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Epigenetic remodelling under hypoxia

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ABSTRACT

Hypoxia is intrinsic to tumours and contributes to malignancy and metastasis while hindering the efficiency of existing treatments. Epigenetic mechanisms play a crucial role in the regulation of hypoxic cancer cell programs, both in the initial phases of sensing the decrease in oxygen levels and during adaptation to chronic lack of oxygen. During the latter, the epigenetic regulation of tumour biology intersects with hypoxia-sensitive transcription factors in a complex network of gene regulation that also involves metabolic reprogramming. Here, we review the current literature on the epigenetic control of gene programs in hypoxic cancer cells. We highlight common themes and features of such epigenetic remodelling and discuss their relevance for the development of therapeutic strategies.

1. Introduction

Hypoxia occurs when the demand for oxygen exceeds the supply and arises in several homeostatic and pathological contexts such as embryonic development [1], ischemia-induced cardiovascular disease [2], and, of importance for the present review, under tumorigenesis. Indeed, because of their rapid growth and their dysfunctional vascular supply, solid tumours contain large hypoxic areas [3,4]. Tumour hypoxia is associated with a poor prognosis for cancer patients due to increased malignancy, metastasis, and treatment resistance [4]. Mechanistically, the reduction of oxygen levels directly triggers a cascade of epigenetic events, and this epigenetic remodelling sustains the chronic hypoxic phenotypes. As described below, epigenetic mechanisms are thus pivotal in the initial response to hypoxia as well as in the adaptation of cancer cells to chronic low levels of oxygen.

Epigenetic mechanisms correspond to reversible and heritable changes to the chromatin fibre with consequences on gene expression, without altering the primary nucleotide sequence [5,6]. The repeating functional unit of the chromatin fibre is the nucleosome: a segment of DNA wrapped around an octamer of histone proteins (Fig. 1) [7,8]. Chemical modifications of the DNA and histone tails, as well as changes in the degree of nucleosome compaction, distinguish states of chromatin organization that dictate DNA-templated processes such as transcription. Specifically, heterochromatin is a densely compacted form of chromatin that displays little transcriptional activity [9], whereas euchromatin corresponds to looser chromatin, accessible to the transcriptional machinery. Epigenetic processes can additionally be directed by non-coding RNA (ncRNA)-mediated modifications of the chromatin structure and can alter the three-dimensional organization of chromatin domains in the nucleus (Fig. 1). Here, we extensively review the epigenetic mechanisms resulting from the early sensing of oxygen reduction in cancer cells. We further discuss the contribution of epigenetic mechanisms in the establishment and maintenance of transcriptional programs under chronic hypoxia in oncogenesis.

Cancer cells have adapted in a remarkable manner to survive and proliferate in chronically low levels of oxygen. This cellular response to

Abbreviations: 5-AzadC, 5-aza-2'-deoxycytidine; 5hmC, 5-hydroxymethylcytosine; 5fc, 5-formylcytosine; 5caC, 5-carboxylcytosine; 5mC, 5-methylcytosine; α-KG, alpha-ketoglutarate; bp, base pairs; CGI, CpG island; DNMTs, DNA methyltransferases; FDA, Food and Drug Administration; HAT, histone acetyltransferase; HDAC, histone deacetylase; HDACi, histone deacetylase inhibitor; HIF, hypoxia-inducible factor; *HITT*, HIF-1α inhibitor at translation levels; HKMT, histone lysine methyltransferase; HREs, hypoxia-response elements; JHDM, Jumonji C (JmjC) domain-containing histone demethylase; KAT, lysine acetyltransferase; kb, kilobases; lncRNA, long non-coding RNA; LSD, lysine-specific demethylase; miRNA, microRNA; ncRNA, non-coding RNA; piRNA, piwi-interacting RNA; PRMT, protein arginine methyltransferase; PTM, post-translational modification; SAM, S-adenosyl-methionine; TAD, topologically associating domain; TET, ten-eleven translocation; TFs, transcription factors; TSG, tumour-suppressor gene.

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hypoxia is largely guided by hypoxia-sensitive transcription factors (TFs), such as hypoxia-inducible factor 1α (HIF-1α) and its paralogues HIF-2α and HIF-3α [10,11]. Upon hypoxia, HIF-1α is rapidly stabilized and dimerizes with HIF-1β, after which it translocates to the nucleus and binds specific DNA motifs (HREs, hypoxia-response elements). This promotes the transcription of genes that counter and accommodate hypoxia, being involved in angiogenesis, proliferation, and metabolic adaptation [11]. However, if the role of HIF-1α in hypoxic programs is interlinked with epigenetic mechanisms, and if HIF-1α stability and binding to its cognate HREs is dependent upon epigenetic marks, the hypoxic epigenome of cancer cells encompasses global remodelling beyond HIFs [11,12]. In the present review, we further explore the different mechanisms of epigenetic reprogramming occurring under hypoxia and discuss their contribution to tumorigenesis and metastasis.

