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Dysregulation of different modes of programmed cell death by epigenetic modifications and their role in cancer

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ABSTRACT

Modifications of epigenetic factors affect our lives and can give important information regarding one's state of health. In cancer, epigenetic modifications play a crucial role, as they influence various programmed cell death types. The purpose of this review is to investigate how epigenetic modifications, such as DNA methylation, histone modifications, and non-coding RNAs, influence various cell death processes in suppressing or promoting cancer development. Autophagy and apoptosis are the most investigated programmed cell death modes, as based on the tumor stage these cell death types can either promote or prevent cancer evolution. Therefore, our discussion focuses on how epigenetic modifications affect autophagy and apoptosis, as well as their diagnostic and therapeutical potential in combination with available chemotherapeutics. Additionally, we summarize the available data regarding the role of epigenetic modifications on other programmed cell death modes, such as ferroptosis, necroptosis, and parthanatos in cancer and discuss current advancements.

1. Introduction

Epigenetic modifications, such as DNA methylation, histone modifications, and non-coding RNA, play an important role in our everyday lives, as they influence cell division and development indicating one's state of health [1]. Although aging is a naturally occurring process, different factors including metabolic dysregulation, chronic inflammation, and mitochondrial dysfunction can accelerate it [2]. The complex interaction between DNA methylation, histone modification, and non-coding RNA plays a vital role in the epigenetic control of gene expression, greatly influencing important cellular processes such as apoptosis and autophagy. These modifications not only take place during the aging process but are key to both inhibition and progression of cancer [2,3]. Epigenetic silencing, which involves DNA methylation or histone modifications, is a prevalent characteristic observed in different types of malignancies [4]. Epigenetic aberrations disrupt normal cell death processes, which can result in uncontrolled cell proliferation and the development of cancer. Hence, restoring or normalizing these processes can inhibit tumor growth and improve the effectiveness of cancer treatments [4,5]. Autophagy is a process of particular interest because of its dual role (pro-survival, death) in cancer and because of its interconnection with apoptosis where any changes in the autophagic process can cause defects in the apoptotic pathway [5,6]. Research from the past decades has shown the implications of epigenetic alterations in cancer and has led to the development of new drug classes, which manipulate the expression of these epigenetic factors and prevent tumor progression [3,7,8].

1.1. DNA methylation

DNA methylation occurs through the binding of a methyl group to the C5-position of cytosine, forming 5′-methylcytosine (5 mC), at the CpC site. The reaction is catalyzed by DNA methyltransferases (DNMTs), mostly DNMT1, DNMT3A and DNMT3B. Aberrant DNA methylation patterns are associated with tumor progression [9,10]. DNMTs overexpression or alterations (mutations) are frequent in many types of cancer, and the overexpression causes hypermethylation of tumor suppressor genes (TSGs) [11]. The most common mutation occurs in *DNMT3A*, which is often also overexpressed and indicates a bad prognosis in patients with acute myeloid leukemia (AML) [12,13]. *DNMT1* and *DNMT3B* mutations in cancer are rare and there are only a few studies reporting them, but *DNMT1* overexpression indicated poor survival outcome in patients with cervical cancer [11,14]. New therapeutic strategies inhibiting either one DNMT (DNMTi) or targeting DNMTs in combination with other enzymes (HDAC or mTOR inhibitors) have been developed to target different types of cancer, including AML, pancreatic,

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thyroid, lung, and ovarian cancer [11]. Through aging, DNA methylation decreases, as the expression of DNMTs is affected in human tissues [2]. Changes in the DNA methylation process usually occur with advanced aging and have been also observed in tumor cells, suggesting a correlation between the age processes and tumorigenesis [15]. DNA hypomethylation at the cytosine-guanine (CpG) site has been associated with upregulation of different oncogenes such as short interspersed nuclear elements (*SINEs*) in acute myeloid leukemia (AML), engulfment and cell motility 3 (*ELMO3*) in metastatic non-small cell lung cancer, Iroquois homeobox 1 (*IRX1*) in primary and metastatic osteosarcoma cancer [16]. On the other hand, DNA hypermethylation can inhibit tumor suppressor genes (*e.g.*, *BRCA1* in breast and ovarian cancer) and deregulate noncoding RNA leading to poor survival rates in cancer patients (*e.g.*, suppression of the microRNA miR-124a in patients with acute lymphoid leukemia or ncRNA nc866 in acute myeloid leukemia) [16].

