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Insight into the multi-faceted role of the SUV family of H3K9 methyltransferases in carcinogenesis and cancer progression

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Abstract

Growing evidence implicates histone H3 lysine 9 methylation in tumorigenesis. The SUV family of H3K9 methyltransferases, which include G9a, GLP, SETDB1, SETDB2, SUV39H1 and SUV39H2 deposit H3K9me1/2/3 marks at euchromatic and heterochromatic regions, catalyzed by their conserved SET domain. In cancer, this family of enzymes can be deregulated by genomic alterations and transcriptional mis-expression leading to alteration of transcriptional programs. In solid and hematological malignancies, studies have uncovered pro-oncogenic roles for several H3K9 methyltransferases and accordingly, small molecule inhibitors are being tested as potential therapies. However, emerging evidence demonstrate onco-suppressive roles for these enzymes in cancer development as well. Here, we review the role H3K9 methyltransferases play in tumorigenesis focusing on gene targets and biological pathways affected due to misregulation of these enzymes. We also discuss molecular mechanisms regulating H3K9 methyltransferases and their influence on cancer. Finally, we describe the impact of H3K9 methylation on therapy induced resistance in carcinoma. Converging evidence point to multi-faceted roles for H3K9 methyltransferases in development and cancer that encourages a deeper understanding of these enzymes to inform novel therapy.

Keywords

H3K9methylation; G9a/GLP, SETDB1/2; SUV39H1/2; carcinoma; leukemia; therapy induced resistance; epithelial-to-mesenchymal transition; hypoxia; small molecule inhibitors

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Author's Contribution

N.S. performed literature search, organized and wrote the manuscript. N.S and A.G.M critically reviewed and edited the manuscript and contributed to designing of the figures and tables. All authors approved the final manuscript.

Declaration of Competing Interest

Authors declare no competing interest

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1. Introduction

Organismal development requires intricate regulation of gene expression. Post-translational modifications (PTMs) on histones influence gene regulation independent of underlying DNA sequence. Amino acids on histone tails are modified by epigenetic enzymes that deposit or remove different types of chemical moieties which influence transcriptional states. Though di- and tri-methylation of histone H3 at lysine 9 (H3K9me2, H3K9me3) is thought to participate in gene silencing [1,2] in concert with other transcriptional repressors [3], H3K9me1 has been associated with active transcription [4]. Densely packed and transcriptionally silent heterochromatin is broadly enriched with stable H3K9me2/3. H3K9me2/3 is also present at more loosely packed and transcriptionally accessible euchromatin where it plays a role in repressing active genes to dynamically modulate gene expression [2,3]. Chromatin compaction and gene silencing is conserved across eukaryotes, though different modalities have evolved in different organisms. For example, the fission yeast *Schizosaccharomyces pombe* uses a H3K9methylation-based mechanism for gene silencing and heterochromatin spreading [5], whereas the budding yeast *Saccharomyces cerevisiae* uses a mechanism analogous to Sir-based heterochromatin formation in metazoans [6,7], which may reflect differential heterochromatin features in these organisms. DNA methylation is also intrinsically linked to heterochromatin formation, where the cooperative action of DNA methyltransferases, histone H3K9 methyltransferases and HP1 protein facilitate heterochromatin formation [8,9]. It has become increasingly clear that deregulation of H3K9 methylation machinery is a common pathogenic feature of solid tumors and hematological malignancies. In this review, we discuss our current understanding of H3K9 methyltransferase function in the progression and pathogenesis of human cancers.

2. Writers of H3K9 methylation

Enzymatic machinery involved in the formation of repressive chromatin is conserved from yeast to humans. Suppressor of variegation (Su(var)3–9) was first discovered in *Drosophila melanogaster* in a mutagenic screen to identify proteins involved in suppressing position effect variegation or heterochromatin formation [10]. Subsequent studies led to the identification of other enzymes involved in gene silencing. Two mammalian homologues of Drosophila Su(VAR)3–9 (SUV39H1 and SUV39H2) were shown to be expressed in a tissue specific manner [11,12]. G9a and GLP were discovered to have substrate specificity similar to SUV39H depositing H3K9me2 modifications on chromatin [13]. Through a biochemical analysis of KAP-1 binding proteins, SETDB1 was discovered to catalyze H3K9 trimethylation. Homology studies discovered the SETDB2 H3K9 methyltransferase is expressed in a tissue specific manner [14,15]. Thus, early screening assays in Drosophila to identify proteins involved in heterochromatin formation laid the foundation for discovering a number of H3K9 methyltransferases and understanding the role of H3K9 methylation in gene regulation in development and disease.

The SUV3–9 family of enzymes comprised of G9a (*EHMT2;KMT1C*), GLP (*EHMT1;KMT1D*), SETDB1 (*ESET;KMT1E*), SETDB2 (*KMT1F*), SUV39H1 (*KMT1A*) and SUV39H2 (*KMT1B*) contain a highly conserved SET domain responsible for methylation of histone H3 at lysine 9, which is associated with gene silencing and

heterochromatin formation. Graphical representation of these protein structures is shown in Figure 1.

G9a and the related GLP are highly homologous proteins and possess identical substrate specificities on histones [13,16]. G9a and GLP form a heteromeric complex and contribute to mono and di-methylation of H3K9 [17]. A function of G9a is to silence euchromatic genes by depositing di-methylation marks at lysine 9 of histone H3. Structurally, G9a and GLP proteins harbor ankyrin repeats which are required for the recognition of histone H3 substrate and interaction with the *de novo* DNA methyltransferase DNMT3A [18–20]. The catalytic SET domain, flanked by Pre-SET and Post-SET motifs, deposits methyl groups on histone H3K9. In addition, G9a/GLP contains a nuclear localization signal at the N-terminus and a cysteine rich (Cys) domain [21]. A recent report indicated that G9a interacts with CyclinD1 via the Cys domain, suggesting this motif might act as an interaction platform for protein interactions [22]. *G9a*-deficiency in mouse embryo abolishes H3K9me2 by E9.5 and leads to early embryonic death indicating G9a is critical for development [23]. In addition, G9a/GLP plays a significant role in stem cell commitment to lineage specific cells. During early embryogenesis, lineage commitment and specification requires G9a to suppress pluripotent genes, such as OCT3/4, in co-operation with DNMT3A [18,24]. G9a is also involved in lineage commitment in the hematopoietic system, as well as skeletal myogenic and adipocyte differentiation [21]. A number of studies have demonstrated a role for G9a in cell cycle progression and DNA damage repair [25–28].

SETDB1 deposits H3K9me2/3 at euchromatic regions of the genome and is thought to be involved in silencing active genes as well as telomeric heterochromatin formation [14,29,30]. In addition, SETDB1 has been shown to be involved in establishment of H3K4me3/H3K9me3, H3K14Ac/H3K9me3 bivalent domains, thus indicating a dynamic role in chromatin modification and gene regulation [31–33]. Unlike domain (MBD), a domain involved in protein-protein interaction and DNA methyl-CpG binding [34]. SETDB1/2 contain a SET domain split into two domains leading to their nomenclature, SET bifurcated 1 (SETDB1) and SET bifurcated 2 (SETDB2). SETDB1 possesses triple tudor domains at its N-terminus, which recognize H3K14Ac/H3K9me modifications and facilitate recruitment of SETDB1 complexes to active chromatin sites for gene silencing [32,35]. SETDB1 associates with a variety of co-repressor complexes such as the HUSH complex and PML bodies associated with gene silencing [36,37]. SETDB1 is essential for development as *SETDB1*-knockout causes early embryonic lethality with defects in neural and hematopoietic development [38–41]. SETDB1 plays a role in suppressing endogenous retroviruses, meiotic progression, and maintenance of methylation homeostasis [42–45] thereby helping to safeguard the genomic integrity of cells. SETDB2 is also important for embryonic development and chromosomal segregation [15,46,47].