2. DNA methylation dynamics under hypoxia

DNA methylation is an epigenetic mark that consists of the covalent addition of a methyl group onto the fifth carbon position of cytosine pyrimidine rings (5mC), in mammals, mainly in the context of CpG dinucleotides [13]. Dense clusters of CpGs can be found in specific loci termed CpG islands (CGIs) that are often associated with core promoters of housekeeping genes [14,15]. DNA methylation of promoter CGIs leads to transcriptional repression [16] and is involved in a variety of biological processes, including oncogenesis [17–20]. Genome-wide mapping has shown that dynamic DNA methylation also occurs in other topographic regions than CGIs, such as CGI shores, defined as the 2 kb sequences flanking a CGI [21,22], CGI shelves [23], and open sea sites [24], although the biological significance of these DNA methylation marks for transcriptional control remains largely elusive.

DNA methylation patterns are controlled by two classes of epigenetic enzymes. Three DNA methyltransferases (DNMTs) – DNMT1, DNMT3a and DNMT3b – catalyse the transfer of methyl groups from S-adenosylmethionine (SAM) deriving from the one-carbon metabolism to cytosines [25,26]. Canonically, DNMT1 is considered a maintenance epigenetic enzyme, responsible for copying DNA methylation patterns during replication and repair [27,28], whereas DNMT3a and DNMT3b are responsible for *de novo* DNA methylation during development [29]. Note however that this functional segregation between DNMTs appears oversimplified, as several studies now show that all three DNMTs cooperatively contribute to DNA methylation profiles in somatic cells [25,30]. Erasure of DNA methylation marks, or DNA demethylation, can occur passively through the loss of maintenance of methylation patterns during DNA replication [31]. An active mechanism of DNA demethylation also occurs through the activity of the ten-eleven translocation (TET) family of epigenetic enzymes [32–35]. The three TET enzymes, TET1, TET2 and TET3, are alpha-ketoglutarate (α-KG)-dependent dioxygenases that iteratively catalyse the hydroxylation of 5mC in 5-hydroxymethylcytosine (5hmC), then in 5-formylcytosine (5fC) and 5-carboxylcytosine (5caC), that can be efficiently removed by base-excision DNA repair machinery [35,36].

Several layers of regulation are involved in the dynamic control of DNA methylation. First, 5mC, 5hmC, and derivative forms of cytosines can be bound by specific classes of TFs that serve as epigenetic integrators and recruitment scaffolds for TETs and/or DNMTs, particularly on regulatory regions [16,37]. For instance, HIF-1α binding to its cognate HREs is inhibited by DNA methylation [38] and in hypoxic neuroblastoma, HIF-1α was demonstrated to recruit TETs to maintain its HREs in an unmethylated, accessible state [39]. Second, the enzymatic activity of TETs and DNMTs can be modulated in response to varying environmental cues. For example, since TETs are dioxygenases, their enzymatic function is directly impaired by limiting O_2 concentration [36]. As a consequence, pathophysiological levels of hypoxia were shown to directly provoke a decrease in global levels of 5hmC in cancer cells, which caused focal increases in DNA methylation [40]. Finally, and as we will discuss further below, cellular metabolism also impacts