1.2. Histone modifications

Histones are nuclear proteins which compress the DNA into structural units called nucleosomes and help to condense it into the chromatin. The N-terminal tail of histones can be chemically altered through acetylation, methylation, phosphorylation, or ubiquitylation, which can then change the chromatin conformation [17]. Histone modifications (methylation, acetylation, phosphorylation) influence key biological processes including aging and tumorigenesis [18]. Histone methylation takes place at the lysine (K) residues of histone H3 and H4 and are catalyzed by histone methyltransferase (HMT). Methylation of H3K4, H3K36, H3K79, H3K9, H3K27, and H4K20 have been reported and aberrant methylation of H3K9 and H3K27 is used as a prognostic biomarker in colorectal cancer [19]. Histone acetylation is regulated through specific enzymes, called histone acetyltransferases (HATs) and histone deacetylases (HDACs) [17]. In certain diseases (cancer, Alzheimer's, Parkinson's, and Huntington diseases), the level of HATs or HDACs is abnormal, leading to the development of new classes of drugs called histone acetyltransferase (HAT) inhibitors and histone deacetylase (HDAC) inhibitors [8,20,21]. There are 18 known HDAC enzymes, which are divided into four classes: class I contains HDAC1,2,3, and 8 and is localized in the nucleus, class II is subdivided into class IIa (HDAC4, 5, 7, and 9), which shuttle between cytoplasm and nucleus and class IIb (nuclear HDAC6 and10). Class III is known as sirtuins (SIRT1-7) and class IV contains HDAC11, localized in the nucleus [22,23]. HATs and HDAC inhibitors have been tested in preclinical and clinical trials for their geroprotective effect and anticancer potential [8,20,21,24,25]. Histone phosphorylation takes place at the serine, threonine, and tyrosine residues in the N-terminal of histone proteins and is regulated by kinases and phosphatases [17,18]. High expression and phosphorylation of H2AX have been observed in breast cancer and colorectal cancer patients [26,27]. The Cancer Genome Atlas Program has managed to identify numerous mutations in epigenetic regulators in more than 33 cancer types, which is the most valuable resource in the understanding of cancer and development of potential drug targets [28,29].

1.3. Non-coding RNAs

Non-coding RNAs (ncRNAs) influence multiple biological processes including genome stability, gene expression at the transcriptional level, protein modification at the post-transcriptional level, DNA homeostasis, and lipid interaction. They can be classified based on their size in short RNAs containing up to 25 nucleotides, long-noncoding RNAs (lncRNAs), containing up to 200 nucleotides, and circular RNAs (circRNAs) resistant to RNAse. Short RNAs include microRNAs (miRNAs), transfer RNAs (tRNAs), tRNAs-derived fragments (tRFs), and P-element-induced wimpy testis (PIWI) interacting RNAs (piRNAs). Other ncRNAs include ribosomal RNAs (rRNAs) and small nucleolar RNAs (snoRNAs) [30]. The dysregulation of ncRNAs through modulation of the autophagy process promotes cancer development, metastasis, and drug resistance but also cancer stem cell proliferation [30]. ncRNAs as important cellular modulators also influence the aging process and the development of neurodegenerative, cardiovascular, and metabolic diseases [24].

In this review, the focus will be on how changes in epigenetic factors affect different types of programmed apoptotic cell death (apoptosis), programmed non-apoptotic cell death (autophagy), iron-dependent cell death (ferroptosis), mitochondrial-dependent cell death (parthanatos), and other types (necroptosis), as well as the role they play in suppressing or promoting cancer development. In the case of autophagy, its dual role in promoting cell survival and not just cell death will also be discussed.

2. Autophagy – a double-edged sword in cancer

Autophagy is a highly regulated cell death process that leads to the degradation of damaged cellular components (proteins, organelles) and maintains cellular and tissue homeostasis. The autophagy process is initiated by phosphorylation of the unc-51-like kinase 1 (ULK1) complex, which is regulated by 5′ adenosine monophosphate activated protein (AMPK) (activator) and mammalian target of rapamycin kinase (mTOR) (inhibitor) [1,9]. This step is followed by phagophore initiation and formation, which is dependent on the production of phosphatidyl-inositol-3-phosphate (PI3P). Next, the elongation and maturation of the autophagosome takes place and in the last step the fusion of the autophagosome with the lysosome induces product degradation [1,9]. There are different factors which may influence autophagy and deregulate this process, including oxidative stress, hypoxia, inflammation DNA damage, and infections, leading to a defective autophagy, which has been associated with numerous pathologies, including Parkinson's disease and cancer [1]. Dysregulation in the mTOR signaling cascade, mainly through mTORC1, inhibits autophagy, and increases tumor growth. MTOR controls both *ULK1*, *ATG13* genes and ATG14L-associated VPS34 complex, all of which influence the autophagic process, making mTOR inhibition an important therapeutic target [31]. In cancer, autophagy plays a very controversial role. While in the early stages it can inhibit tumor growth, during the metastatic process, autophagy induces cancer cell survival and resistance, linked to poor survival outcome [10,32,33]. Epigenetic modifications such as DNA methylation, histone modification, and microRNAs influence gene transcription and post-translational processes impacting the entire autophagy regulation process and consequently cancer survival or death.

2.1. Dysregulated DNA modification modulates autophagy processes

By affecting the gene expression, aberrant DNA methylation (hypo- and hypermethylation) modifies different cellular processes including autophagy, silences tumor suppressors, and leads to cancer development.