SUV39H1/2 are paralogous nuclear proteins that also participate in the formation of constitutive heterochromatin, maintenance of genomic stability, and cell cycle progression [48]. SUV39H1/2 catalyze H3K9 trimethylation through a conserved C-terminal SET domain [49]. H3K9me3 is bound by HP1 at pericentric satellite repeats and contributes to a transcriptional repressive heterochromatin state [5]. They also possess an N-terminal chromo domain that binds H3K9me2/3 and is essential for catalytic activity [50,51].other members

of the SUV family of proteins, SETDB1 and SETDB2 contain a methyl CpG binding In mouse, SUV39H1 is detected throughout development from early embryogenesis to adulthood, while SUV39H2 expression is limited to early embryogenesis and adult testes [11,12]. SUV39H1 and SUV39H2 appear to have overlapping functions as either protein is sufficient for embryonic development [52]. Interestingly, deletion of both SUV39H1 and 2 results in a hematopoietic defect [53].

3. Implications of H3K9methyl transferases in carcinogenesis

Epigenetic abnormalities are common during neoplastic transformation and result in altered chromatin landscapes and transcriptional deregulation. Altered DNA methylation and histone PTMs are hallmarks of tumorigenesis [54–56]. Aberrant DNA methylation is common in several types of malignancies and recent work in ovarian and lung carcinoma suggest DNA methylation and histone H3K9 methylation are closely linked in the pathogenesis of malignancies [57–59]. The reversible nature of these epigenetic changes, their altered signatures in cancer cells and plasticity employed to avoid drug sensitivity makes them an attractive avenue for therapeutic intervention [60,61]. Wen et al., described the presence of large organized chromatin K9 modifications (LOCKs), which are silent chromatin domains marked by H3K9me2 and associated with developmentally regulated genes. Notably, LOCKs are reduced in cancer cells, suggestive of a role in phenotype plasticity [62,63]. Abnormalities in H3K9methylation arise from mis-expression or regulation of the epigenetic factors that contribute to this modification (H3K9 methyl transferases and demethylases). Genomic alterations to H3K9 methyltransferase genes are observed in different kinds of solid tumors and hematological malignancies (Figure 2, 3 and 4). The different types of gene lesions detected in different cancers may imply non-overlapping roles for H3K9 methyltransferases. Here, we describe the mis-regulation of all H3K9 methyltransferases of the SUV3–9 family and how this affects different types of malignancies. The differential function of H3K9 methyltransferases in carcinogenesis is summarized in Table 1 and 2.

3.1. Breast Cancer

Meta-analysis of breast cancer patient specimens display amplification of *G9a*, which is associated with poor survival [64,65]. Mechanistically, G9a is required for breast cancer tumor growth and metastasis and promotes cell proliferation [64,66]. Multiple gene regulatory networks have been associated with G9a. A recent study reported G9a interacts and represses MYC target genes through deposition of H3K9me2 and is required for MYC dependent breast tumorigenesis [67]. In addition, G9a plays a role in hypoxia, which promotes migration and insensitivity to chemotherapy [68]. Indeed, hypoxia results in enrichment of global H3K9me2 through increased expression of G9a [69,70], which may suppress activity of hypoxia-induced tumor suppressors [69].

H3K9 methyltransferases also play a role in epithelial to mesenchymal transition (EMT) in breast cancer [71]. For example, G9a and SUV39H1 associate with the SNAIL transcription factor to repress anti-EMT genes such as E-cadherin through H3K9me2/3 deposition at its promoter [72,73]. Accordingly, loss of function studies suggest G9a and SUV39H1 promote

breast cancer metastasis. Inhibition of SUV39H1 in breast cancer cell lines restores E-cadherin expression through depletion of H3K9me3 at the promoter region [72–74]. Thus, G9a/SUV39H1 and associated H3K9me2/me3 act as important mediators of EMT in breast cancer pathology.

Interestingly, Khanal et al., reported that SUV39H1 suppresses oncogenic transformation in breast cancer cells overexpressing PIN1 [75]. Thus, potential H3K9 methyltransferase therapeutics for breast cancer treatment may require knowledge of underlying genetics.

Recent studies implicate SETDB1 as an oncogenic driver of breast cancer where it is amplified compared to normal tissue [76–78]. SETDB1 depletion blocks tumor cell growth [76,77] consistent with an oncogenic role in breast cancer. Recently, SETDB1 was associated with upregulation of SNAIL1 and SMAD7 expression aiding in EMT, which may promote metastasis [78,79]. The mechanism, however, of SETDB1-mediated activation of SNAIL1 and SMAD7 remains unclear. Paradoxically, Du et al., demonstrated reduced SETDB1 fosters breast cancer metastasis. They found SETDB1 inhibits TGF-β induced EMT and SETDB1-deficiency increased cancer migration in a zebra fish model [80]. These data suggest multiple functions for SETDB1 in breast cancer transformation and EMT that warrants further investigation.

3.2. Lung Carcinoma

Studies in the last decade have implicated gene silencing machinery in lung carcinogenesis and metastasis, including oncogenic roles for G9a in lung carcinoma. Amongst H3K9 methyltransferases, G9a displays the highest expression in several lung cancer cell lines [81]. In a cohort of lung cancer patient samples comprised of lung adenocarcinoma and lung squamous cell carcinoma, G9a expression is elevated compared to normal tissue and correlated with poorer survival [82–85]. Functional studies showed G9a is required for tumor development and enhances dissemination potential of lung carcinoma [84,85]. G9a silences expression of anti-EMT genes, such as EPCAM and CASP1, thus promoting EMT and tumor activity [82,85]. G9a is also involved in activation of WNT signaling by repressing WNT signaling inhibitors such as APC2, DKK1, and WIFI, thus facilitating cell proliferation [84]. Importantly, G9a oncogenic function is dependent on its H3K9 dimethylation activity [82,84,85]. Interestingly, G9a appears to induce expression of OCT4, NANOG and CD133 to maintain stemness in lung cancer cells, though the mechanism remains unclear [83]. In contrast to these oncogenic functions, Rowbotham et al., demonstrated increased proliferation of primitive lung cancer cells upon depletion of G9a suggesting a tumor suppressive role at the initiation stage of transformation. Loss of *G9a* in tumor propagating cells resulted in a global reduction in H3K9me2, expansion of tumor cells and increased lung cancer dissemination. Clinically, early stage lung cancer patients expressing elevated levels of G9a show better survival. These data suggest a critical balance of H3K9me2 by G9a for cellular homeostasis [86].

A report by Watanabe et al. reported high expression of SUV39 in human lung cancer cell lines, which is important for the growth of transformed human bronchial epithelia [81]. Transcriptomic and immunohistochemistry data demonstrate Suv39H2 is elevated in lung adenocarcinoma patients relative to normal tissue and higher SUV39H2 expression

correlates with a poorer survival [87]. A study testing a newly synthesized SUV39H2 inhibitor suggested blocking SUV39H2 activity suppresses the growth of lung cancer cells [88]. SUV39H2 is required for repression of *Optoneurin*, a gene associated with adenocarcinoma [87], suggesting SUV39H2 catalytic activity contributes to oncogenesis. Lung cancer cell lines treated with the H3K9me inhibitor, Chaetocin, display increased apoptosis and reduced H3K9me3 [140]. While, these studies point to an oncogenic role for SUV39H2 in lung carcinoma, Kim et al. reported SUV39H2 inhibits proliferation and induced cell cycle arrest of the A549 lung adenocarcinoma cell line. Furthermore, clinical data showed a better survival for lung cancer patients with higher SUV39H2 levels [139].

Clinicopathological data indicate SETDB1 expression is elevated in lung cancer and associated with a poorer prognostic outcome [81,107,108,141,142]. Functional analyses indicate SETDB1 exerts pro-proliferative effects on human lung cancer cell lines, [108,143]. Mechanistically, the oncogenic functions of SETDB1 have been attributed to hyperactivation of WNT signaling and suppression of TP53 expression [108]. Interestingly, SETDB1 can also suppress lung cancer migration. Expression of SETDB1 is downregulated in highly metastatic cell lines. In a Zebra fish model, SETDB1 inhibits lung cancer metastasis due to SETDB1-SMAD2/3 cooperative deposition of H3K9me3 and subsequent repression of *ANXA2* [133]. Furthermore, inactivating mutations in *SETDB1* were found in malignant pleural mesothelioma (MPM), a rare but aggressive form of lung cancer [131,132]. As with other H3K9 methyltransferases, data point to a complex role for SETDB1 in lung carcinoma.