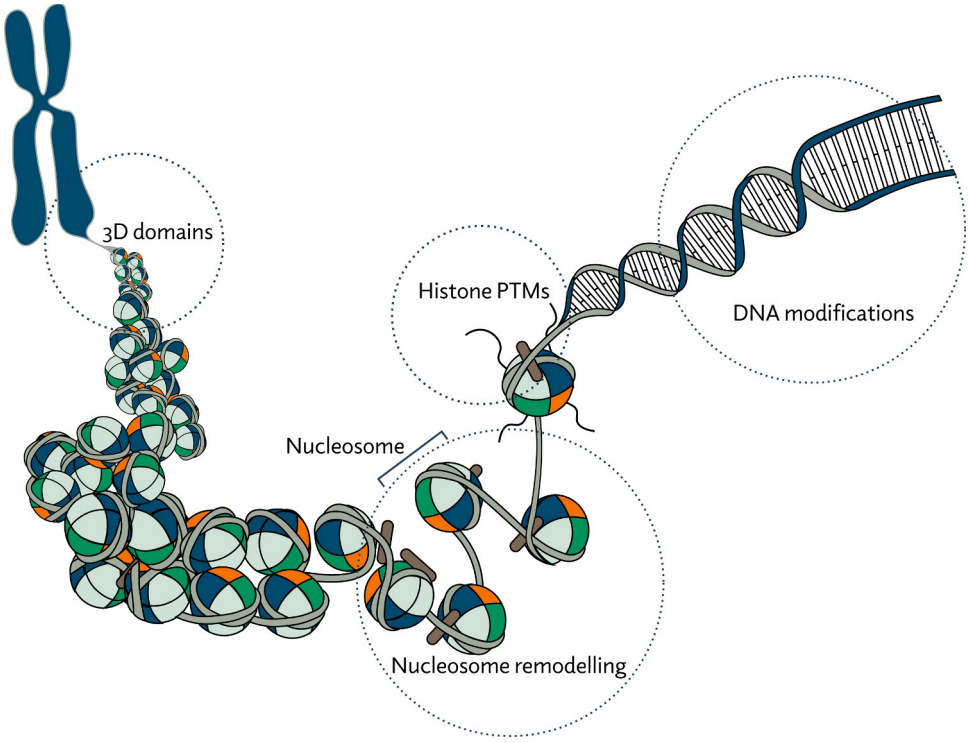

Fig. 1. The chromatin fibre is a substrate for epigenetic modifications. The nucleosome is the fundamental repeating unit of chromatin, in which 146 base pairs of DNA are wrapped around an octamer composed of two copies of each histone protein H2A, H2B, H3 and H4. Each nucleosome core is linked to the next by a segment of linker DNA that varies in length, from 10 to 80 bp. The nucleosomal array further arranges in higher-order condensed structures stabilized by the linker histone H1.

the bioavailability of key metabolites involved in epigenetic modifications, with consequences on gene expression [41,42].

The redistribution of DNA methylation marks is a hallmark of cancer with some loci displaying hypermethylation in a globally hypomethylated genome [17–19,43]. Hypermethylation of promoter CGIs of tumour-suppressor genes (TSGs) leads to their inactivation and contributes to oncogenesis through changes in transcriptional programs associated with cell cycle control, DNA repair and angiogenesis [17–20]. Hypermethylation of non-promoter CpGs that control gene expression (for instance on enhancers) has also been linked to neoplastic progression in multiple cancer types [18]. In general, hypoxia reduces global DNA methylation levels through the concomitant control of DNMTs and TETs expression levels and enzymatic activity (Fig. 2).

During the initial phase of oxygen reduction in cancer cells (1–24 h), DNMTs expression was shown to transiently increase [44,45] before steadily decreasing upon chronic hypoxic conditions over several weeks [44,46]. In particular, the lack of DNMT1 maintenance of DNA methylation profiles, combined with the proliferation of hypoxic cancer cells, would reinforce global hypomethylation [46,47]. Of note, similar decreased expression of DNMTs has been reported in non-cancerous hypoxic contexts such as endometriosis [48], pointing towards a conserved control of DNMT expression under chronic hypoxia. Indeed, the promoter regions of DNMT1 and DNMT3a present HREs [49], suggesting that HIFs control DNMT expression. In addition to a control of DNMT expression, their enzymatic activity might also be perturbed under hypoxia. In liver cancer cells cultured under 1% of O_2, the level of SAM was increased [50], while another study showed a decreased level of SAM in xenograft liver tumours under the same conditions [45]. Discrepancies between these studies might result from different cellular contexts, the timing of oxygen reduction and variations in the techniques used to quantify SAM accurately. Nevertheless, changes in local SAM concentrations might impact the methylation potential of hypoxic cancer cells, although more studies are needed to clarify this metabolic-mediated layer of epigenetic regulation. Taken together, studies show that DNMT expression and activity are diminished under chronic hypoxia in cancer cells. This reinforces the genome-wide hypomethylation that is a hallmark of cancer. Although the biological significance of such decreased DNA methylation under hypoxia remains obscure, global hypomethylation is a feature of stem-cell programs [51]. In this sense, hypoxia-induced global DNA hypomethylation would participate in tumour pathobiology through cancer stemness [52,53]. In cancer cells, global DNA hypomethylation can also drive ectopic transcription initiation, by licensing otherwise silent enhancers and cryptic promoters [54]. Methylation-sensitive transcription factors including HIFs are particularly responsive to this reduced methylation and can drive overexpression of novel, unconserved transcripts that can activate immune response programs through viral mimicry [38,54–56].

