expression, such as 1,10-phenanthroline and flavonoid quercetin [37, 38]. Given that hypoxia tolerance can provide protection against ischemic and inflammatory diseases, many drug discovery studies have been launched to develop effective inhibitors to PHD enzymes [39].

In 1998, Zelzer et al. [40] demonstrated that insulin and IGF-1 treatments stimulated the formation of HIF-1 α /HIF-1 β complexes, which could bind to HRE sites in Hep-G2 and muscle L8 cells. These complexes also transactivated the expression of HIF-1 α -dependent target genes. Subsequently, many studies confirmed that insulin and IGF-1 induced the HIF-1 α signaling via the phosphatidylinositol 3-kinase/target of rapamycin (PI3K/mTOR) pathway [41-43]. Moreover, the expression of phosphatase and tensin homolog (PTEN), an antagonizing phosphatase for the PI3K/mTOR pathway, inhibited the accumulation of HIF-1 α protein [41], whereas the loss of PTEN enhanced the PI3K/Akt-mediated HIF-1 α signaling [44]. Recently, Seok et al. [45] demonstrated that HIF-1 α stimulated the expression of miR-382, which targeted PTEN and thus could facilitate the PI3K/mTOR-mediated HIF-1 α signaling, e.g. potentiate tumor angiogenesis. It seems that mTOR activates the HIF-1 α signaling through increasing the transcription and translation of HIF-1 α rather than inhibiting its degradation [43, 46]. There are observations that AMP-activated protein kinase (AMPK) can inhibit the activity of PI3K/mTOR/HIF-1 α pathway [47]. In addition, mitogen-activated protein kinases (MAPK), especially p42/p44 MAPK, can phosphorylate HIF-1 α protein and thus increase its transactivation capacity [48], whereas glycogen synthase kinase 3 (GSK-3) phosphorylates HIF-1 α and consequently enhances its proteasomal degradation [49]. These observations indicate that the major protein kinase cascades can also control the HIF-1 α signaling (Fig. 1).

Inflammatory milieu of tissues commonly involves hypoxia and thus directly triggers the PHD-dependent activation of HIF-1 signaling. However, a substantial literature indicates that cytokines and the NF- κ B signaling can stimulate a pseudohypoxic HIF-1 α expression through different mechanisms [50-52] (Fig. 1). Pro-inflammatory cytokines, especially interleukin-1 β (IL-1 β)

and tumor necrosis factor- α (TNF- α), can increase the expression of HIF-1 α protein, which subsequently augments the expression of target genes [53-55]. There seems to be an autocrine loop in inflammation since HIF-1 α can bind to the HRE site at the promoter of *IL-1 β* gene and stimulate its expression [55]. van Uden et al. [56] demonstrated that the NF- κ B transcription factor induced the expression of HIF-1 α protein, and moreover, they reported that HIF-1 α expression promoted by TNF- α was mediated by the NF- κ B signaling in normoxia. Sun et al. [52] revealed that TNF receptor-associated factor 6 (TRAF6), a major activator of NF- κ B, could bind to HIF-1 α protein and induce its K63-linked polyubiquitination, which stabilized HIF-1 α protein against proteasomal degradation. On the other hand, an increased expression of HIF-1 α can repress the NF- κ B signaling and consequently suppress inflammatory responses [57]. Given that HIF-1 α can stimulate the expression of PHD2/3 [25], there seems to be a negative feedback route to inhibit NF- κ B system, enhanced by HIF-1 α expression. The cross-talk between NF- κ B and HIF-1 α in inflammation might be organized in cell type and context-dependent manner. In addition to the NF- κ B system, the JAK-STAT signaling, mediating cytokine and growth factor signaling, can also stimulate the expression of HIF-1 α protein (Fig. 1). Jung et al. [58] demonstrated that signal transducer and activator of transcription 3 (STAT3) can bind to the HIF-1 α protein and restrict the binding of pVHL ligase, thus stabilizing HIF-1 α protein in normoxia. Moreover, there are observations that the TGF- β /Smad3 signaling can increase the expression of HIF-1 α in normoxia by either inhibiting the expression of PHD2 [59] or activating the mTOR complex [60]. Sphingosine-1-phosphate (S1P) can also induce the expression of HIF-1 α protein in normoxia, indicating that ceramide pathway might also control the HIF-1 α signaling [61]. There may be different mechanisms since S1P can stimulate both the NF- κ B and STAT3 signaling pathways, which are the activators of HIF-1 α expression (see above). Nizet et al. [62] have reviewed the close interactions between hypoxia and innate immunity responses in the immune system and related diseases.

Aging and age-related degenerative diseases are associated with oxidative stress, probably partly linked to increased inflammation. Interestingly, there is abundant literature indicating that reactive oxygen species (ROS), such as hydrogen peroxide (H₂O₂) and nitric oxide (NO), can stabilize HIF-1 α protein in normoxia [63, 64]. However, there is still debate whether ROS can directly stabilize HIF-1 α in either normoxia or hypoxia [65, 66]. Mateo et al. [63] observed that increased NO production stabilized HIF-1 α protein in mitochondria-dependent or -independent manner in cultured HEK-293 cells. Metzen et al. [67] reported that NO inhibit PHDs, and thus it could

stabilize HIF-1 α protein. This same mechanism could also inhibit other 2-OGDO enzymes, such as KDMs [68], probably controlling the iron redox status. It seems that ROS affect the HIF-1 α signaling in a context-dependent manner and differently in cancer and ischemia [69].