DNA hypermethylation can down-regulate several autophagy genes, such as *ATG2B, ATG4D, ATG9A, ATG9B, ATG5, ANKDD1A, Beclin-1, ULK2, BCLB, TCF21,* and *PCDH17* leading to reduced autophagy and promotion of cancer progression. Restoring the expression of some of these genes such as *ANKDD1A* or *PCDH17* induced anti-proliferative effects on glioblastoma cancer cells, as well as gastric and colorectal cancer cells [9]. Autophagy inhibition caused by methylation silencing of *MAP1LC3Av1, ULK1/2 and BCLN1* have been associated with gastric cancer in patients with *H. pylori* and tumor growth in glioblastoma and breast tumor respectively [34–36]. Increased levels of *ATG2B, ATG4D, ATG9A,* and *ATG9B* have been observed in breast carcinoma [37]. CREB-1 modulators together with DNA methylation and histone deacetylation decrease the expression of *GABARAPL1*, a gene which promotes autophagy in breast cancer models. Upregulated *GABARAPL1* proved to be a good prognostic marker in breast cancer patients, suggesting that epigenetic inhibitors could provide valuable anti-cancer therapies [38].

On the other hand, DNA hypomethylation induced *ATG4A* and *ELFN2* expression promoting autophagy and tumor growth [9,10] (Fig. 1). Hypomethylation of *ATG4A* and *HIST1H2BN* has been reported as a poor prognostic marker for patients with ovarian carcinoma [39]. Reduced levels of ten-eleven translocation (TET) proteins have been correlated with decreased expression of *ATG13* and DNA damage-regulated autophagy modulator protein 1 in breast cancer. TET activates DNA demethylation and by regulating autophagy acts as a tumor suppressor [40]. Changes in the expression of DNMTs can also influence the autophagic pathway, through the role they play in DNA methylation. Methylation of *BCLN1* via H19/SAHH/DNMT3B induced tamoxifen resistance in breast cancer. On the other hand, phthalimido-alkanamide derivative, MA17, inhibits DNMTs (DNMT1, DNMT3A, and DNMT3B) activity and triggers both autophagy and apoptosis in glioblastoma cells [41,42]. Increased expressions of DNMT1, DNMT3a and DNMT3b in cancer cells, have been observed in patients with acute myeloid lymphoma, and DNMT1 is increased in women suffering from cervical cancer and is associated with poor prognostics [43]. DNMTs inhibitors (DNMTi), azacytidine, and decitabine are currently being tested in clinical trials. Decitabine upregulates ATG proteins (Beclin-1, Atg3, Atg5 and LC3) and downregulates the p53-induced glycolysis and apoptosis regulator (TIGAR) inducing autophagy and apoptosis in acute myeloid leukemia [44]. Treatment with decitabine also increases the expression of brain acid-soluble protein 1 (*BASP1*) a regulator of multiple apoptosis genes (*BCL-2* family, *C-MYC*) and causes cell death in AML cell lines [45]. Decitabine and guadecitabine (second generation of DNMTi) have become the most used drug to treat AML [11]. DNMTi are tested in combination with immune check-point inhibitors and other drug targeting epigenetic factors [43]. The combination of DNMTi and HDACi has been evaluated for its therapeutical potential in lung and ovarian cancer [11]. Additionally, the administration of both rapamycin (an mTOR inhibitor) with 5-aza-deoxycytidine increased apoptosis and decreased the volume of the tumor in a colorectal cancer mouse model [11,43].

2.2. Deregulation in histone modifications

Histone acetylation and deacetylation-mediated autophagy have also been linked to various cancer models. Inactivation of *HDAC1* activates autophagy and has anti-proliferative effects on hepatocellular carcinoma cells [9]. Silencing of *HDAC7* in mucoepidermoid carcinoma cells reduced cell proliferation and c-MYC expression and induced G2/M phase cell cycle arrest leading to apoptosis and autophagy [9]. *HDAC8* is overexpressed in oral squamous cell carcinoma, *HDAC10* upregulation allows autophagy-mediated cell survival in neuroblastoma and was associated with cancer resistance to treatment and poor survival rates, while *HDAC6* is overexpressed in hepatocellular carcinoma and cancer stem cells proliferation [9,46]. Cytosolic HDAC6 is the main modulator of the acetylation process and modulates the autophagic pathway (Fig. 2). Dysregulation of this process has been associated with neurological disorders (Morbus Alzheimer) and multiple cancer types [22]. The sirtuin family also play a bivalent role in cancer. While in prostatic intraepithelial neoplasia *SIRT1* can induce autophagy and inhibited the tumor development, the overexpression of *SIRT1* induced autophagy and proliferation of endometrial cancer cells [47,48]. Ubiquitin-conjugating enzyme E2C (UBE2C), by activating *SIRT1* ubiquitination and decreasing H4K16 deacetylation levels, inhibited autophagy and promoting endometrial cancer progression [49].

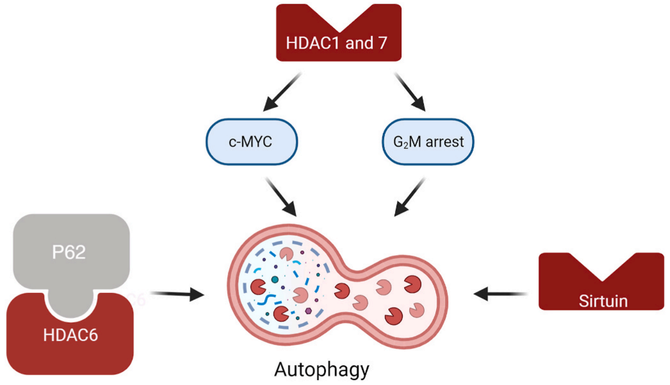

Fig. 2. Histone acetylation and deacetylation regulate autophagy. Inhibition of HDAC1 and HDAC7 reduces c-MYC expression and arrests the cells in the G2/M phase and eventually activating autophagy. HDAC6 and sirtuin also mediated autophagy induction. Created with BioRender.com.