Smoking is a major contributor to lung cancer and is attributed with altering chromatin landscapes and accelerated cell growth and transformation. In normal lung development, Gong et al., found that expression of the tumor suppressor PPAR-γ is reduced upon exposure to nicotine with concomitant increased H3K9me3 and H3K27me3 at its promoter [144,145]. Finally, SETDB1 expression was found to be upregulated in lung cancer patients with a history of smoking compared non-smokers [107].

3.3. Colorectal Carcinoma

Colorectal carcinoma (CRC) is also influenced by H3K9 methyltransferases. Elevated expression of G9a in CRC specimens and functional studies have pointed to an oncogenic role in colorectal carcinoma [90,146–148]. G9a protects against DNA double stranded breaks and may facilitate cancer cell survival. This may occur through reduced surveillance of cell cycle checkpoints caused by G9a-mediated epigenetic repression of PP2A, a phosphatase required for the G2/M checkpoint and cell cycle arrest [90,149,150]. Loss of *G9a in vivo* attenuated tumor growth and increased sensitivity to radiation treatment and DSB inducing cytotoxic drugs [149]. Modification of non-histone proteins by G9a is also associated with progression of colorectal carcinoma. For instance, G9a-mediated methylation of the transcription factor FOXO1, a tumor suppressor in CRC, reduces protein stability [151] enabling cancer progression.

SUV39H1 and SUV39H2 display oncogenic characteristics and are elevated in CRC. Functional assays indicate SUV39H1/2 promote cell proliferation *in vitro* and facilitate tumor growth and metastasis *in vivo* [122,128]. SUV39H1-mediated repression of FAS

expression may protect cancer cells against apoptosis as downregulation of FAS is prevalent in CRC [152,153]. Small molecule inhibition of SUV39H1 in CRC cell lines results in derepression of FAS, cell cycle arrest and apoptosis [122,154].

SETDB1 expression is also elevated in CRC patients and associated with a poor prognostic outcome [109,155–158]. Molecular and biochemical characterization indicate SETDB1 functions as an oncogenic driver in colorectal carcinoma. Functionally, SETDB1 is required for cell proliferation, colony formation and cell migration *in vitro* and accelerates tumor growth *in vivo* [109,155–158]. Notably, depletion of SETDB1 leads to downregulation of transcription factors that govern cell cycle and stemness including MYC [157]. In addition, SETDB1 suppresses the cell cycle inhibitor, p21 [110]. CRC cells also display increased sensitivity to cancer therapeutic drugs, such as 5-Fluorouracil (5-FU), and cetuximab upon depletion of SETDB1 [109,158], suggesting SETDB1 may be a potential therapeutic target in CRC.

3.4. Gastric Cancer

Recent studies have demonstrated the efficacy of treating gastric cancer (GC) by targeting H3K9 methyltransferases. Molecular analyses of clinical samples indicate G9a is amplified in gastric carcinoma and correlated to increased metastasis and poor survival [91,159,160]. Indeed, depletion of G9a reduces tumor growth and metastasis *in vivo*, establishing a requisite role for G9a in gastric cancer progression [91,159,161]. Recent studies reveal multiple biological processes are affected by G9a to facilitate transformation. Inhibition of G9a induces apoptosis and an autophagic response through downregulation of the mTOR pathway [91,159,161]. Importantly, G9a was found to activate mTOR by modulating H3K9 monomethylation, suggesting elevated G9a in gastric cancer induces mTOR and suppresses autophagy [91]. Further, kaempferol, a flavonoid present in fruits and vegetables, inhibits G9a and induces autophagic cell death in gastric cancer cell lines [161]. Notably, combination treatment of kaempferol and a G9a inhibitor augments autophagy mediated cell death [161]. Supporting an oncogenic role, in hypoxic conditions G9a delivers H3K9me to the RUNX3 tumor suppressor gene [92]. Finally, ITGB3, an important factor for promoting GC metastasis, was found to be activated by G9a in an enzyme independent manner, suggesting multiple functions in promoting tumorigenesis [160].

Roles for SUV39H1/H2 and SETDB2 in GC stem from research linking these proteins playing a role in silencing tumor suppressors *Gastrokine1* and *Cdkn2A* [123,124,129]. Nishikawaji et al, showed that SETDB2 is overexpressed in GC patient samples, which is correlated with a poor prognosis. SETDB2 also enzymatically silences tumor suppressor genes such as *Wwox*, and *Cadm1* [119].

3.5. Melanoma

A large percentage of melanoma patients present with activating mutations in the serine-threonine kinase BRAF, thereby hyperactivating the MAPK signaling pathway [162]. In addition to BRAF mutations, amplification of chromosome 1q21 (chr1: 147.2–149.2megabases) harboring *SETDB1* has been identified in melanoma tumor samples [163,164]. Notably, highly metastatic tumors display elevated global H3K9me3 [165].

Increased *SETDB1* copy number and elevated expression are observed in melanoma patient samples relative to benign nevi samples. Further, high SETDB1 expression corresponds to worse prognoses [166]. SETDB1 accelerates cellular migration resulting in more aggressive disease development [114,166]. SETDB1 may suppress the cell cycle inhibitor p16 to promote cellular proliferation [115] Repression of developmental genes, such as *HoxA* by SETDB1 may also promote melanoma [114]. SUV39H1 also promotes melanoma tumorigenesis and is upregulated in melanoma samples. Functionally, SUV39H1 promotes melanoma *in vivo* [126]. Targeting the catalytic activity of either SETDB1 or SUV39H1 by genetic manipulation or chemical inhibitor suppresses melanoma tumorigenesis [126,166].

Studies also point to pro-oncogenic roles for G9a in melanoma. Activating G9a mutations (G1069 mutated to L/W) and amplified G9a expression are observed in melanoma cancer samples [98,99]. Further, high G9a expression correlates to poor patient survival. Forced G9a expression promotes melanoma tumorigenesis [98,99]. G9a expression leads to upregulation of Microthalmia-Associated Transcription Factor (MITF), a master regulator of melanocyte survival and melanoma oncogene through activation of the PI3K/AKT pathway [99,167]. G9a enzymatic activity is required to suppress the WNT signaling antagonist DKK1, resulting in activation of WNT signaling and MITF expression [98]. EMT is associated with elevated G9a [99], which may be related to abnormal WNT and PI3K/AKT pathway activity.

3.6. Hepatocellular Carcinoma

H3K9 methyltransferases play a role in hepatocellular carcinoma (HCC) and are being pursued as potential drug targets. Studies demonstrate copy number gains and amplified expression for G9a expression in HCC samples. Clinically, high G9a expression negatively correlates with HCC patient survival [93,94,168]. Testing with genetic models and chemical inhibitors revealed that the enzymatic activity of G9a is required for HCC tumorigenesis [93,94]. G9a suppresses the expression of the tumor suppressor RARRES3 through H3K9me2 deposition at its promoter [94,169]. G9a is also involved in HCC tumor metastasis [95,168]. Notably, G9a forms a complex with EMT regulators SNAIL2 and HDAC1 to repress key anti-EMT genes such as E-Cadherin [95,168].

SETDB1 expression is elevated in HCC compared to non-tumor control and elevated SETDB1 leads to increased cell proliferation and enhanced HCC tumorigenicity and metastasis [111–113,170]. The function of SETDB1 in HCC is related to p53 mutation status. Fei et al., found gain of function mutations in *p53* (R249S) conferred sensitivity to *Setdb1* deletion [111]. In addition, SETDB1 represses p53 target genes such as *Cdkn1a*, *Puma* and *Gadd45* and protects HCC cells against irradiation [170]. Similar to SETDB1, SUV39H1 is also upregulated in HCC patient samples and associated with aggressive carcinoma [125,171]. Biochemical characterization indicate SUV39H1 facilitates migration and proliferation of HCC cells [125] and SUV39H1 depletion causes induction of autophagy and increased apoptosis [125,171].