The acetylation of HIF-1 α protein is one of the post-translational modifications, which control both the stability of HIF-1 α and its transcriptional activity. It is known that histone acetyltransferases, p300/CBP [70] and PCAF [71], can acetylate HIF-1 α protein and thus increase its stability and expression level in cultured cells. On the other hand, Lim et al. [72] demonstrated that SIRT1, a class III protein deacetylase, could bind to and subsequently deacetylate HIF-1 α protein, which blocked the recruitment of p300 acetyltransferase to target gene promoters, preventing the HIF-1 α -dependent gene transcription. This repression was more important in normoxia, since the activity of NAD⁺-dependent SIRT1 is repressed in hypoxia, attributable to a decrease in the level of NAD⁺ in hypoxia. However, Chen et al. [73] demonstrated that HIF-1 α increased the expression of SIRT1 in hypoxia, which might compensate the loss of SIRT1 activity. There are studies that some members of histone deacetylases (HDAC) of class IIA, such as HDAC5 [74], and HDAC7 [75], can increase the transcriptional activity of HIF-1 α , although mechanisms are mostly elusive. Interestingly, Chen et al. [74] revealed that HDAC5 deacetylated heat shock protein 70 (HSP70) in the cytosol, which dissociated the complex between HSP70 and HIF-1 α proteins and consequently increased the nuclear accumulation of HIF-1 α , both under hypoxia and low glucose conditions. They also reported that the AMPK-induced phosphorylation of HDAC5 increased its transfer back to the cytosol and thus enhanced the capacity of HDAC5 to translocate HIF-1 α proteins into the nuclei. HIF-1 α is a client protein of HSP90, which interaction stabilizes HIF-1 α protein against proteasomal degradation in normoxia [76]. Liu et al. [77] demonstrated that the receptor of activated protein kinase C (RACK1) competed with HSP90 for the binding to the same domain in HSP-1 α protein. RACK1 is a multifunctional scaffold protein which stimulated the O₂-independent proteasomal degradation of HIF-1 α . Subsequently, Liu et al. [78] reported that calcineurin, a Ca²⁺-activated protein phosphatase, stimulated the expression of HIF-1 α since it dephosphorylated RACK1, which blocked its dimerization and binding to HIF-1 α protein. These observations indicate that disturbances in calcium homeostasis, observed in many age-related diseases, can stabilize HIF-1 α protein in normoxia.

In conclusion, it seems that a plethora of stress-related signals in normoxia can stimulate the HIF-1 α signaling and in that way enhance survival responses but also

aggravated pathological processes associated with the HIF-1 α signaling.

Table 1. HIF-1 α -inducible histone lysine demethylases (KDMs)

KDM	Target	References
KDM2B FBXL10, JHDM1	H3K4me3& H3K36me1,2	[89]
KDM3A JMJD1A, JHDM2A	H3K9me1,2	[85-91, 93]
KDM4B JMJD2B	H3K9me2,3 & H3K36me2,3	[85-87, 89, 91, 92]
KDM4C JMJD2C	H3K9me2,3 & H3K36me2,3	[85, 86, 89]
KDM5B JARID1B	H3K4me2,3	[87, 89]
KDM6B JMJD3	H3K27me2,3	[89, 95]

The formerly used symbols of KDMs are marked below the official symbols.

HIF-1 α induces the expression of distinct histone lysine demethylases

DNA and histone methylation are the two major epigenetic mechanisms which regulate gene expression. The methylation status of histones is controlled by histone methyltransferases and histone demethylases [79]. The methylation of histone C-terminal lysines can either activate or repress gene expression, i.e. typical activating marks are histone 3 di- or trimethylated lysine 4 (H3K4me2,3) and H3K36me2,3, whereas H3K9me1,2 and H3K27me2,3 are common repressive sites (Table 1). There are six Jumonji C domain containing histone lysine demethylases (KDM2-7), which can remove both activating and repressing methyl groups in an enzyme specific manner [21, 80, 81]. For instance, the demethylases of KDM3 and KDM6 subgroups are the potent activators of gene expression erasing the methyl groups from the repressive H3K9 and H3K27 sites, respectively. The Jumonji-type of KDMs contain different protein-protein binding domains through which they can specifically interact with distinct chromatin proteins, such as histone deacetylases, transcription factors and other chromatin proteins [21, 80]. All

Jumonji-type of histone demethylases are the members of 2-oxoglutarate-dependent dioxygenase family (2-OGDO); this means that they are dependent on the availability of oxygen and 2-oxoglutarate, a Krebs cycle intermediate, similarly to PHDs (see above). However, they are not as sensitive oxygen sensors as PHDs [82-84]. In 2008, Pollard et al. [85] screened the effects of hypoxia on the expression levels of several Jumonji-type of histone demethylases in many cultured cell lines. They observed that the expression of *KDM3A* and *KDM4B* mRNAs but not that of several other demethylases were significantly induced in U2OS, MCF7, HeLa, IMR32 and HL60 cells cultured in 0.5% O₂ pressure. They also revealed that the promoters of *KDM3A* and *KDM4B* genes contained three putative HRE binding sites, which were not present in the promoters of the non-responsive demethylases. Moreover, they reported that HIF-1 α proteins could directly bind to these sites at the promoters of *KDM3A* and *KDM4B* genes. Beyer et al. [86] also demonstrated that hypoxia stimulated the HIF-1 α -dependent expression of *KDM3A* and *KDM4B* mRNAs and proteins in cultured cells (Table 1). Moreover, they observed that hypoxia did not affect the global levels of di- and trimethylated H3K9 indicating that *KDM3A* and *KDM4B* proteins have specific binding partners and distinct targets in the genome. Krieg et al. [87] reported that only a few of the hypoxia-inducible genes are dependent on the presence of *KDM3A* (53 out of 821) in RCC4 cells. This subset included e.g. adrenomedullin (*ADM*), heme oxygenase 1 (*HMOX1*), and *SERPINE1*. The *KDM3A*-induced increase in the expression of these genes was associated with a decrease in the level of repressive H3K9me₂ marks at the target promoters. Many other studies have also reported that hypoxia stimulated the expression of *KDM3A* and *KDM4B* genes in different cellular contexts [88-92] (Table 1). Interestingly, Wellmann et al. [93] demonstrated that the normobaric hypoxia (8% O₂) of rats robustly increased the expression of *KDM3A* in all tissues studied, e.g. brain, heart, and liver. Given that *KDM3A* and *KDM4B* are the major histone demethylases which remove the repressive H3K9 sites, their role as transcriptional cofactors seems to be important in the activation of HIF-1 α signaling.