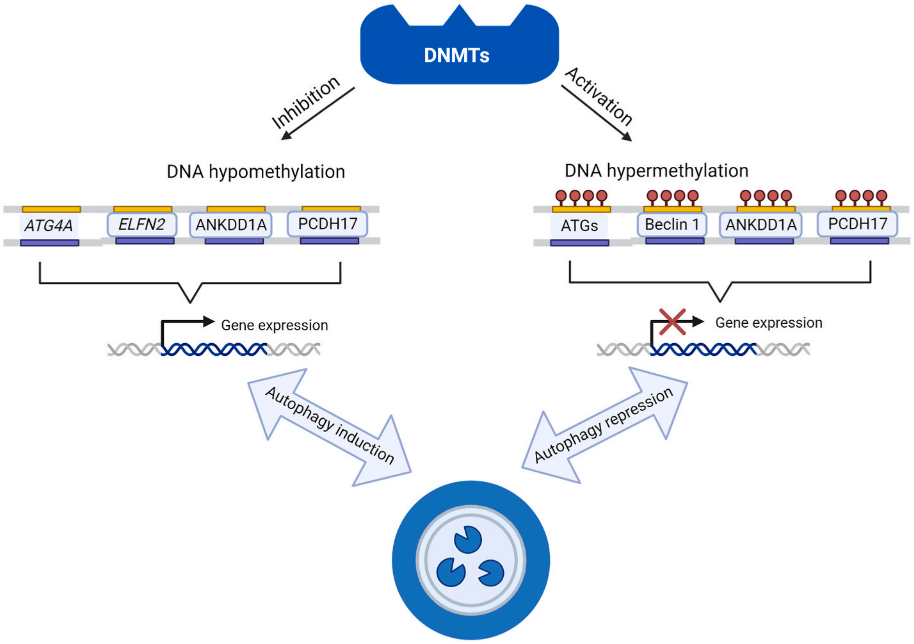

Fig. 1. Effect of DNMTs on the methylation status of DNA on the expression of autophagy markers. DNA hypermethylation downregulates the autophagy gene and suppresses autopay while DNA hypomethylation leads to activation of gene expression and then autophagy induction. Created with BioRender.com.

The decisive roles of these epigenetic modifications play for tumor development and resistance have led to the development of HDACs inhibitors (HDACi) with promising therapeutical potential in multiple pathologies including cancer and are currently being tested in both preclinical and clinical trials [22,50–53]. However, these compounds are non-specific and non-selective HDACi, and their mechanism of action is not yet fully deciphered. This together with their strong side effects are the reasons why the use of HDACi in clinical trials is still limited, and they are often administered in combination with other approved chemotherapeutics [22]. Interestingly, some HDACi, such as SAHA (Vorinostat) and ITF2357 (Givinostat) inhibited oncogenic BRAF in melanoma cells and switched the balance between autophagy and apoptosis in favor of apoptosis [54]. Furthermore, in AML the administration of a therapy combination containing DNMTs and HDACi downregulated oncogenes (e.g., *C-MYC*) and epigenetic modifiers: lysine demethylase *KDM2B*, protein arginine methyltransferases (*PRMT5* and *PRMT7*) and the histone-lysine methyltransferase *SUV39H1* [55]. *PRMT5* and *SUV39H1* inhibitors are currently being tested in preclinical and clinical trials for their anti-cancer effects and results indicate that they can inhibit autophagy and increase the sensitivity of cancer cells to the respective therapy [56,57]. Another compound potassium bisperoxo-(1,10-phenanthroline)-oxovanadate (bpV (phen)) blocked the interaction of p62 with HDAC6 and as such the autophagosome-lysosome fusion and autophagosome accumulation, triggering apoptosis and pyroptosis [58].

2.3. *Deregulation of non-coding RNAs (ncRNAs)*

Non-coding RNAs (ncRNAs) regulate the autophagy process through various mechanisms, from the initiation step to phagophore nucleation and autophagosome elongation and maturation. NcRNAs also influence the expression of various autophagy-related genes (ATGs) and of autophagy regulators (SQSTM1 and DRAM1) [30,59]. Enhanced expression of SQSTM1 and DRAM1 caused by dysregulated ncRNAs (miRNAs and lncRNAs) promotes carcinogenesis and metastasis [30,59]. The implications of ncRNAs and the pathways they influence in the autophagy process are shown in Table 1.