3.7. Hematological Malignancy

Epigenetic dysregulation is a common feature in hematological malignancies [172,173] and H3K9 methyltransferases have become an attractive target for therapeutic intervention [174]. However, studies have described roles for H3K9 methyltransferases in both promoting and suppressing hematologic malignances. For example, G9a was shown to be essential for acute myeloid leukemia (AML) progression by promoting HOXA9/MEIS1 transcriptional activity. Importantly, *G9a* deletion has no deleterious effect on normal hematopoiesis, suggesting G9a could be a potential target in AML [105]. Small molecules inhibiting G9a/GLP have shown promise in treating AML [175–178]. In acute T-lymphocytic leukemia (T-ALL) G9a/GLP facilitates cell proliferation by repressing cell cycle inhibitor genes such as *Cdkn1a* and *Cdkn2b* [106]. Additionally, G9a/GLP is implicated in the development of chronic lymphocytic leukemia (CLL) where G9a/GLP inhibition induces cell death [179]. Recently, G9a has been shown to contribute to multiple myeloma [180]. G9a/GLP inhibitors induces apoptosis of leukemic cells while minimally effecting differentiation [106,181]. These data point to an essential function for G9a/GLP in leukemia cell survival. SETDB1 is also essential in mouse models of leukemia but is also essential for normal hematopoiesis [38]. In this context, SETDB1 suppresses endogenous retroviral elements and silences interferon response in leukemic cells [116]. SETDB2 also displays pro-oncogenic functions in leukemia potentially through suppression of *Cdkn1a* [120,121]. Interestingly, SETDB2 is also deleted in CLL, which may point to context specific functions [182]. Indeed, treatment with the H3K9 methyltransferases inhibitor chaetocin relieves the differentiation blockade in leukemic cells with a concomitant increase in apoptosis [181,183–185].

Homeobox proteins, including HOXA9 and its co factor MEIS1, are pro-leukemic transcription factors that block differentiation and promote AML and ALL. The posterior HOXA gene cluster is exquisitely regulated by H3K79 methylation, which is deposited by DOT1L [186]. Genetic or small molecule inactivation of DOT1L impairs HOXA9 and MEIS1 expression and leukemia progression [186,187]. Importantly, H3K79 methylation inhibits SUV39H mediated H3K9me3 deposition at the HOXA gene cluster and points to a potential suppressive role for H3K9me in leukemogenesis [188]. Indeed, SETDB1 expression also catalyzes H3K9me3 at the HOXA gene cluster including HOXA9, its co-factor MEIS1 and others [117,134]. Consistent with a suppressive role, forced SETDB1 expression extends AML disease latency in mouse models. Importantly, AML patients with higher SETDB1 expression display a significantly better prognostic outcome than patients with reduced SETDB1 expression [117]. Similar suppressive roles for G9a have been reported in leukemia. For example, G9a/GLP-specific inhibitor treatment of hematopoietic stem and progenitor cells preserves cellular stemness [189,190]. Moreover, overexpression of G9a in leukemic cells impairs proliferation and induces differentiation [117]. A similar tumor suppressive role for SUV39H1 in AML was recently reported. SUV39H1 overexpression induces apoptosis and increased disease latency in AML mouse models. Notably, SUV39H1 expression led to downregulation of HOXB13 in leukemic cells [137]. Together, these data suggest H3K9 methyltransferase-mediated repression of HOX genes is key regulatory mechanism of leukemia inhibition. Forced differentiation of leukemic cells is associated with an increase in G9a-induced H3K9me2 [191,192]. Also consistent with a

suppressive role, knockout of *SUV39H1* predisposes mice to the development of B-cell lymphoma [52].

Together, these studies point to a potential context and cell specific function for H3K9 methyltransferases that may result in requisite and suppressive roles in hematologic malignancies. These also suggest a fine-tuned molecular mechanism to tightly regulate expression of H3K9 methyltransferases in the hematopoietic system, whose disruption may contribute to leukemogenesis.

3.8. In other types of cancers

Beside the malignancies described above, studies have revealed roles for H3K9 methyltransferases in several other types of cancer. H3K9 methyltransferases expression is altered in cancers of human reproductive organs. In ovarian and cervical carcinoma, G9a and H3K9me2 display cancer promoting functions [100,193]. G9a enhances peritoneal dissemination of ovarian cancer, however, is not required for cell proliferation. Conversely, in cervical cancer, SUV39H1 impedes cancer metastasis and low SUV39H1 levels correlate with poor patient survival [135]. SETDB1 and SUV39H1 are upregulated in prostate cancer cells, which stimulate cell proliferation [118,127]. Recently, G9a was implicated in driving oncogenesis in highly aggressive cholangio carcinoma [96]. G9a also enhances head and neck squamous cells carcinoma metastasis [104]. In glioma, a role for G9a is not well understood. One study reports G9a inhibits cancer stemness by repressing self-renewing genes [130], while others show a cell proliferation defect and increased apoptosis in glioma cells upon treatment with G9a inhibitor [101,194]. SUV39H1 and SETDB1 have also been implicated in glioma [195]. A recent report demonstrates that SETDB1 promotes glioblastoma growth and metastasis through activation of the AKT/mTOR signaling pathway [196]. G9a suppresses autophagy by repressing autophagy promoting genes [197,198], and targeting of G9a leads to induction of autophagy dependent cell death or cellular differentiation in bladder carcinoma, oral squamous cell carcinoma, gastric carcinoma, breast cancer cells, and neuroblastoma cells [91,97,102,103,161,199,200]. In parathyroid carcinoma, SUV39H1 likely has tumor suppressive function as it associates with CDC73 to repress transcription of cell cycle genes such as Cyclin D [136]. These studies point to important functions for H3K9 methylation in tumorigenesis, which require further study.

4. Regulation of H3K9 methyl transferases and implications in tumorigenesis

Several cis and trans acting mechanisms can influence H3K9 methyltransferase activity during oncogenesis. In addition to cis-genomic regulatory regions and transcription factor deregulation that influence KMT expression, microRNAs, PTMs and others impart catalytic regulation during neoplastic development. Here we review our understanding of molecular regulatory mechanisms governing KMT function as well as how these might inform development of therapeutics.

microRNAs (miRNA), such as miRNA-29 and miRNA-621, directly target SETDB1 transcription, which can impede HCC tumorigenesis [112,170]. Reduced expression of these microRNAs in HCC clinical samples with elevated SETDB1 may reflect a mechanism to maintain SETDB1 expression. Though correlational, data suggests miRNA-621 might block WNT mediated cell proliferation by regulating SETDB1 expression [108,201]. SETDB1 is also a target of miRNA-7. Mechanistically, miRNA-7 suppresses EMT in breast cancer by reducing SETDB1 [202]. Another study found miRNA-1 targets G9a and loss of miRNA-1 promotes HCC by increasing G9a activity [94]. Thus, microRNA regulation of H3K9 methyltransferases may safeguard cells from neoplastic transformation and maintain cellular homeostasis.

PTMs on H3K9 methyltransferases can affect catalytic activity and cellular processes. PTMs on G9a/GLP can switch activity from transcriptional repressor to activator. For example, SUMOylation of G9a (K79, K152, K256, and K799) facilitates PCAF mediated activation of E2F1 target genes and promotes myoblast proliferation [25,203]. Interestingly, automethylation of G9a/GLP (G9a; lysine185/GLP; lysine205) facilitate interaction with HP1γ. G9a/GLP, HP1γ, and glucocorticoid receptor form a ternary complex on chromatin to activate glucocorticoid target genes, which block cell migration in lung cancer cells and enhance cell death in B-ALL cells. Conversely, phosphorylation of G9a/GLP (G9a; T186, GLP; T206) by Aurora kinase B compromises co-activator function by destabilizing binding with HP1γ [204,205]. Finally, ubiquitination at lysine867 on SETDB1 by the UBE2E family of E2 enzymes enhances the methyltransferase activity of SETDB1 [206,207]. Thus, multiple mechanisms regulate H3K9 methyltransferase catalytic activity and a more complete understanding is needed to determine the impact on tumorigenesis.