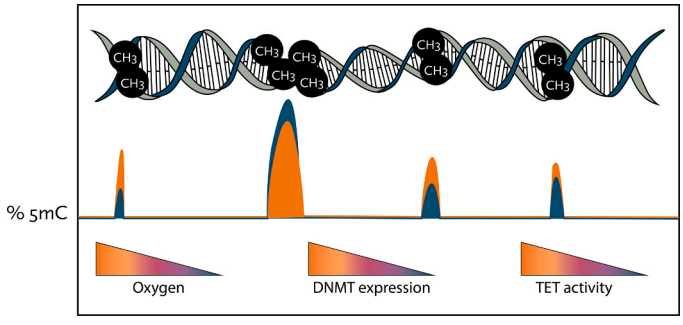

Fig. 2. DNA methylation profiles are remodelled under hypoxia. Hypoxia is associated with a general decrease in DNA methylation profiles due to decreased DNMT expression and activity. TET activity is directly impaired by the lack of oxygen but their expression increases, which may suggest compensatory mechanisms. This results in some loci being hypermethylated. Normoxic DNA methylation profiles (%5mC) are represented in orange, whereas hypoxic profiles are in blue.

In parallel to alterations in DNMT expression and stability, the balance of DNA methylation in hypoxic cancer cells is also controlled through tight regulation of TET expression and activity. Loss of TET expression is a hallmark of solid tumours and leads to growth, invasiveness, and metastasis [57]. Paradoxically, under hypoxic conditions, TET expression levels are upregulated in multiple cancer types through HIF1-α binding of their promoter HREs [58,59]. This may suggest that non-catalytic functions of TETs are of importance in cancer hypoxia, or that TET overexpression is required to maintain DNA methylation turnover under catalytic activity-limiting conditions [57]. Indeed, as discussed above, pathophysiological hypoxic conditions maintain an environment that is unfavourable for TET methylcytosine dioxygenase activity, leading to decreased 5hmC levels [40]. In these non-physiological conditions, hypoxia rather than HIF-1α appears to control the dynamics of DNA demethylation in cancer cells, as treatments that stabilize HIF-1α do not rescue TET activity in cells with only a modest TET upregulation [40]. In addition to the restriction of oxygen levels, hypoxic conditions also maintain a metabolic environment that limits TET activity, through multiple mechanisms of regulation of α-KG levels [11]. Interestingly, if hypoxic conditions are maintained over time, the hypoxia-induced decrease in 5hmC is accompanied by a specific increase in local 5mC on the promoters of genes repressing cell cycle arrest, DNA repair and apoptosis, consistent with these transcriptional programs being altered in tumour hypoxia [40]. Chronic and severe hypoxia thus leads to a redistribution of DNA methylation marks in cancer cells: while hypomethylation is reinforced, hypermethylation of TSGs and repetitive elements is also observed (Fig. 2)[40].

3. Nucleosome and histone remodelling under hypoxia

In addition to DNA modifications, epigenetic mechanisms include nucleosome positioning, remodelling and post-translation modifications (PTMs) of histone tails. Here, we briefly review the evidence for the role of these epigenetic modifications in tumour hypoxia.

3.1. *Nucleosome positioning*

Nucleosomes play a crucial role in gene expression by directly affecting the assembly or the progression of the transcriptional machinery, in addition to serving as structural components of the chromatin [60,61]. Multiple factors dictate nucleosome positioning, including the DNA sequence itself, DNA-binding proteins, and chromatin remodellers [62]. Chromatin remodellers rely on the energy provided by ATP hydrolysis to weaken DNA:histones interactions, thereby resulting in sliding, spacing, transfer or eviction of nucleosomes from specific loci [62]. While much less studied than DNA methylation, several works have revealed that the genes encoding ATP-dependent chromatin remodellers are often mutated in human cancers [63,64], pointing towards their role in driving oncogenic programs. In non-cancerous hypoxic contexts, a recent chromatin accessibility study has indicated the important role of HIF-1α in the control of nucleosome deposition under chronic deprivation of oxygen [65]. More generally, the few works that have investigated the role of chromatin remodellers in tumour hypoxia indicate an interplay with HIF-1α, either through regulation of its expression [66,67] or by co-regulation of its target genes [68–70]. However, some evidence also suggests that chromatin remodellers may modulate gene expression under hypoxia independently of HIFs since their nuclear localization is directly subjected to oxygen regulation [71]. Whether chromatin remodellers participate in the initial response to oxygen deprivation in cancer cells still needs to be determined. Another open question is the functional role of chromatin remodelling in the oncogenic programs of tumour hypoxia, which has further implications for the development of anti-cancer therapies [64].

3.2. Histone acetylation

Several PTMs of histone amino-terminal tails have been associated with variations in chromatin structure and gene expression regulation [72,73]. Acetylation of histone lysine residues by acetyltransferases (HATs) neutralizes their electric charge and weakens their interaction with the negatively charged DNA, resulting in a loosened chromatin structure, and heightened transcriptional capacity [72,74]. In this case, acetyl-coA serves as the acetyl group donor, thereby further linking epigenetic reactions and metabolism [75]. Acetylated lysines can be bound by specific classes of bromodomain-containing proteins that serve as a scaffold for the binding of effector proteins in transcriptional regulation [76]. Furthermore, HATs, more generally referred as to lysine acetyltransferases (KATs), are also responsible for the acetylation of non-histone proteins, such as general transcription factors [77], which leads to an additional layer of gene expression regulation. Histone acetylation is thus a dynamical and versatile epigenetic mark in the regulation of gene expression.