Furthermore, aberrant expression of ncRNAs suppressed apoptosis and enhanced autophagy and increased cancer stem cells stemness as well as drug resistance [30,60]. In cancer, ncRNAs modulate aberrant epithelial-to-mesenchymal transition (EMT) and cancer stem cell proliferation, and they promote angiogenesis and metastasis [60]. Cancer drug resistance was induced by ncRNAs through complex mechanisms involving changes in the apoptotic pathways, such as B-cell lymphoma-2 (Bcl-2) family and Wnt/β-catenin signaling pathway via nuclear factor kappa B (NF-κB) signaling, mitogen-activated protein kinase (MAPK), and PI3K/Akt pathways. Additionally, ncRNAs altered the expression of ATP-binding cassette (ABC) transporters to increase drug efflux and consequently drug resistance [60]. Using the data of The Cancer Genome Atlas (TCGA), multiple authors identified new autophagy-related lncRNAs that could be used as prognostic biomarkers in different cancer types (*e.g.*, bladder, ovarian, breast, lung cancer, etc.), as well as diagnostic biomarkers, and drug response predictors [60–66].

In cancer development, ncRNAs can function as tumor suppressors or promoters depending on the targeted pathway. Hence, new therapeutic strategies either use them as targets or therapeutic agents [60]. Given the complexity of cancer multiple therapeutic strategies are being developed, including targeted therapies (*e.g.*, combination of EZH2 with Bcl-2 inhibitors), combining epigenetic drugs with chemotherapy (*e.g.*, decitabine and carboplatin) or two different epigenetic drugs (DNMTs and HDAC inhibitors) [53].

Table 1
Autophagy-mediated ncRNAs and their cancer involvement.

Autophagy step	Signaling pathway	ncRNAs	Cancer type
Initiation	AMPK-mTOR-ULK1	miR-100,	Renal cell carcinoma colorectal cancer,
		miR-126, miR-204, miR-378,	renal cell carcinoma, skeletal muscle, hepatocellular carcinoma,
		miR-159D,	cervical squamous cell carcinoma,
		mirR-106A, miR-129,	osteosarcoma hepatocellular carcinoma,
		HIF1A-AS1, *HAGLROS*,	gastric cancer, hepatocellular carcinoma,
		PTENP1,	pancreatic ductal adenocarcinoma,
		PVT1	squamous cell carcinoma
Phagophore formation and nucleation	PI3K complex/ PI3K-Akt-mTOR	miR-381, miR-375, miR-320, miR-519a, *HAGLROS*,	Prostate cancer, gastric cancer, retinoblastoma, glioblastoma, hepatocellular carcinoma,
		HOTTIP,	renal cellular carcinoma,
		SNHG14, *PVT1*,	colorectal cancer, pancreatic ductal adenocarcinoma,
		hsa_circ_0005567	breast cancer
autophagosome elongation and maturation	ATG12-system	miR-101,	Breast cancer osteosarcoma,
		miR-570, miR-224, *HAGLROS*,	glioblastoma, gastric cancer, hepatocellular carcinoma,
		HCAL,	hepatocellular carcinoma
		HULC	Hepatocellular carcinoma

3. Apoptosis and its mechanism

Apoptosis, or programmed cell death, is a conserved pathway responsible for organism development during the embryogenesis process and maintaining tissue homeostasis [67]. Both excessive cell death and resistance to it may lead to pathological conditions. For example, cancer cells resist undergoing apoptosis, followed by uncontrolled cell proliferation [68]. Cancer cells frequently overexpress several anti-apoptotic molecules that prevent the initiation of the apoptotic pathway. On the other hand, cells could avoid programmed cell death by downregulation of pro-apoptotic molecules [69].

Apoptosis is activated either via signals from mitochondria (named intrinsic pathway) or through extracellular signals (called extrinsic pathway) and it is normally receptor-mediated [70].

3.1. *Role of hypo/hypermethylation of DNA on apoptosis*

Both apoptosis signaling pathways involve several genes that are classified based on their contribution to the initiation phase of apoptosis, such as p53, p14^{ARF}, p73, BNIP3, XAF1 APAF1, Fas, DR4 and DR5, DcR1 and DcR2, DAPK, and TMS1, or to the execution phase such as caspase-8. Based on studies in many cancer types, the expression of those apoptosis genes is affected by DNA methylation [69]. The p53 protein is a transcription factor known to function as a tumor suppressor. It controls the expression of death receptors (FAS, TRAILR2) as well as mitochondria-mediated apoptosis (BAX, BAK, BID, NOXA, PUMA, APAF1, and p53AIP1) [71]. Aberrant methylation resulted in down-regulation of p53 and p14ARF, and hypermethylation of the *TP53* promoter was reported in acute lymphatic leukemia patients [69,72].