5. H3K9 methyltransferases in therapy induced resistance

Resistance to chemo-therapeutic drugs and radiation therapy are significant and serious obstacles to successful cancer treatment. Sub-populations of induced drug tolerant cancer cells (IDTC) or drug-tolerant persisters (DTPs) [61,208] emerge, in part, through epigenetic mechanisms. Substantial enrichment of repressive H3K9me2/3 and depletion of activation modifications is observed in DTP cancer cells following treatment with chemotherapeutic agents [193,208,209]. Thus, H3K9 methylation may impact chemotherapy resistance and a greater understanding is needed for future therapeutic design.

The role of G9a in resistance to chemotherapies has been explored in several cancer models. G9a is implicated in chemo and radiation therapy resistance in malignant glioma and colorectal cancer. G9a acts as a radioprotector in glioma cell lines by promoting DNA double stranded break repair [194]. In addition, G9a inhibition induces apoptosis in glioma cells by enhancing sensitivity to chemo agents like Temozolomide [210]. Radioresistant colorectal cancer cells display elevated G9a expression and are re-sensitized following G9a depletion. G9a-led protection of CRC cells occurs through heightened DNA repair [149]. G9a/GLP facilitates DSB repair and is observed in high-grade serous cell ovarian carcinoma (HGSOC) resistant to PARP inhibitors (PARPi). G9a/GLP expression and H3K9me2 are elevated in PARPi resistant HGSOC cells. Importantly, disrupting G9a/GLP activity sensitizes resistant cells to PARPi, which leads to increased DNA damage [193].

Gemcitabine (GEM) is a widely administered for several types of malignancies including pancreatic, lung, bladder, cervical, breast, ovarian and head and neck cancers [211]. In pancreatic cancer, expression of G9a is increased upon GEM administration and G9a inhibition sensitizes cells to GEM [212]. Additionally, a correlative study implicates G9a in GEM resistance in cervical cancer [213]. In head and neck squamous cell carcinoma (HNSCC) patients, high G9a expression is correlated with a poor response to chemotherapy. Elevated G9a levels also confer protection of HNSCC cells to cisplatin [214]. From a therapeutic standpoint, treatment of colorectal carcinoma with the H3K9m2/3 inhibitor Verticillin A increased sensitivity to 5-FU [147]. Given that many chemo agents potentiate DNA damage [215], cancer cells may utilize H3K9 methyltransferases to facilitate DNA damage repair and escape the cytotoxic effect of chemo drugs.

Transposable elements are also thought to be implicated in cancer progression. H3K9 methylation plays a role in normal cell homeostasis by silencing transposable elements in the genome [2,216]. LINE-1 elements are the most common form of Long Interspersed Nuclear Elements (LINEs) spanning the human genome. Transposition of non-LTR retrotransposon elements require expression of LINE-1 encoded endonuclease, which generates staggered cuts in DNA triggering DNA damage response [217]. SETDB1 catalytic activity is essential for repression of such endogenous retroviral elements, including LINE-1 [218]. Chemo-resistant cancer cells express elevated levels of SETDB1/2 with simultaneous enrichment of repressive H3K9me3 over LINE-1 genomic loci. Drug sensitivity is restored upon de-repression of LINE-1 elements following inactivation of SETDB1/2 activity [208,209]. Overall, H3K9 methylation machinery is linked with chemoresistance warranting further investigation into H3K9 methylation and cancer.

Cancer Stem cells, or tumor propagating/initiating cells, are a subpopulation of self-renewing cells with the capacity to give rise to bulk tumors and thought to play a key role in the development of resistance to chemotherapeutic treatments. Epigenetic alterations modulate signaling pathways important to cancer stem cells, including WNT and Notch signaling [219]. Because H3K9 methyltransferases contribute to the regulation of signaling pathways like WNT, H3K9 methylation likely plays a role in maintenance of cancer stemness. Indeed, G9a was shown to regulate stem cell programs in neurons [220]. Further, G9a was recently reported to regulate stemness in NSCLC through modulation of DNA methylation. G9a is highly expressed in $CD133^{+}$ cancer stem cells and inhibition of G9a suppresses CD133 expression and tumor growth in xenograft models [57]. On the contrary, G9a/GLP has been shown to suppress lung adenocarcinoma tumor propagating cells. Inhibition of G9a led to increased cell surface expression of stem cell antigen-1 (Sca-1) and increased disease pathogenicity *in vivo* [86]. Notably, we have shown that SETDB1 overexpression leads to downregulation of the self-renewal genes HOXA9 and MEIS1 in AML [134]. Though our current knowledge in cancer stem cells is incomplete, the above studies implicate H3K9 methyltransferases in the regulation and/or maintenance of cancer stem cells and evading chemotherapeutics. Future studies will be critical to elucidating the functions of these enzymes in regulating stem cell features in different cancer models.

6. Conclusions and Future Directions

Repressive H3K9me2/3 is important in development cellular transformation. Deregulated H3K9me2/3 results in widespread abnormalities in various cellular functions such as cell proliferation, hypoxia, inflammation, cellular senescence, autophagy, and apoptosis, which can contribute to tumorigenesis. Elevated H3K9 methyltransferases can lead to hyperactivation of prosurvival signaling pathways, (PI3K/AKT, Notch, WNT) and repression of tumor suppressors (p21, p16). EMT is tightly regulated by transcriptional factors and signaling molecules and is a hallmark of cancer metastasis in solid tumors. Several studies implicate H3K9 methyltransferases in tumor migration, indicating these factors play a central role in solid tumor metastasis by suppressing key anti-EMT genes. These findings point to pro-oncogenic functions for H3K9 methyltransferases. Consequently, several promising small molecule inhibitors have been developed targeting H3K9 methyltransferases. For example, the fungal mycotoxin, chaetocin was identified in 2005 as the first H3K9 methyltransferase inhibitor, however this was later found to be not selective. Subsequent studies have identified several new small molecules capable of inhibiting G9a/GLP, including the non-SAM competitive G9a inhibitors BIX-01294, UNC0638 and others (reviewed in [221]). While molecules like UNC0638 have shown efficacy in delaying cancer in mouse models [105], no H3K9 methyltransferase inhibitors are currently in clinical trials. However, as we have noted, studies have also revealed tumor suppressive roles for H3K9 methyltransferases in various cancers and the multi-faceted role of H3K9 methyltransferases is summarized in Figure 5. The dual nature of these proteins suggests tight regulation of H3K9 methyltransferase expression in different cellular and temporal contexts. This also raises the possibility of cell specific roles for H3K9 methyltransferases in different tissues that may reflect their pro- and anti-tumorigenic functions in cancer. As such, care must be taken when targeting H3K9 methyltransferases in tumors to eliminate the possibility of promoting carcinogenesis in other tissues. Thus, a thorough understanding of the role of H3K9 methyltransferases in different tumor environments is essential before small molecule inhibition is pursued as a cancer therapy. This is reinforced by a recent publication showing an early response of melanoma cells to G9a inhibitors only to result in cancer stem cell enrichment and aggressive carcinoma with prolonged latency [222]. Besides tumorigenic and tumor suppressive roles, H3K9 methyltransferases also impact resistance to chemo and radiation therapy. Given our understanding of pro- and anti-tumorigenic roles in cancer, it will be imperative to investigate the optimal levels of H3K9 methylation in disease states. Further, it will be interesting to understand the molecular mechanisms (transcriptional and/or post-transcriptional) utilized by cancer stem cells to maintain (or modulate) H3K9 methylation to promote self-renewal or evade drug treatment. Finally, thorough testing of H3K9 methyltransferase inhibitors in different disease models will be necessary to fully explore the long term effects of H3K9 methylation inhibition on stem and progenitor cell populations. Thus, H3K9 methylation function spans large modalities of cancer biology, which await further investigation.