The di- and trimethylated H3K27 (H3K27me_{2,3}) is another major repressive histone site in the control of gene transcription. Moreover, H3K27me₃ marks are associated with the polycomb complexes, which can repress long genomic domains and also organize the chromosomal 3D structures [94]. *KDM6A* (UTX) and *KDM6B* (JMJD3) are the two major H3K27me_{2,3} demethylases [80, 81]. Recently, Lee et al. [95] demonstrated that the hypoxic conditions clearly increased the expression of *KDM6B* in a HIF-1 α -dependent manner in NIH-3T3, 3T3-L1, and mouse embryonic fibroblasts (MEF) (Table 1). They also

reported that the promoter and first intron of human *KDM6B* gene contained several HRE sites. Moreover, clioquinol, an iron chelator and pseudohypoxic inducer of HIF-1 α expression, strongly induced the expression of *KDM6B* in human adipose-derived stem cells. In addition to HIF-1 α , the expression of *KDM6B* can be stimulated by NF- κ B, STAT3, and ATF4 signaling pathways [96]. A robust induction of *KDM6B* by HIF-1 α suggests that *KDM6B* is an important hypoxia-inducible transcriptional cofactor, which demethylates repressive H3K27me_{2,3} sites, although its role in the modification of global chromatin landscape still needs to be clarified.

Xia et al. [89] used a genome-wide screening to identify the direct binding targets of HIF-1 transcription factor. They observed that *KDM4C* (*JMJD2C*) and *KDM5B* (*JARID1B*) also contained HRE sites for the binding of HIF-1 factors, in addition to the above mentioned demethylase genes (Table 1). The expression of these enzymes was significantly increased in HepG2 cells in the hypoxic conditions [89]. Moreover, Pollard et al. [85] and Beyer et al. [86] reported that the expression of *KDM4C* was modestly increased in cultured hypoxic cells. Accordingly, Krieg et al. [87] confirmed that *KDM5B* also was a hypoxia-inducible gene (Table 1). Moreover, the genome-wide screening by Xia et al. [89] revealed that the expression of *KDM2D*, *KDM3B/3C*, *KDM5C*, and *KDM6A* were up-regulated in a HIF-1 α -dependent manner in Hep G2 cells. These observations have not been confirmed by other studies. It seems that hypoxia stimulates both activating and repressive epigenetic marks to enhance or inhibit the expression of distinct genes in hypoxic conditions although excessive activation can aggravate pathological processes.

Oxygen deprivation inhibits the activity of histone lysine demethylases

Molecular oxygen is an obligatory co-substrate for the Jumonji-type histone demethylases [21] as well as for other 2-OGDO enzymes, e.g. PHD1-3 [18]. However, there is a great variation for the requirement of O₂ tension in the catalytic mechanism of different 2-OGDO enzymes [68, 83, 86, 91, 97]. PHDs are clearly more sensitive hypoxic sensors than Jumonji-type histone demethylases. For instance, Beyer et al. [86] demonstrated that the 1% O₂ tension did not affect the activity of transfected *KDM3A* and *KDM4B*, whereas the reduction of O₂ pressure down to 0.2% compromised the activity of *KDM3A* and *KDM4B*. In contrast, it is known that a modest decrease in O₂ level can stimulate a robust hypoxic response, e.g. in mouse kidney with a chronic treatment at 11% O₂ pressure [98] or disturb coronary

artery development in a HIF-1 α -dependent manner at 15% O₂ tension [99].

There is a complex situation in the control of Jumonji-type demethylases in the conditions where oxygen availability is reduced. Tausendschön et al. [91] demonstrated that the 1% O₂ exposure robustly increased the expression of KDM3A and KDM4B in mouse macrophages, although simultaneously there was a slight increase in the methylation levels of H3K9me_{2,3} and H3K36me₃, which might indicate a decrease in the activity of these demethylases. On the other hand, it is possible that the effects of hypoxia on the activity of Jumonji-type histone demethylases is not caused by the deficiency of O₂ as a substrate but through the hypoxia-induced other responses, e.g. increased NO production (Fig. 1). Hickok et al. [68] demonstrated that the NO exposure inhibited the activity of KDM3A enzyme in vitro by forming a nitrosyl-iron complex in the catalytic domain of this 2-OGDO enzyme. They also reported that NO production in cultured cells increased the global level of H3K9me₂ indicating an inhibition of KDM3A although other Jumonji-type of demethylases targeting H3K9me₂ could also have been inhibited. Moreover, NO can inhibit PHDs, including in 2-OGDO enzymes, and thus stabilize HIF-1 α protein [67]. This might also explain why the NO treatment increased the expression of KDM3A and some other Jumonji-type histone demethylases in cultured cells [68].