The tumor suppressor gene (TSG), Zinc Finger DHHC-Type

Containing 1 (ZDHHC1, also known as ZNF377) was frequently silenced by methylation in various tumor types and was also correlated to inflammatory bowel disease (IBD)-associated neoplasia [73]. Restoration of the ZDHHC1 expression inhibited cell proliferation and induced apoptosis in MCF7 and HONE1 cells. *In vivo* studies confirmed that ZDHHC1 expression cleaved caspase-7, caspase-3, and PARP and stimulated apoptosis and pyroptosis through activation of oxidative stress and endoplasmic reticulum (ER) stress [74]. Treatment with the DNMT1 inhibitor 5-azacytidine restored the nuclear localization of Mouse double minute 2 (MDM2) and activated the expression of p53 [75]. On the other hand, guadecitabine (gDEC), another DNMT1 inhibitor, showed anti-proliferation activity *in vitro* and *in vivo,* but it did not induce apoptosis. Hypomethylation of the promoter region of certain genes induced cancer and drug resistance. In glioblastoma tumors, the small nucleolar RNA host gene 12 (*SNHG12*) was overexpressed in temozolomide (TMZ)-resistant cells and tissues. Hypomethylation was observed within the promoter region of the *SNHG12* gene, which made the area more reachable by the transcription factor (SP1). Clinically, *SNHG12* overexpression was linked with poor survival of glioblastoma patients and resistance to TMZ treatment via upregulation of MAPK1 and E2F7 [76]. Treatment with the DNMT1 inhibitor 5-azacytidine restored MDM2 to the nucleus and activated the expression of p53 [75]. Another DNMT1 inhibitor, guadecitabine (gDEC), showed anti-proliferative activity *in vitro* and *in vivo,* but it did not induce apoptosis [77]. Fig. 3 illustrates the key regulators of DNA methylation and apoptosis.

Chemical modification of m.RNA, N6-methyladenosine (m6A) was linked to programed cell death processes in general and apoptosis in particular. m6A could activate apoptosis by four ways: governing apoptosis-related genes, shutting off methylating or demethylating enzyme genes, and decreasing the expression of YTHDC2-related genes. The expression of YTHDC2 increased the translation efficiency of Smc3 (target *YTHDC2* in spermatogenesis) and significantly increased the gene expression of apoptosis markers such as caspase-3, Bcl-2, and Bid in neck squamous cancer cells [78]. Nevertheless, the underlying mechanism is still poorly understood. LNC942 functions as oncogenes in breast cancer cells by directly promoting METTL14 (member of m6A methyltransferase complexes), controlling the expression and stabilizing LNC942-dependent genes such as *CXCR4* and *CYP1B1*. Upregulation of LNC942 and METTL14 via the upregulation of m6A levels in cancer cells increased cell proliferation and colony formation and reduced apoptosis rates through the LNC942-METTL14-CXCR4/CYP1B1 signaling axis [79]. The upregulation of FTO m6A demethylase was significantly associated with apoptosis reduction in breast cancer. Hence, *BNIP3* is a pro-apoptotic gene demethylated by FTO in the m.RNA 3′UTR, and enhanced BNIP3 degradation takes place via an YTHDF2-independent mechanism [80]. The absence of FTO activated *TP53* mRNA and protein levels and increased the fraction of apoptotic cells in cisplatin-treated kidney tumors [81].

3.2. Histone modifications affect apoptosis

The post-translational modifications (PTMs) of histone are long-standing hallmarks of apoptosis. There is increased evidence that combinations of histone modifications have an impact on cellular processes including apoptosis [82]. In this review, two histone post-translational modifications are highlighted: phosphorylation and acetylation.

Dephosphorylation of the linker histone H1 is the first histone PTM associated with the apoptotic pathway. Hence, under normal condition, H1 is highly phosphorylated. H1 linked two adjacent nucleosomes at the site of DNA cleavage and activated DNA fragmentation factor 40 (DFF40/CAD), the nuclease proteins that cut DNA during apoptosis. However, recent studies concluded, that there is no strong correlation between the initial apoptotic step (histone H1 dephosphorylation) and DNA fragmentation. Dephosphorylation of H1 was not necessary for internucleosomal or overall cleavage [83]. The phosphorylation of H3 on Ser-10 by the pro-apoptotic kinase protein kinase C (PKC) was required for apoptosis induction and chromatin condensation after treatment with DNA damaging agents [84].

Another example is phosphorylation of H2B at Serine 14 (H2B-S14ph). It has been associated with apoptotic cells, while the acetylation at the Lysine 15 of the same histone (H2B-K15ac) was a feature of living cells. H2B-S14ph modification played a role either in chromatin condensation or internucleosomal DNA fragmentation [85–87]. The deacetylation of H2B-K15 was essential to phosphorylate H2B-S14 by