As for the other epigenetic marks discussed in the present review, acetylation of histones can be linked to tumour hypoxia independently of, or in conjunction with, HIFs (Table 1). In particular, the interaction of HIF-1α with p300/CREB-binding protein (CBP) was one of the first indications of hypoxia-induced epigenetic reprogramming [78]. Since then, multiple studies have shown that several HATs serve as epigenetic co-activators together with HIF-1α in promoting oncogenic programs [79,80] and that HIF-1α expression and stability themselves are dependent on acetyltransferases [81–84]. However, genome-wide interrogation of histone acetylation in hypoxic cancer cells is still lacking. In non-cancerous hypoxic contexts, severe hypoxia has been shown to decrease the global levels of H3 acetylation [85] and H4 acetylation [86], which may act together with decreased DNA methylation in the transcriptional control of cellular proliferative programs [86]. Still, the mechanisms involved in hypoxia-induced regulation of histone acetylation need to be determined. In particular, whether HIFs control the expression of HATs or whether HATs can sense variations in oxygen levels remain open questions. This is particularly important since it appears that histone acetylation is regulated at the global level through common mechanisms in different hypoxic contexts. Furthermore, histone acetylation and DNA methylation appear to crosstalk in regulating gene expression under hypoxia.

Histone deacetylases (HDACs) are a group of enzymes responsible for erasing acetylation from lysines[87]. In opposition to HAT activity, HDACs strengthen the electric interaction between DNA and histones and are thus generally involved in gene repression [87]. Again, HDACs also regulate gene expression through the deacetylation of other substrates than histones [87]. In this context, HIF-1α stability, binding and epigenetic control of gene expression are finely tuned by several HDACs [88–93], which expression is also increased under hypoxia (Table 1) [94]. This has led to the proposition of using different HDAC inhibitors (HDACi) to counteract HIF-1α-induced transformation as anti-cancer therapeutic approaches [95,96]. Although with off-target effects and a poor understanding of the fundamental epigenetic mechanisms at play, current clinical strategies are now exploring the combination of HDACi with immunotherapies [97].

Table 1
Histone modifiers involved in the epigenetic reprogramming of cancer cells under hypoxia. Histone modifiers, classified by family, involved in the epigenetic reprogramming of cancer cells either in a HIF-dependent manner or independently of HIF are in bold.

Histone acetyltransferases		
Family	Members	References
GNAT	KAT2A/GCN5, **KAT2B/PCAF**	[84]
MYST	**KAT5/TIP60**, KAT6A/MOZ/MYST3, KAT6B/MORF/MYST4, KAT7/HBO1/MYST2, **KAT8/MOF/MYST1**	[80,83]
p300/CBP	**KAT3B/p300, KAT3A/CBP**	[78,81,82]
Histone deacetylases		
Family	Members	References
Class I	**HDAC1, HDAC2, HDAC3**, HDAC8	[82,88,94]
Class IIa	**HDAC4, HDAC5, HDAC7**, HDAC9	[90–92]
Class IIb	**HDAC6**, HDAC10	[93]
Class III (Sirtuins)	**SIRT1–7**	[89]
Class IV	HDAC11	n/a
Histone demethylases		
Family	Members	References
KDM	**LSD1/KDM1A**, LSD2/KDM1B	[166]
JMJD	**KDM2–8** classes that contain over 30 members	[110–112]
Histone methyltransferases		
Family	Members	References
HKMTs	ASH1L, DOT1L, **EHMT1–2**, EZH1, **EZH2**, MLL1–4, NSD1–3, **SETD1A**, **SETD1B**, SETD2, SETD7, **SMYD2–3**, SUV39H1–2, SUV420H1–2,	[121–124]
PRMTs	CARM1/PRMT4, PRMT1, **PRMT5**–7	[125]