The hypoxia-induced alterations in the methylation status of H3K4, H3K9, H3K27, and H3K36, at either global or specific promoter level, are commonly explained as changes in the activities of specific KDMs. However, this is not the correct parameter since hypoxia also affects the expression of histone lysine methyltransferases. For instance, hypoxia stimulates the expression of G9a, an H3K9 site methyltransferase, in cultured cells [100]. Hypoxia can also increase the recruitment of histone methyltransferases to specific promoters, e.g. that of SuvH1 and SuvH2 (both are H3K9 methyltransferases) to the promoter of surfactant protein A (SP-A) gene [101]. Moreover, Set7, an H3K4 methyltransferase, can directly methylate HIF-1 α and HIF-2 α proteins and thus inhibit their transcriptional activity [102]. These examples emphasize the complexity to interpret the mechanisms behind the changes in histone methylation induced by hypoxic conditions.

Hypoxia modifies histone methylation

Several studies have revealed that hypoxia provokes epigenetic changes in the chromatin landscape, which consequently affect the transcriptional profiles of tissues [28, 103-105]. However, hypoxia is a complex subject since results are dependent on many details in hypoxic

treatments, e.g. the type of model (acute/chronic or constant/intermittent), oxygen level during exposure, and post-hypoxia timing, even transgenerational changes. Moreover, hypoxic training can induce hypoxic/ischemic tolerance [106], which involves an appearance of specific epigenetic signature [107]. Hypoxia tolerance is also associated with increased lifespan, e.g. in the case of naked mole rats [108]. Moreover, hypoxia is present in the pathogenesis of many age-related diseases, such as cardiovascular diseases and Alzheimer's disease, which involve substantial epigenetic alterations in the chromatin landscape [109, 110]. Currently, it is not known how hypoxia generates chromatin changes, which can be either protective enhancing hypoxic tolerance or detrimental provoking pathological changes. However, it is clear that epigenetic alterations, such as the stimulation of distinct KDMs, are crucial mechanisms in the induction of HIF-1 α -mediated hypoxic response [111] (Fig. 1).

Histone methylation in collaboration with DNA methylation has a key role in the control of chromatin structure and gene expression [112]. Histone demethylases control gene expression via different mechanisms, i.e. they can (i) enhance or repress the initiation of transcription by binding to the initiation complex and demethylating epigenetic histone marks, (ii) increase the rate of transcription elongation by binding to Pol II and removing methyl groups from the histones locating in gene bodies, (iii) recruit co-activators to the initiation complex in a demethylase-independent manner [80, 113]. There are many studies indicating that the hypoxia-inducible KDMs control gene expression through the histone demethylation of target gene promoters [87, 89, 92]. Fu et al. [92] demonstrated that the hypoxia-induced overexpression of KDM4B decreased the level of H3K9me₃ at the promoters of target genes, whereas the depletion of KDM4B increased H3K9 methylation. Johnson et al. [114] reported that the promoters of hypoxia-activated genes (*VEGF* and *EGRI*) displayed a marked increase in the acetylation of H3K9 sites, while there was a significant loss in the levels of H3K9me₂ and H3K27me₂. In contrast, at the promoters of hypoxia-repressed genes (*AFP* and *ALP*), hypoxia caused a decrease in the acetylation of H3K9 sites, whereas the methylation of H3K9 and H3K27 increased. These examples underline the crucial role of hypoxia-inducible KDMs as the amplifiers of HIF-1 α -mediated hypoxic stress responses. However, the induction of KDMs by hypoxia/pseudohypoxia might have other targets than HIF-1 α -dependent genes, which could affect the global gene expression and even the maintenance of chromatin structure. For instance, the KDM4 family members are associated with carcinogenesis, i.e. they are highly expressed in many cancers and an experimental overexpression increased tumor growth and enhanced

invasion [115, 116]. Toyokawa et al. [115] revealed that KDM4B promoted cell cycle progression by demethylating H3K9me3 sites at the promoter of cyclin-dependent kinase 6 (CDK6). Awwad and Ayoub [117] demonstrated that the overexpression of KDM4 genes increased genomic instability by disrupting the DNA mismatch repair system. It is known that the DNA mismatch repair pathway is impaired with aging and age-related pathologies [118]. Moreover, the overexpression of KDM6B can induce the expression of specific genes linked to the senescence-associated secretory phenotype (SASP) and consequently provoke cellular senescence including blebbing of nuclei in glioma cells [119]. The nuclear blebbing indicates profound disturbances in the polycomb-driven 3D maintenance of nuclear structure, which we will discuss later.

Severe chronic hypoxia, as commonly used in experimental models, induces a reduction in gene transcription and protein synthesis, which consequently impair the appearance of HIF-1 α -dependent responses [114, 120]. Most probably this also affects histone methylation during hypoxia since some processes are dependent on protein synthesis, e.g. hypoxia-inducible KDMs, whereas others are independent. This could explain why the results on global histone methylation during hypoxia are inconclusive. Many studies have detected a hypermethylation e.g. in H3K9me2,3, and H3K36me3 levels [83, 84, 105]. This is in line with the repression of transcription observed during hypoxia. As discussed earlier, hypoxia also stimulates the expression of G9a, which could induce the hypermethylation of H3K9 sites [100]. However, it is not known whether this is a counteraction to the induction of KDM3A and KDM4B. Interestingly, many studies have indicated that hypoxia also induces global DNA hypermethylation in several model systems [121-123]. This effect seems to be linked to the induction of DNA methyltransferases 1 (DNMT 1) and 3b (DNMT3b) in hypoxia. Currently, it is recognized that histone methylation can control DNA methylation and *vice versa* [112]. DNA methylation is a more permanent epigenetic mark than histone methylation and thus disturbances in histone methylation status might trigger profound changes in chromatin landscape, e.g. with aging and in associated diseases.