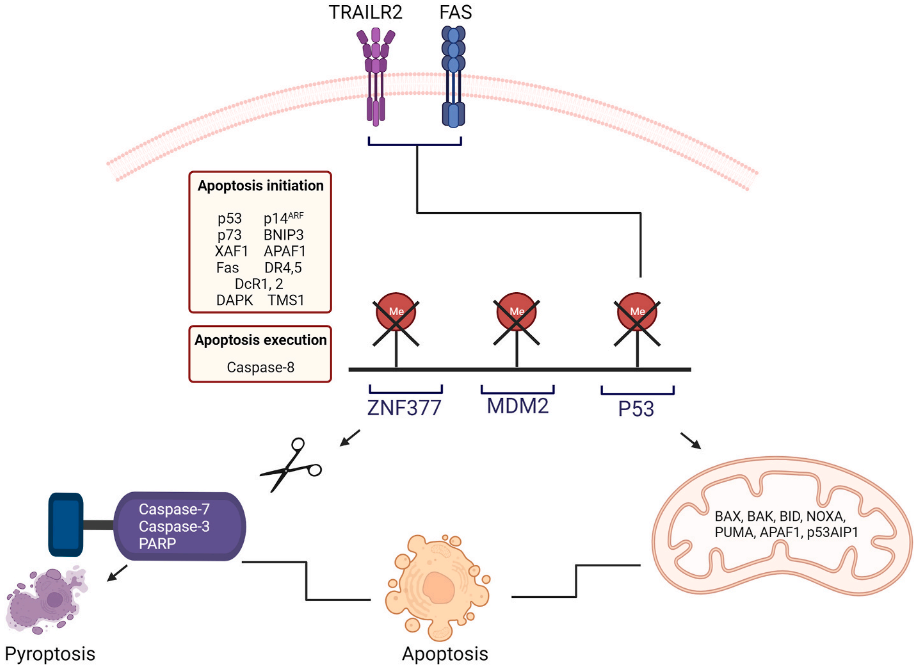

Fig. 3. The expression of the key players of apoptosis pathways is controlled by DNA methylation. Both extrinsic and intrinsic pathways genes are affected by the methylation status at their promoter region. The absence of the methyl group from the promoter of the tumor suppressor genes (TSG) allows their expression and then their function. The TSG then expresses the apoptosis-dependent genes even the one for mitochondria-mediated apoptosis pathways. Created with BioRender.com.

mammalian sterile twenty (Mst1) kinase. Cleavage and activation of Mst1 was achieved by caspase 3. Then, it translocated to the nucleus and caused chromatin condensation [88]. H2B-S14ph is not only a hallmark of apoptosis, but also inactivated survival pathways including NF-κB-p65. Through its immobilization on chromosomes, H2B-S14ph reduced the level of RanGTP in the nucleus and subsequently inhibited the nuclear transport machinery. Then, the nuclear localization signal-containing proteins such as NF-κB, could not disassociate from importins α and β in the cytoplasm [82]. Moreover, the existence of H2A.X-Y142ph inhibited the binding of repair factors (MRE11, RAD50, NBS1, 53BP1 and BRCA1) to H2A.X-S139ph through MDC1 and stimulated the pro-apoptotic factors JNK1 [89,90]. The balance of H2A.X-Y142ph phosphorylation/dephosphorylation controlled this novel switch determining cell fate after DNA damage (Fig. 4) [91].

Another histone modification is phosphorylation of histone H3 (H3-T45ph) at the threonine 45 residue. It was dramatically increased in apoptotic cells by protein kinase C-δ (PKCδ) after caspase-3 cleavage [92]. Since H3-T45 has a significant position within the nucleosome, its phosphorylation changed the structure of the nucleosome to facilitate DNA fragmentation [92,93]. Furthermore, the phosphorylation of serine 10 on H3 (H3-S10ph) was linked to chromosome condensation and segregation during cell division, involved in the function of R-loops (specific DNA–RNA hybrids), and contributed to signal transduction and apoptotic signaling [94,95]. However, it remains unclear how H3-S10ph activated the apoptosis pathway [95].

The induction of apoptosis is characterized by biochemical and morphological features [96]. Chemical modifications of histones are responsible for the nuclear changes associated with apoptotic cells and are called apoptotic histone mark. During apoptosis, acetylation of histone H2B, H4 and hypoacetylation of histone H4, together with other modifications, give cells the specific nuclear structures necessary to degrade the nucleus, and to control chromatin condensation [97]. Histone acetylation induced apoptosis in cancer cells by controlling the expression of pro-apoptotic and anti-apoptotic genes of both extrinsic and intrinsic apoptotic pathways [98–100]. Several studied demonstrated the effect of acetylation upon apoptosis using HDACi. The mitochondrial apoptotic pathway was activated by HDACi through upregulation of the proapoptotic genes: thioredoxin binding protein 2, BAK, Bax, Apaf-1, Bad, Bim, Bid, caspase-3, and caspase-9, as well as transcriptional inhibition of the antiapoptotic regulators: thioredoxin, Bcl-2, Bcl-XL, XIAP, Mcl-1, and survivin see Fig. 4 [101].

The local chromatin movement and its higher order of complexity were regulated by acetylation of the lysine amino acid [102]. The acetyl group on lysine 16 of histone H4 (H4-K16ac) was an important and reversible PTM in eukaryotes [103,104]. Hence, it disturbed chromatin condensation and changed the interaction of chromatin-associated proteins, leading to increased chromatin accessibility. Loss of H4-K16ac is a common marker in many types of tumors [104]. HDACis were correlated with increased acetylation of histones H3 and H4, including H4-K16ac, thereby inducing cancer cells sensitivity to apoptosis triggered by DNA damage [105]. The treatment of prostate cancer cells with HDACi (CG-1521) hyperacetylated p53 at Lys373 and stabilized it. CG-1521 caused an elevation of p21 (inducing cell cycle arrest) and promoted Bax translocation from the cytosol to the mitochondria and cleavage, as well as apoptosis. However, it also hyperacetylated p53 at Lys382 and increased p21 levels without inducing Bax translocation or apoptosis in prostate cancer cells [106]. The treatment of malignancies with HDACis in combination with chemotherapies resulted in the overexpression of Bcl-xL [107].