3.3. Histone methylation

Histone methylation corresponds to the addition of one, two or three methyl groups, either on lysine residues of histone tails (H3K4, H3K9, H3K27, H3K36, H3K79 and H4K20) by histone lysine methyltransferases (HKMTs) or one or two methyl groups on arginine residues of histone tails (H3R2, H3R8, H3R17, H326 and H4R3) by protein arginine methyltransferases (PRMTs) [17,98]. The function of histone methylation as an epigenetic mechanism in the regulation of gene expression depends on the number of methyl groups added and their position within the genome on specific regulatory sequences [99]. For instance, trimethylation of H3 histone lysine 4 (H3K4me3) on promoter regions is a signature of active transcription [100] whereas trimethylation of H3 histone lysine 9 (H3K9me3) on the same regions is generally a repressive mark [101]. In particular, the different functions of histone methylation in gene regulation are dependent on the recruitment of specific epigenetic effectors (possessing chromo- or plant homeo- domains) and crosstalk with other epigenetic mechanisms [99]. The reverse mechanism, histone demethylation, is catalysed by two classes of epigenetic enzymes: the lysine-specific demethylases (LSDs) and the α-KG-dependent Jumonji C (JmjC) domain-containing histone demethylases (JHDMs) [102–104]. Together, histone methylation thus emerges as a dynamic epigenetic mechanism that participates in the regulation of gene expression through several modes: depending on its position in regulatory sequences and its recruitment of effector proteins, as well as through the control of the methylation of other proteins than histones [17,99].

The different modes of gene expression regulation by histone methylation are well-represented during tumour hypoxia (Table 1). For instance, HIF-1α is known to induce the expression of multiple JHDMs [105–109]. Some of these JHDMs also serve as epigenetic co-regulators of hypoxia target genes in cancer cells [110–112], including HIF-1α itself [113,114]. Paradoxically to this increased expression, as α-KG-dependent dioxygenases, JHDM enzymatic activity is directly hindered in the early sensing of the lack of oxygen [104] and, to a lesser extent, by the metabolic rewiring that limits α-KG levels [11]. In this regard, it has been proposed that the increased expression of JHDMs might compensate for their decreased enzymatic activity to maintain histone methylation homeostasis under chronic hypoxia [105,107,115]. This phenomenon is reminiscent of TETs, which expression increases when the limiting oxygen concentration restricts their catalytic activity [57] and places both JHDMs and TETs as epigenetic sensors for oxygen. As a consequence of the inhibition of JHDMs' enzymatic activity, hypoxia directly and rapidly promotes the retention of di- and trimethylation on several H3 histone lysine residues (H3K4, H3K9 and H3K27) at specific loci involved in oncogenic transcriptional programs [110,115–118]. Specificity in the control of histone methylation under hypoxia might arise from JHDMs' different sensitivity to oxygen [105,115,118] or

crosstalk with other epigenetic mechanisms [110,119,120]. Of note, the duration of hypoxia (i.e. intermittent vs. chronic) appears to play a differential role in the regulation of JHDMs' expression and activity, indicating how histone methylation turnover is finely tuned in response to oxygen sensing [114]. Finally, more recent works have shown that histone methyltransferases also act as regulators of, and epigenetic co-activators to, HIF-1α [121–125]. These latter results illustrate that histone methylation homeostasis under early and chronic hypoxia still needs to be further addressed in cancer cells. In particular, the mechanisms by which HIFs control the dynamics of histone methylation on their target genes by recruiting different subsets of epigenetic complexes are poorly understood. Whether dynamical histone methylation remodelling occurs over time and across the genome in response to hypoxic signals is also largely unknown.

3.4. Histone PTMs and metabolism

Cellular metabolism has emerged as an important actor in the epigenetic control of cancer programs [41,42,126]. The lack of oxygen directly triggers a metabolic response in cancer cells, through the inhibition of oxidative phosphorylation for instance, and this metabolic remodelling is further rewired by HIF-1α under chronic hypoxia [11]. We have discussed above how metabolites can impact the dynamics of DNA methylation and histone PTMs. In addition, recent works have described novel histone PTMs that are directly linked to cellular metabolism, including different forms of lysine acylation, such as propionylation, crotonylation, malonylation, succinylation, glutarylation [76,127], and lysine lactylation [128]. In particular, under hypoxia, lactate accumulates from the fermentation of pyruvate [11]. Rather than a waste product, emerging evidence suggests that accumulating lactate has biological significance, specifically in epigenetic mechanisms, although how histone lactylation contributes to tumour hypoxia responses still needs to be studied [129].

Finally, histone citrullination is a lesser-known histone PTM wherein arginine residues are hydrolysed to citrulline [130]. Recently, hypoxia was shown to increase the expression of the enzymes involved in histone citrullination, resulting in a HIF-dependent increase in histone citrullination and the transcriptional control of glycolysis [131,132].

Collectively, recent works have shown the extent of the interplay between epigenetics and metabolism in tumour hypoxia. With a constantly expanding repertoire of histone PTMs, future studies will need to assess their interplay in the coordinated control of oncogenic programs under hypoxia.

4. Non-coding RNA-mediated epigenetic regulation under hypoxia

Advances in high-throughput sequencing have shown that most of the human genome does not encode proteins but rather non-coding RNAs (ncRNAs) [133]. Classification of ncRNAs is mainly done by size, with transcripts longer than 200 nucleotides being called long ncRNAs (lncRNAs) and smaller transcripts categorized as microRNAs, piwi-interacting RNAs and other classes [133,134]. The molecular functions of ncRNAs in gene expression are widespread and ever-evolving, nevertheless, some ncRNAs have been shown to participate in the epigenetic control of gene expression [134]. It is well appreciated that ncRNAs play a role in the regulation of oncogenesis [135,136]. Several works also show an epigenetic function for lncRNAs in tumour hypoxia, mainly in a HIF-dependent fashion [137,138].