Hypoxia-inducible histone demethylases control chromatin landscape and function

Jumonji histone demethylases have many important functions in addition to the gene-specific activation or repression of HIF-1 α -dependent transcription. KDM proteins contain specific binding domains, which can mediate interactions between KDMs and several

chromatin proteins as well as some DNA loci. This means that hypoxia and pseudohypoxia affect not only gene expression but also chromatin structures, e.g. the maintenance of heterochromatin and polycomb complexes which can silence large genome sequences and preserve chromosome configuration. Both the constitutive and facultative heterochromatin involve DNA regions with increased histone methylation of H3K9, H3K27, and H3K36 sites, which are assembled by heterochromatin protein 1 (HP1) and histone methyltransferases, such as those in polycomb complexes [124-126]. Heterochromatin is a platform for the binding of chromatin effector proteins participating in e.g. gene silencing and the formation of 3D higher-order chromosome foldings [94]. However, heterochromatin regions, especially facultative segments, are dynamic structures since HP1 proteins can recruit Jumonji histone demethylases, which activate the transcription in heterochromatin repeats [127-129]. In particular, the hypoxia-inducible H3K9 and H3K27 demethylases have a key role in the dissociation of heterochromatin segments. Transient hypoxia typically causes a short-term induction of HIF-1 α signaling and changes in gene expression, whereas chronic exposure to hypoxia can have detrimental effects on heterochromatin maintenance and DNA integrity (Fig. 1).

There is substantial evidence that the overexpression of KDM3, KDM4, and KDM6 demethylases decreases the methylation level of repressive H3K9 and H3K27 marks (Table 1) and reduces the amount of heterochromatin, a condition which is commonly associated with e.g. cancers [116, 130, 131]. On the other hand, an increased expression of KDM2 and KDM5 down-regulate the methylation of H3K4 sites and thus enhances the maintenance of heterochromatin segments and genome stability [132]. In addition to histone demethylase-dependent functions, many KDMs also have enzyme-independent, linker protein properties via their different protein-protein binding domains. Abe et al. [133] demonstrated that KDM3A has a key role in the β -adrenergic-induced gene expression by interacting with the SWI/SNF nucleosome remodelling complex. Protein kinase A (PKA) phosphorylated KDM3A at S265, which subsequently triggered its interaction with the SWI/SNF complex. Consequently, this larger complex was located to the target gene promoters with peroxisome proliferator-activated receptor γ (PPAR γ) transcription factor. Currently, it is not known whether KDM3A is involved in the other activities of the SWI/SNF complex, e.g. those of DAF-16/FOXO-mediated stress resistance and increased longevity [134]. Mimura et al. [135] reported that KDM3A interacted with HIF-1 α at the promoter of *GLUT3* gene in hypoxic vascular endothelial cells increasing the expression of *GLUT3* and subsequently

enhancing glycolysis. They also revealed that the binding of KDM3A to HIF-1 α induced changes in the chromatin conformation at the *SLC2A* (*GLUT3*) locus under hypoxia. This indicates that KDM3A affects chromatin structures to facilitate transcription in hypoxia.

There is an interesting diversity how the members of KDM4 subfamily respond to hypoxia, i.e. the expression of KDM4B and KDM4C increases but that of KDM4A and KDM4D is unaffected [85, 86, 89]. All KDM4 enzymes are highly expressed in many cancers, most likely they have different functions in carcinogenesis [116]. KDM4A has an important role in the regulation of heterochromatic loci in the collaboration with HP1 α . Some studies indicate that HP1 α can target and consequently stimulate the activity of KDM4A [128], although some experiments suggest that HP1 α can antagonize the function of KDM4A [136]. KDM4A can also induce a site-specific increase in gene copy number, a typical phenomenon in cancers [137]. Moreover, KDM4 members are involved in the repair of DNA damages [138-140]. Zheng et al. [138] demonstrated that tumor suppressor p53 protein promoted heterochromatin DNA repair by inducing the expression of hypoxia-inducible KDM4B, which enhanced the relaxation of constitutive heterochromatin and thus improved DNA repair. In addition, Young et al. [140] reported that γ -irradiation recruited KDM4B to DNA damages in a PARP-1 - dependent manner and that the overexpression of KDM4B enhanced the repair of double-strand breaks (DSB). However, Awwad and Ayoub [117] observed that the overexpression of KDM4A-C, especially that of KDM4C, could disrupt the integrity of the DNA mismatch repair system, subsequently impairing the maintenance of genomic stability. These studies indicate that the members of KDM4 subfamily have a crucial role in the DNA repair systems, although the responses seem to be enzyme-specific and appear in a context-dependent manner.

The CpG islands are important DNA sequences in gene promoters controlling gene expression [141]. KDM2A and KDM2B proteins contain a domain called ZF-CxxC, which mediates the binding of these demethylases to non-methylated CpG islands (CGI) [21]. In 2012, Farcas et al. [142] demonstrated that both KDM2A and KDM2B proteins interacted with non-methylated CGIs, and remarkably, those sites enriched with KDM2B also contained protein components of polycomb repressive complex 1 (PRC1). Farcas et al. [142] and Wu et al. [143] revealed that KDM2B interacted with the RING1B component of PRC1 complex, which catalyzed the lysine 119 monoubiquitylation of histone H2A (H2AK119ub1). The ubiquitylated H2AK recruited the PRC2 complex to non-methylated CGI sites, and consequently the EZH2 component, a H3K27 methyltransferase, trimethylated H3K27 sites repressing

the target gene expression [144, 145]. Moreover, Tzatsos et al. [146] demonstrated that the overexpression of KDM2B repressed the expression of two microRNAs, *let-7* and *miR-101*, which are silencers of EZH2 methyltransferase, and thus KDM2B increased the capacity of PRC2 complex to enhance H3K27 methylation, e.g. in the INK4 box preventing cellular senescence (see below). Frescas et al. [147] observed that KDM2B was localized in the nucleolus, where it blocked the transcription of RNA genes. This indicates that KDM2B has a significant role in the regulation of repressive polycomb system and thus it can control, e.g. developmental processes, cancer formation, and cellular senescence [148, 149]. For instance, KDM2B promotes the generation of induced pluripotent stem cells (iPSC) [150].