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Abbreviations

CRC	Colorectal Carcinoma
5-FU	5-Fluorouracil
GC	Gastric carcinoma
MITF	Micro thalmia associated transcription factor
EMT	Epithelial to meshencymal transition
HCC	Hepatocellular carcinoma
AML	Acute myeloid leukemia
CLL	Chronic lymphocytic leukemia
DSB	DNA double stranded breaks
ALL	Acute lymphocytic leukemia
IDTC	Induced Drug tolerance cells
DTP	Drug tolerant persisters
HGSOC	High-grade serous cell ovarian carcinoma
PARPi	PARP inhibitors
PTM	Post-translational modification
GEM	Gemcitabine
HNSCC	Head and neck squamous cell carcinoma
LINE	Long Interspersed Nuclear Elements
LOCKS	Large organized chromatin K9 modifications
Cys	Cysteine rich
MBD	Methy-CpG binding domain

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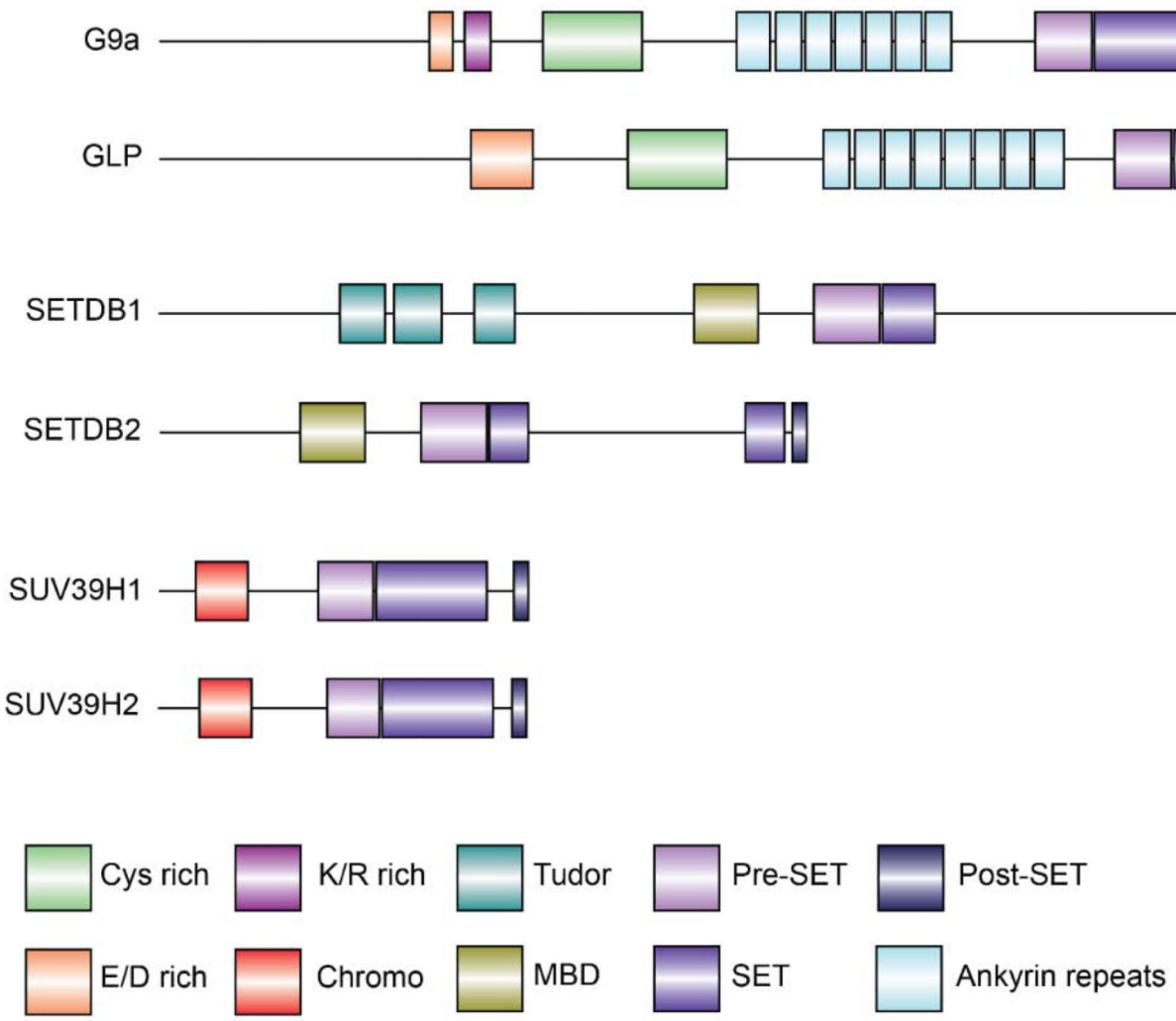

Figure 1.

Graphical illustration depicting human H3K9 methyltransferase protein structures. G9a; 1210 amino acids (aa) Uniprot: Q96KQ7, GLP; 1298 aa Uniprot: Q9H9B1, SETDB1; 1291 aa Uniprot: Q15047, SETDB2; 719 aa Uniprot: Q96T68, SUV39H1; 412 aa Uniprot: O43463, SUV39H2; 410 aa Uniprot: Q9H5I1. Protein structures are drawn using Dog2.0 tool [223].

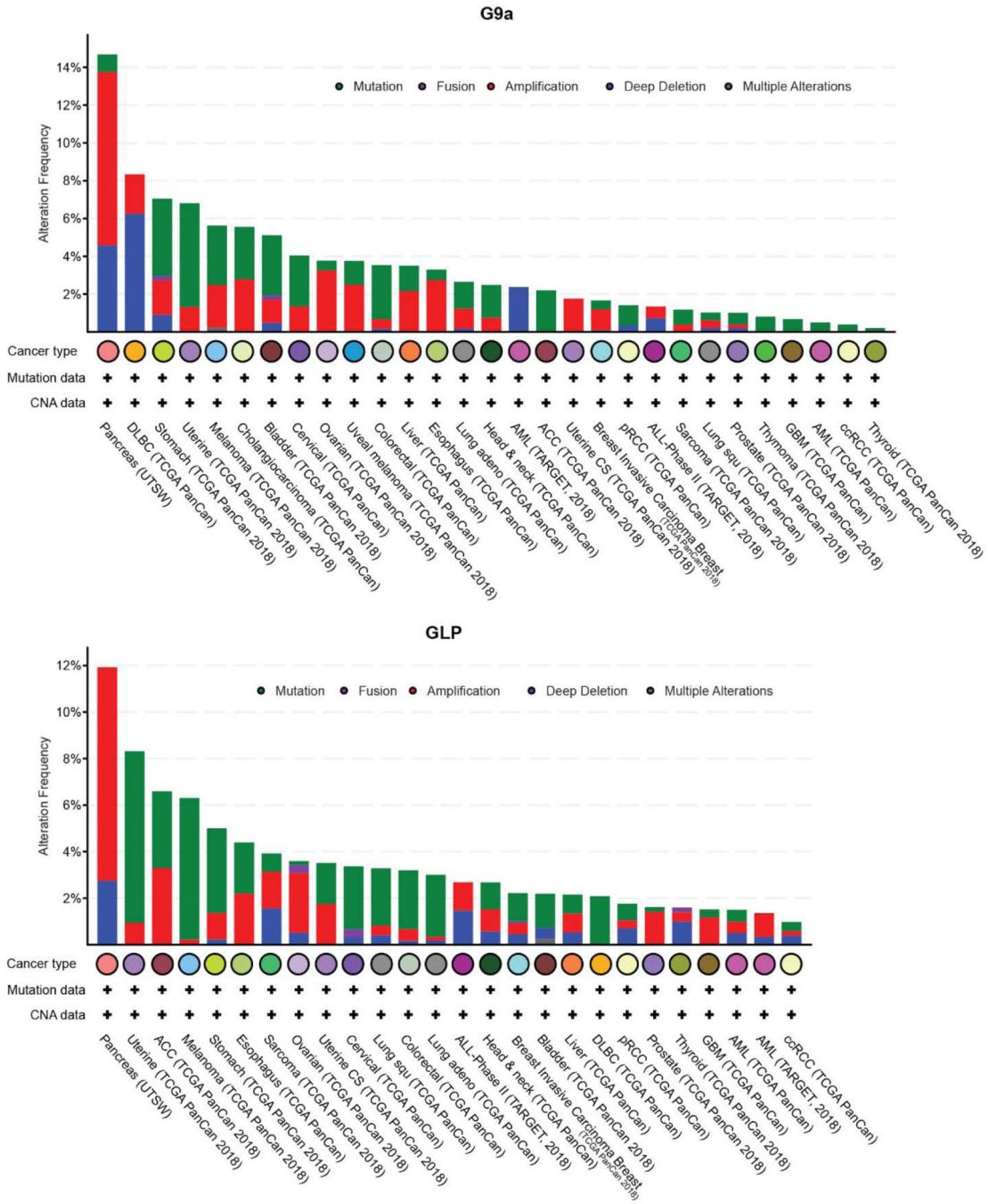

Figure 2.