Multiple cellular lncRNAs are upregulated through HIF-1α binding of their HREs and contribute to the general transcriptional programs associated with cancer progression [139,140]. In addition, some of these hypoxia-induced lncRNAs serve as co-regulators to HIF-1α, although the mechanisms at play are often lacking [137,138]. LncRNAs are known to participate in the concerted epigenetic control of gene expression through crosstalk with other epigenetic mechanisms, mainly by serving as a scaffold in the recruitment of epigenetic enzymes [134]. In this context, one study showed that *HITT* (HIF-1α inhibitor at translation levels), a lncRNA whose expression decreases under hypoxia, directly recruits repressive histone methyltransferases on the HIF-1α promoter [141]. Thus, *HITT* was shown to suppress hypoxic adaptative survival by inhibiting HIF-1α expression, which explains why this lncRNA is frequently downregulated in human cancers [141]. Another recent study showed that *HIFAL* (HIF Antisense lncRNA) accumulates in the nuclei of breast cancer cells upon hypoxia where it promotes HIF-1α transactivation activity on its target genes through the recruitment of multiple co-activators, including p300/CBP [142]. Importantly, in vivo targeting of both *HIFAL* and HIF-1α showed synergistic effects in repressing breast cancer growth in xenograft tumours [142]. Indeed, beyond fundamental mechanisms, lncRNAs can serve as biomarkers for disease progression and as therapeutic targets [143], which warrants further investigation into their general role in tumour hypoxia.

Collectively, several lines of evidence demonstrate the remodelling of the non-coding transcriptome under hypoxia in cancer cells. While the vast majority of studies have focused on lncRNAs, other classes of ncRNAs, such as piwi-interacting RNAs, have emerged in recent years as epigenetic mediators in the control of gene expression [144]. Further studies will thus need to establish how expression profiles of ncRNAs are altered in response to oxygen reduction in cancer cells and how they contribute to oncogenesis. Another interrelated layer of regulation might also arise from the post-transcriptional chemical alterations of ncRNAs, or epitranscriptomics [145]. Although, again, additional investigations are needed to confirm their functional significance to tumour hypoxia.

5. Chromatin spatial regulation under hypoxia

It has long been established that individual loci spread along the genome can interact. For instance, promoter and enhancer "looping" allows the physical proximity of the transcription machinery and the control of gene expression [146]. With the advent of genome-wide techniques, this three-dimensional organization of chromatin in the control of transcription has emerged as a widespread and complex epigenetic mechanism [147,148]. Indeed, chromatin transits between higher-order spatial territories possessing different transcriptional competence [147,148]. Furthermore, aberrant chromatin conformation and remodelling of chromatin spatial distribution increasingly appear as hallmarks of cancer [149]. For instance, alterations in enhancer-promoter interactions can directly lead to the transcriptional silencing of TSGs [149]. However, how hypoxia could directly or indirectly affect the chromatin spatial distribution in cancer cells and how this contributes to oncogenesis has scarcely been studied so far. One recent work showed that the induction of hypoxia-responsive gene programs was accompanied by a global spatial remodelling of the genome [150]. In particular, a subset of HIF-1α target genes was relocated within the nucleus upon hypoxia [150]. However, this spatial relocation did not correlate with the transcriptional activity of the HIF-1α target genes [150], which suggests that other regulatory mechanisms might be at play. For instance, HIF-1α target genes relocation might not directly alter their expression but have a more indirect effect in tumorigenesis through modulation of the transcriptome or crosstalk with other epigenetic mechanisms. Furthermore, it is unclear whether specific HIF members might contribute differently to chromatin remodelling in the three-dimensional space. In this regard, another work in thyroid cancers showed that the boundaries of topologically associating domains (TADs), regions of chromatin that frequently interact with one another, were delineated by binding sites for HIF-2α [151]. Thus, it appears that hypoxia modulates the spatial distribution of chromatin. However, the specific molecular mechanisms controlling this remodelling still need to be elucidated.