The four members of human KDM5 subfamily of Jumonji demethylases (KDM5A-D) demethylate H3K4me_{2,3} and thus they repress gene expression [21, 81]. The subfamily has also been called JARID1A-D, since they contain an AT-rich interaction domain (ARID), which mediates the DNA binding of these enzymes. They also comprise the PHD (plant homeobox domain) and zinc finger C5HC2 domains. It is known that KDM5B enzyme is included in many chromatin modifying complexes, such as the nucleosome remodelling and deacetylase complex (NuRD) [151, 152], PRC2 complex [153], and SWI/SNF complex [154]. KDM5B is a potent inhibitor of gene expression not only through the demethylase domain but it also interacts with histone deacetylases (HDAC), those of class I and IIa HDACs [152, 155]. On the other hand, poly (ADP-ribose) polymerase-1 (PARP-1) binds to KDM5B protein and inhibits its activity by poly(ADP-ribosyl)ation [156]. Through this activity, PARP-1 can maintain open chromatin architecture and activate target gene expression. KDM5B can also be SUMOylated, which affects its recruitment to target genes but does not inhibit its demethylase activity [157]. Hendriks et al. [158] demonstrated that DNA damages induced the SUMOylation of KDM5B and KDM5C proteins. Subsequently, the SUMOylated KDM5B protein was ubiquitylated and degraded by proteasomes. Instead, SUMOylated KDM5C was recruited to the chromatin complexes, where it demethylated H3K4me_{2,3} sites inhibiting gene expression. KDM5B has an important role in tissue differentiation during development, since in association with polycomb complexes it silences the lineage-inappropriate genes, e.g. in neural differentiation [159, 160].

KDM6A (UTX) and KDM6B (JMJD3) demethylate repressive H3K27me_{2,3} marks in the transcription of genes as well as they antagonize the polycomb-induced gene silencing processes and enhance the displacement of

polycomb complexes from the specific gene loci, e.g. from the INK4 box (see below). In view of these functions, KDM6 demethylases have a fundamental role in programming of chromatin structures during developmental processes. Saha et al. [161] demonstrated that the first mammalian cell lineage commitments during blastocyst formation are regulated by KDM6B. There is substantial evidence that KDM6B regulates e.g. the neural commitment and neurogenesis [162], endodermal [163], mesodermal and cardiovascular differentiation [164]. Dahle et al. [165] demonstrated that the Nodal-Smad2/3 signaling recruited KDM6B to *Brachyury* locus to displace repressive polycomb complexes in embryonal stem cells to trigger the formation of mesoderm and endoderm. T-box transcription factors recruit KDM6B proteins to specific gene loci to switch on cell-type specific gene expression patterns [166]. The T-bet protein induced commitment of CD4⁺ T cells into different Th subtypes [167] and the activation of *Eomes* gene locus in endodermal differentiation [163] are some examples of the cooperation between KDM6B and T-box factors. Given that KDM6B can regulate the developmental programs, it is interesting that KDM6B can also activate the INK4 box (see below), containing tumor suppressor genes, which induce cellular senescence [168]. Recent studies have revealed that cellular senescence has fundamental role in the aging process and age-related diseases. We will discuss the function of KDM6B in the regulation of INK4B box in the next section.

Does excessive HIF-1 α stimulation disturb chromatin landscape with aging and associated diseases?

Currently, it seems that HIF-1 α signaling can have positive and negative effects on the regulation of longevity [169]. There are some dramatic examples that the living in hypoxic conditions is associated with a significant increase in the lifespan of animals, e.g. subterranean blind mole rats can live for 30 years [108] and ocean quahog *Arctica islandica* for hundreds of years [170]. Shams et al. [171] demonstrated that the expression of HIF-1 α was not only higher in normoxic kidney of *Spalax* compared to *Rattus norvegicus* but the induction of HIF-1 α expression was especially enhanced in hypoxia, being 6-fold higher in *Spalax* than *Rattus norvegicus*. However, it is not known whether increased hypoxic stress tolerance is related to longer lifespan. There are many reports indicating that the stimulation of HIF-1 α expression in hypoxia is declined with aging [172-174]. Interestingly, Ndubuizu et al. [173] revealed that the age-dependent decline in hypoxia-inducible expression of HIF-1 α was correlated with an increased expression of PHD1 in rat brain. Rohrbach et al. [175] reported that the expression of PHD3 was significantly increased in rat

heart, liver, and skeletal muscle with aging. An increased expression of PHDs can be a negative feedback response to increased HIF-1 α expression, since some studies have demonstrated that HIF-1 α induces the transcription of PHDs and thus protects against the chronic stimulation of HIF-1 α [25, 176].