Genomic alterations in *G9a* and *GLP* observed in different types of cancer. Data collected and plotted in c-Bioportal.org

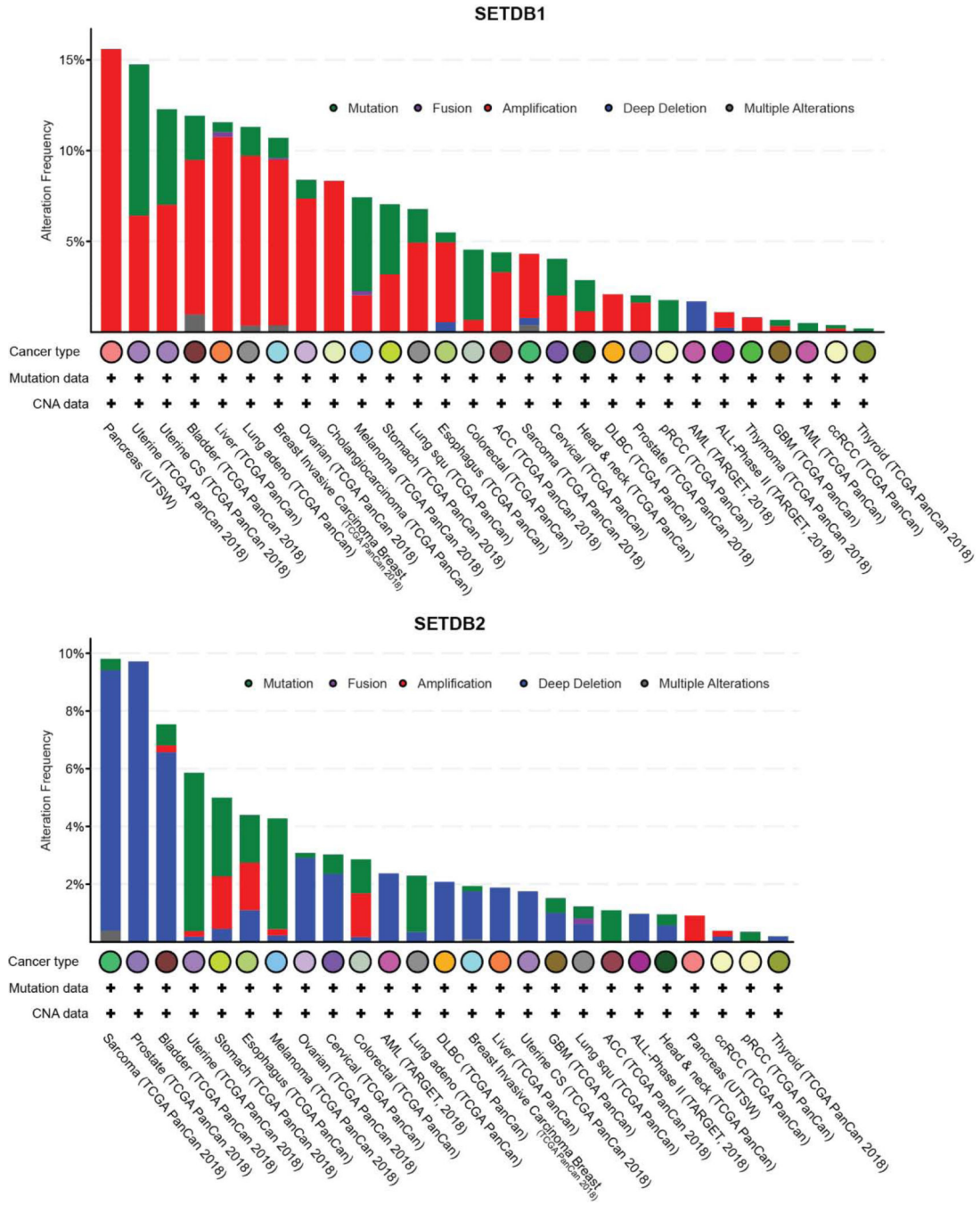

Figure 3.

Genomic alterations in *SETDB1* and *SETDB2* observed in different types of cancer. Data collected and plotted in c-Bioportal.org

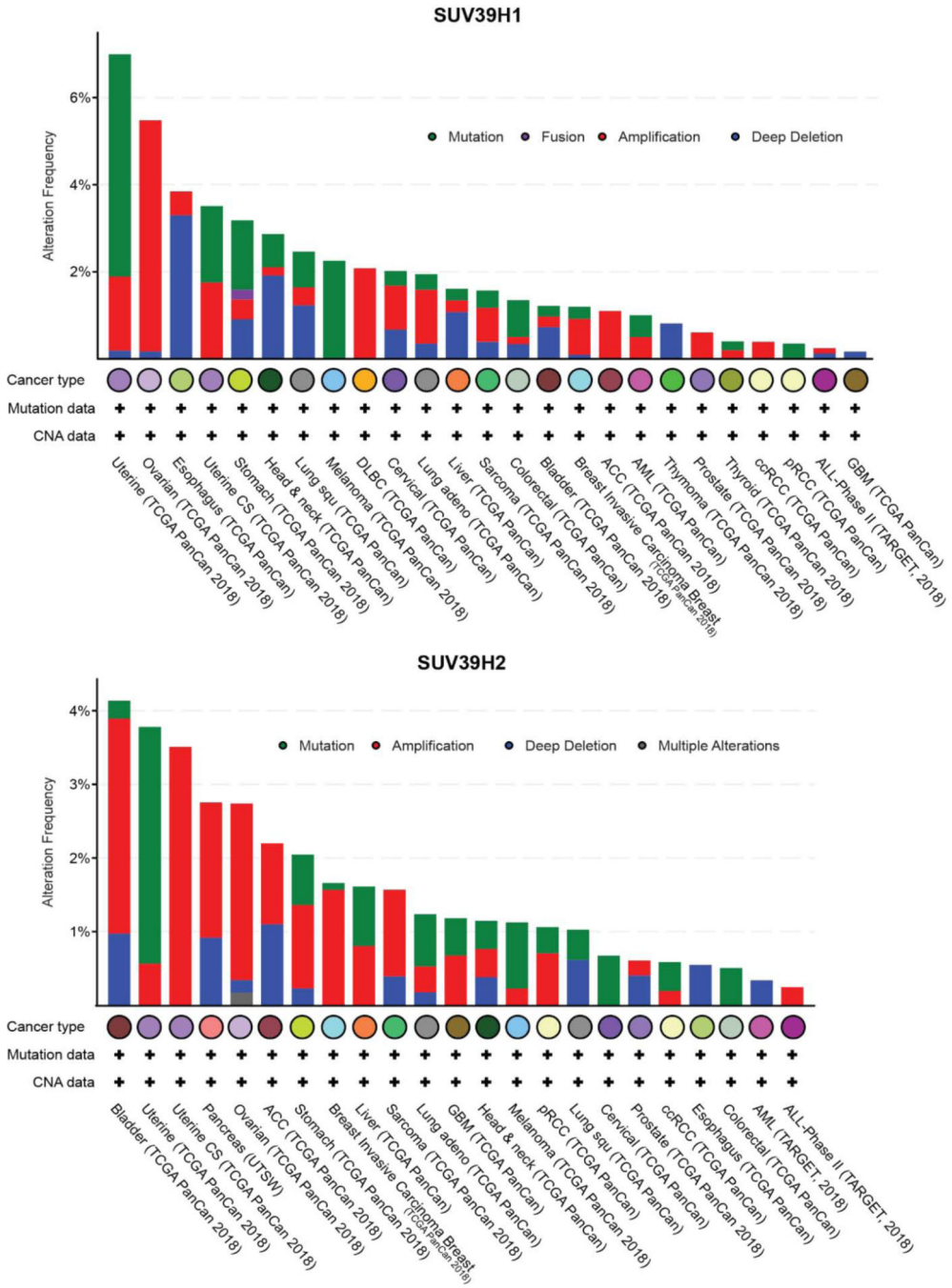

Figure 4.