Beyond the spatial definition of higher-order chromatin domains, recent works have also illustrated that chromatin is organized within

nuclear membraneless compartments, based on its liquid-like properties and the existence of phase separation phenomena [152–154]. The biological significance of such chromatin condensates is only emerging, yet pioneer studies reveal their implication in the epigenetic control of gene expression in cancer [155,156]. So far, no study has addressed the role of chromatin condensates in tumour hypoxia. However, one report recently showed that HIF-1α stability is regulated in nuclear condensates segregated around the mono-ADP-ribosylase TiPARP, which indicates that nuclear membraneless compartments participate in the hypoxic response in cancer cells [157]. With the observation that known epigenetic actors in tumour hypoxia are located within chromatin condensates [155], future studies are expected to demonstrate the role of liquid phase separation in the epigenetic control of hypoxia.

6. Epigenetic-based therapeutic strategies in tumour hypoxia

Tumour hypoxia considerably reduces the efficiency of conventional radiotherapy and chemotherapy while contributing to stemness, invasiveness and metastasis [4]. Because epigenetic mechanisms play a crucial role in the adaptation of cancer cells to low oxygen conditions, epigenetic drugs have been proposed as novel agents, alone or in combination with other selective drugs, in the clinical management of cancer [158]. The proposed strategy is to use drugs that target epigenetic modifiers to reconfigure the chromatin profile of cancer cells to a baseline non-resistant state, a process referred to as episensitization [159].

Since aberrant DNA methylation patterns are a hallmark of cancer, inhibitors of DNA methylation such as the deoxycytidine analogue 5-aza-2'-deoxycytidine (5-AzadC, decitabine) have attracted much clinical interest [160]. In particular, 5-AzadC, branded as Dacogen, has been approved by the US Food and Drug Administration (FDA) for close to twenty years in the treatment of haematological malignancies [160]. However, the clinical efficiency of 5-AzadC in targeting specifically the hypoxic fractions of solid tumours has not been much assessed. One study showed that in renal cell carcinoma, the transporters for 5-AzadC were downregulated upon hypoxia, which therefore prevented the entry of this epidrug in the target cells [161]. Zebularine, another cytidine analogue that acts as a DNA methylation inhibitor [162], was found to potentiate chemotherapy in colorectal cancer cells [163]. However, the authors found that this sensitization was not mediated by DNA methylation, but rather, through a specific effect on HIF-1α protein stability, leading to the inhibition of angiogenesis [163]. Considering the specific redistribution of DNA methylation marks in hypoxic cancer cells and the downregulation of DNMTs in chronic hypoxia [44,46], the broad inhibition of DNMT activity might not be a relevant approach for episensitization. Rather, the understanding of the molecular mechanisms responsible for the maintenance of hypoxic-specific hypermethylated loci might help devise new epigenetic therapies. Additionally, it should be noted that poor vascularization of tumours not only limits the availability of oxygen but also the delivery of therapeutic agents [164], suggesting that a two-tiered approach is needed, involving both inhibition of epigenetic dysregulation and normalization of the blood supply.

Another avenue in the use of epigenetic drugs in the episensitization of hypoxic tumours has been the targeting of histone modifiers [158]. Akin to 5-AzadC, some HDACi have been approved by the FDA and successfully used in the clinical management of haematological malignancies [158]. However, treatment of solid tumours with HDACi has been less successful and, as explained above, associated with extensive off-target effects [95,96]. One proposed approach to achieve more specificity has been the use of combination therapies of different classes of epidrugs, for instance, regimens of 5-AzadC and HDACi [158]. Indeed, the existence of epigenetic crosstalk in the adaptation of cancer cells to hypoxia represents a barrier to the development of efficient therapies. However, our fundamental understanding of the extent of this epigenetic crosstalk is still insufficient in the perspective of developing novel epitherapies.

7. Concluding remarks

Epigenetic processes are crucial for integrating environmental changes into gene expression programs. In cancer, alterations in the tumour microenvironment, such as changes in oxygen levels, directly impact the epigenome, particularly in terms of chromatin methylation. Further adaptation to chronic hypoxia is encoded through a HIF-dependent cellular response that is exquisitely co-regulated at the epigenetic and metabolic levels. Collectively, the epigenetic remodelling under hypoxia in cancer cells is markedly characterized by its complex interplay, its dynamics in oxygen sensing and its adaptation to extracellular changes. Yet, much of the fundamental understanding of the epigenetic mechanisms of tumour hypoxia is still in its infancy. So far, few studies have addressed how multiple epigenetic mechanisms concertedly regulate cancer gene programs. With the development of multi-omics techniques, researchers will be able to investigate combined epigenetic and metabolic effects [165]. In particular, the emergence of multi-omics at the single-cell level will enable the inclusion of epigenetic heterogeneity in each patient and each cancer type [165]. Finally, future studies will need to address how tumour microenvironment and oxygen levels affect not only the epigenome of cancer cells but also of immune cells, in the optics of developing novel therapeutic strategies.

Declaration of Competing Interest

BT holds a patent om markers for determining tumor hypoxia (WO2016142295A1). RV declares no competing interests.

Data availability

No data was used for the research described in the article.

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