Hypoxia-dependent regulation is not the only mechanism, which can stimulate the HIF-1 α signaling (Fig. 1). There are a number of cellular signaling pathways, which can induce the transcription of HIF-1 α factor, stabilize its expression, or enhance its transactivation capacity (see above). Interestingly, many of these pathways are associated with the ageing process and age-related diseases. For instance, there is an abundant literature indicating that excessive oxidative stress can be a causative factor in the aging process and many age-related diseases [177]. Oxidative stress is commonly linked to a chronic, low-grade inflammation and the activation of NF- κ B signaling [178, 179], also an inducer of HIF-1 α expression. The ceramide and TGF- β signaling pathways are involved in the pathogenesis of many age-related diseases, such as atherosclerosis [180, 181]. The insulin/PI3K/mTor signaling pathway is a well-known regulator of longevity through the species [182]. Moreover, dysfunctions in mitochondrial metabolism can affect both the aging process and age-related diseases [183]. All the above-mentioned mechanisms can increase the level of HIF-1 α and thus stimulate the expression of hypoxia-inducible KDMs in normoxia (see above). There is substantial evidence that the HIF-1 α signaling has a protective function in acute insults, e.g. in ischemic conditions [184], whereas the effect seems to be harmful in chronic diseases, such as age-related macular degeneration (AMD) [185], cancer progression [186], chronic kidney disease [187], cardiomyopathies [188], and adipose tissue fibrosis and inflammation [189]. Most of these chronic responses are caused by damaging effects of excessive angiogenesis and fibrosis induced by HIF-1 α . It appears that there is no negative feedback loop in the PHD-independent control of HIF-1 α signaling (Fig. 1). This may cause detrimental effects, which are linked to epigenetic changes, e.g. in fibrotic lesions of myocardium and atherosclerotic arteries [188, 190, 191]. Recent epigenetic studies have clearly shown that the aging process is associated with significant changes in the chromatin landscape [192-194]. Genome-wide DNA methylation screenings have revealed a so-called epigenetic drift, which shows a decline in global DNA methylation although distinct DNA regions, e.g. CpG islands, display an increase in DNA methylation with aging. Moreover, it was observed that the progeroid mutations of Hutchinson-Gilford and Werner syndromes abundantly promoted the age-related changes in DNA methylation and chromatin structure, e.g. decrease in the

amounts of H3K9me3 and constitutive heterochromatin [195-197]. Loss of heterochromatin also is a typical hallmark in cellular senescence and aging process [198-200], which impairs the maintenance of DNA integrity with aging. Larson et al. [199] reported that enhanced heterochromatin formation promoted longevity in *Drosophila*. Concurrently, the aging process is linked to global decrease in the levels of H3K9me3 and H3K27me3, repressive epigenetic marks [201]. Given that gene silencing by polycomb complexes and heterochromatin loci are dependent on trimethylation of H3K9 and H3K27 sites, it implies that the activation of KDM4 and KDM6 demethylases might induce changes in chromatin landscape with aging. Fodor et al. [130] reported that KDM4B antagonized the generation of H3K9me3 at the pericentric heterochromatin. Recently, many studies have revealed that there are remarkable epigenetic changes in atherosclerotic vessels, e.g. reduced levels of H3K9me_{2,3} and H3K27me_{2,3} [190, 191]. Epigenetic alterations have also been reported in cardiovascular diseases [202] as well as in obesity and metabolic syndrome [203]. Angiogenesis, critically involved in cancer and AMD progression, can be augmented by the stimulation of KDM3A [204], KDM5B [205], and KDM6B [206], the expression of which is highly enhanced by HIF-1 α (Table 1).

Cellular senescence, i.e. an irreversible cell growth arrest, is associated with remarkable global alterations in chromatin landscape [207, 208] along with changes in cellular morphology, metabolism, and function [209]. Several studies have demonstrated that the presence of senescent cells in tissues increases with aging [210, 211] as well as in chronic age-related degenerative diseases [212, 213]. Senescent cells secrete many inflammatory mediators, growth factors and proteases, and thus they can promote the aging process and age-related diseases [209, 214]. The INK4 box, containing *INK4a*, *INK4b*, and *ARF* genes, is a crucial tumor suppressor locus and an inducer of cellular senescence [168, 215]. *INK4a* (p16) and *INK4b* (p15) are cyclin D-dependent kinase inhibitors, while *ARF* (p19) is an activator of p53-dependent functions. It is known that the expression of these factors controls not only proliferation but also cellular senescence. A substantial literature indicates that the function of INK4 box is under a tight epigenetic regulation [216, 217]. The INK4 box is repressed in proliferating cells through the local transcription of *ANRIL*, a non-coding RNA, which recruits the PRC2 complex to the INK4 box. Subsequently, the EZH2 methyltransferase of PRC2 trimethylates H3K27 sites and silences the transcription in the INK4 locus. KDM6B has a key role in the activation of transcription in the INK4 box since it demethylates H3K27me₃ sites and releases polycomb complexes from the locus [218-220]. Different

types of stresses can activate the transcription in the INK4 box and trigger cellular senescence through the demethylation of H3K27me₃ sites and thus displacing polycomb complexes. Given that most of the pseudohypoxic inducers of HIF-1 α are associated with cellular stress, it is conceivable that an increased expression of KDM6B can provoke the transcription in the INK4 locus. Interestingly, the *ANRIL* gene is a genetic susceptible locus for many age-related diseases [221].