Genomic alterations in *SUV39H1* and *SUV39H2* observed in different types of cancer. Data collected and plotted in c-Bioportal.org

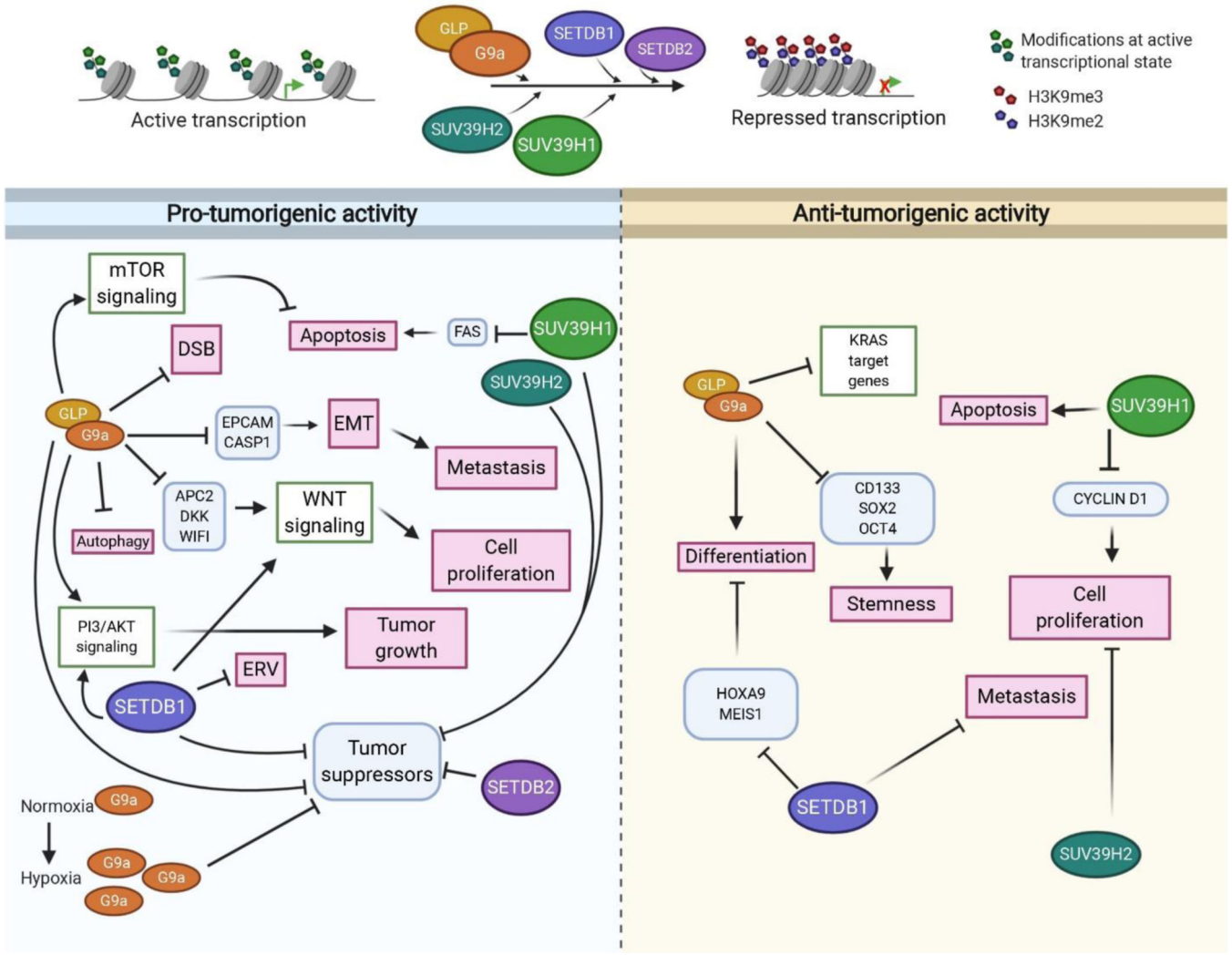

Figure 5.

Graphical illustration summarizing the oncogenic and tumor-suppressive functions of H3K9 methyltransferases. Signaling pathways are shown in green boxes; Genes regulated by H3K9 methyltransferases are shown in blue boxes and affected processes are shown in pink boxes. The bubbles representing H3K9 methyltransferases are not to scale. Created with BioRender.com

Table 1.

Pro-tumorigenic functions of H3K9 methyl transferases

Pro-tumorigenic activity H3K9 methyl transferase	Cancer type	Biological process affected
G9a	Lung carcinoma [84,85]	Enhanced EMT [82,85] Activation of WNT signaling [84] Maintenance of stemness [83]
	Breast carcinoma [64,66]	Enhanced EMT [72] Suppression of autophagy [89]
	Colorectal carcinoma [90]	Enhanced DNA double strand break repair [90]
	Gastric cancer [91]	Suppression of autophagy [91] Suppression of tumor suppressors [92]
	Hepatocellular carcinoma [93,94]	Enhanced EMT [95] Suppression of tumor suppressors [94]
	Cholangio carcinoma [96]	Suppression of tumor suppressor [96]
	Bladder carcinoma [97]	Suppression of autophagy [97]
	Melanoma [98]	Activation of WNT signaling [98] Activation of PI3K/AKT pathway [99]
	Ovarian and cervical carcinoma [100]	Promotes metastasis [100]
	Glioma [101]	Suppression of apoptosis [101]
	Neuroblastoma cells [102]	Suppression of autophagy [102]
	Oral squamous cell carcinoma [103]	Suppression of autophagy [103]
	Head and neck squamous cell carcinoma [104]	Supports EMT [104]
G9a/GLP	Hematological malignancies [105]	Suppression of cell cycle inhibitors [106]
SETDB1	Lung carcinoma [107,108]	Activation of WNT signaling [108]
	Breast carcinoma [76,77]	Promotes EMT [78,79]
	Colorectal carcinoma [109,110]	Suppression of tumor suppressors [109,110]
	Hepatocellular carcinoma [111,112]	Enhanced metastasis [112,113]
	Melanoma [114]	Enhanced metastasis [114] Suppression of cell cycle inhibitors [115]
	Hematological malignancies [116,117]	Suppression of endogenous retroviral elements [116]
	Prostate Cancer [118]	-
SETDB2	Gastric cancer [119]	Suppression of tumor suppressors [119]
	Hematological malignancies [120]	Suppression of cell cycle inhibitor [121]
SUV39H1	Colorectal carcinoma [122]	-
	Gastric cancer [123]	Suppression of tumor suppressors [124]
	Hepatocellular carcinoma [125]	Enhanced metastasis [125]
	Breast carcinoma [73]	Enhanced EMT [73]
	Melanoma [126]	-
	Prostate Cancer [127]	-
SUV39H2	Lung carcinoma [87]	-
	Colorectal carcinoma [128]	Promotes cell proliferation and metastases [128]
	Gastric cancer [129]	Suppression of tumor suppressors [129]

Pro-tumorigenic activity H3K9 methyl transferase	Cancer type	Biological process affected
- Further evaluation required		

Table 2:

Onco-suppressive functions of H3K9 methyl

Anti-Tumor activity

H3K9 methyl transferase	Cancer type	Biological process affected
G9a	Lung carcinoma [86]	-
G9a/GLP	Glioma [130]	Suppression of self-renewal genes [130]
	Hematological malignancies [117]	-
SETDB1	Lung carcinoma [131,132]	Suppressor of metastasis [133]
	Breast carcinoma [80]	Suppressor of metastasis [80]
	Hematological malignancies [117,134]	Induced differentiation and suppression of self-renewal genes [134]
SUV39H1	Breast carcinoma [75]	Suppression of cell cycle gene [75]
	Ovarian and cervical carcinoma [135]	-
	Parathyroid carcinoma [136]	Suppression of cell cycle gene [136]
	Hematological malignancies [52,137] Rhabdomyosarcoma [138]	Induced apoptosis[137]
SUV39H2	Lung carcinoma [139]	Induced cell cycle arrest [139]

- Further evaluation required