It is known that the retinoblastoma (RB) tumor suppressor pathway has a major role in the onset of cellular senescence [209]. There are observations that KDM5B can trigger cellular senescence in association with the RB pathway [222, 223]. RB protein recruits KDM5B to the promoters of E2F target genes, many of which are cell-cycle regulators, silencing their expression and subsequently inducing senescence. Narita et al. [224] observed that the formation of senescence-associated heterochromatic foci (SAHF) was also triggered by the RB-dependent inhibition of E2F genes, probably through the KDM5B-mediated H3K4 demethylation. It appears that KDM6B protein activates the expression of tumor suppressors in the INK4 box, whereas KDM5B proteins directly inhibit the transcription of E2F-dependent cell-cycle factors. However, the role of HIF-1 α in the generation of cellular senescence seems to be more complicated. There are observations that acute hypoxia can stimulate cell-cycle arrest but does not provoke cellular senescence in all contexts, even it can suppress the oncogene-induced senescence [225, 226]. There are studies indicating that mTOR activation is required to trigger the conversion of arrested cells to senescent ones (geroconversion) [227]. The nuclear translocation of p53, mediated by KDM6B, can also enhance the geroconversion through the expression of p21/CIP1, a cyclin-dependent kinase inhibitor [228]. On the other hand, hypoxia and HIF-1 α stimulate the expression of KDM2B and KDM5B, which can repress gene expression through the demethylation of activating H3K4me_{2,3} marks in the INK4 box and thus enhance proliferation [148] (see above). It seems that HIF-1 α can control cellular fate in adult animals, either stimulating proliferation or triggering cellular senescence, by regulating the expression of different KDMs in a context dependent manner.

The HIF-1 α signaling has an important role in the innate immunity responses, e.g. in inflammation, macrophage polarization, and T cell activation [229]. It is known that KDM6B has important functions in immune host defence responses. We have recently reviewed the role of KDM6B in the regulation of inflammatory responses associated with the aging process [96]. Given that cellular senescence is linked with inflammatory phenotype [209], it is interesting that KDM6B is a potent

enhancer of inflammatory genes, especially in association with NF- κ B signaling [230, 231]. Remarkably, the NF- κ B pathway is an important inducer of cellular senescence-associated secretory phenotype (SASP) [232]. Moreover, there are studies indicating that KDM6B is an important activator of TGF- β signaling pathways by binding to Smad3 factor [165]. Subsequently, Smad3 can cooperate with NF- κ B signaling [233]. The TGF β -Smad3 signaling controls fibrosis and inflammation, e.g. in chronic kidney diseases [234]. Perrigue et al. [119] observed that the overexpression of KDM6B induced the expression of genes related to the SASP. Zhao et al. [235] observed that the level of KDM6B protein was significantly increased in senescent cells and it promoted the formation of heterochromatic SAHF foci. Cells expressing the properties of SASP accumulate during ageing and age-related diseases, although their role in the tissue ageing process and pathology needs to be clarified [214].

Hypoxia is an important inducer of fibrogenesis, or fibrosis, in many tissues and especially, it is linked to the pathogenesis of many age-related diseases [189, 236, 237]. Pathological fibrosis involves excessive deposition of fibrous connective tissue into healthy or injured organs, e.g. myocardium, lungs, kidney, and adipose tissue. There seems to be two mechanisms, (i) the conversion of fibroblasts or other stromal cells to myofibroblasts and (ii) the transition of epithelial or endothelial cells to mesenchymal cells, i.e. the epithelial-mesenchymal transition (EMT). EMT is also a critical mechanism in embryonal morphogenesis and cancer metastasis [238]. The HIF-1 α and TGF- β signaling pathways are the major inducers of EMT, although signaling networks also contain other factors in a context dependent manner [239-241]. Many studies have indicated that epigenetic factors control the hypoxia-induced EMT, as reviewed by Stadler and Allis [242] and Wu et al. [241]. Ramadoss et al. [243] demonstrated that KDM6B promotes the TGF- β -induced EMT by enhancing *Snail* expression in mammary epithelial cells, whereas its knockdown prevented EMT. Dahle et al. [165] revealed that the TGF- β /Nodal signaling activated the *Brachyury* locus by recruiting Smad2/3 and KDM6B to its promoter in embryonal stem cells. It is known that the induction of Brachyury expression promotes interstitial fibrosis in renal tubuli [244]. The Brachyury protein is included in the T-box

transcription factors. Given that KDM6B cooperates with T-box factors in cell lineage commitment (see above), it is obvious that KDM6B also drives EMT fibrosis in adult tissues as soon as the HIF-1 α and TGF- β signaling pathways are excessively activated in pathological conditions. The stimulation of KDM6B and T-box factors reorganize the chromatin structures and consequently induce either cancerous growth or fibrogenesis, which is a common age-related deleterious response in many tissues.

Conclusions

The HIF-1 α signaling is a principal survival mechanism in acute hypoxic insults, where hypoxia-inducible KDMs are confined to support the transcription of genes comprising hypoxia response. However, it can be converted to detrimental response in some host defence condition, e.g. in chronic hypoxia and long-term pathological stresses, as soon as the activation of KDMs disturbs the maintenance of chromatin structures, e.g. heterochromatin repressed DNA segments and 3D folding of chromosomes, or stimulates embryonal processes, such as the EMT fibrosis. It seems that the HIF-1 α -inducible KDMs have a crucial role in the activation of genes in the INK4 box as well as the RB-stimulated tumor suppressor genes, which both provoke a cell fate called cellular senescence. Senescent cells are deleterious for neighbouring cells since they secrete inflammatory mediators and thus they can activate signaling pathways known to stabilize the HIF-1 α signaling. Given that cellular senescence is an irreversible alteration, it provides an inflammatory milieu which activates the HIF-1 α -inducible KDMs and thus jeopardizes the nearby cells. This vicious cycle is increasingly present in the aging process and especially in the age-related diseases.

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Conflicts of interests

The authors declare no conflict of interest.

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