3.3. *Non-coding RNAs regulate apoptosis*

Different types of non-coding RNAs displayed their regulatory effects towards apoptosis. Based on their expression patterns, they could play pro- or antitumorigenic roles [108].

Recently, studies have revealed that miRNAs are involved in regulating apoptosis of breast cancer cells. For example, miR-15a/miR-16 targeted the anti-apoptotic B-cell-specific Molony murine leukemia virus integration site 1 (BMI1) and activated mitochondrial-dependent apoptosis [109,110]. On the other hand, cells over-expressing miR-519a-3p resisted apoptosis because miR-519a-3p bound and degraded its direct targets TRAIL-R2 (TNFRSF10B) and caspase-8

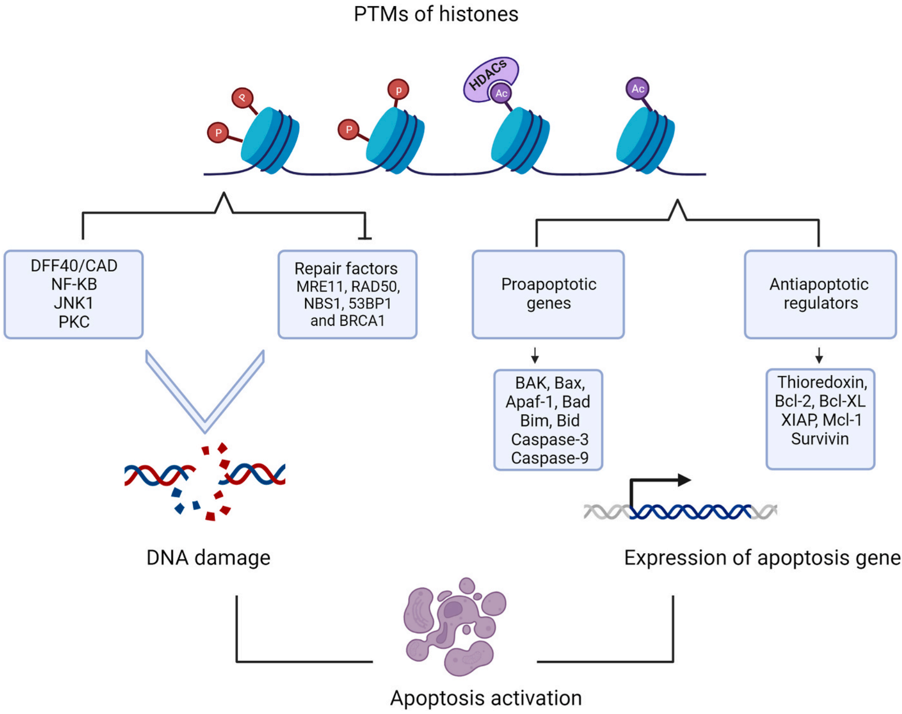

Fig. 4. Post-translational modifications (PTMs) of histone influence apoptosis. The phosphorylation/dephosphorylation of histones has an impact on mainly DNA damage while the acetylation status of histone regulates the expression of pro-apoptotic and anti-apoptotic genes. Created with BioRender.com.

(CASP8) [111]. Also, the upregulation of miR-182–5p induced apoptosis via targeting and activating the apoptosis executioner caspase-9 [112]. Numerous other miRNAs are important for the intrinsic or extrinsic pathways of apoptosis. Some examples are listed in Table 2.

lncRNAs have a dual role in apoptosis, they can activate or suppress apoptosis pathways [127]. Dysregulated lncRNAs have been associated with cancer proliferation, metastasis and chemoresistance [128,129]. For instance, the lncRNA taurine upregulated gene 1 (*TUG1*) was found to act as a sponge for several miRNAs involved in apoptosis such as miR-145 [130]. *TUG1* acts as a tumor suppressor in glioblastoma by inducing apoptosis. *TUG1* activated Wnt signaling and subsequently inhibited apoptosis [131]. In addition, downregulation of *TUG1* suppressed Bcl-2 expression resulting in increased cleavage of caspase-3 [131]. In glioblastoma, overexpression of lncRNA *CRNDE* inhibited apoptosis and promoted cancer cell proliferation, *HOTTIP, HOTAIR* and *MALAT1* upregulation also dysregulate the apoptosis pathway. These genes were overexpressed in glioblastoma patients and associated with a negative prognostic [129]. Additionally, a new lncRNA, *TODL1* promoted aberrant cell proliferation and controled apoptosis in liposarcoma. It might be used as a potential diagnostic biomarker in liposarcoma [132]. Other lncRNAs were also identified to dysregulate apoptosis, such as *MEG3* lncRNA, *GAS5* lncRNA, *PTENpg1*, *LINC00675*, LncRNA *HOXA-AS2*, and lncRNA *UCA1* [127].

CircRNAs are non-coding, single-stranded, and closed RNA which are not linear. They have similar functions as lncRNAs, and both serve as miRNA sponges. This directly influences miRNA activity and thereby miRNA target genes [133–135]. Yet, the knowledge about CircRNAs expression, function, and their molecular mechanisms is sparse. The level of circRNA-HIPK3 was higher in non-small cell lung cancer (NSCLC) tissues and cell lines [136]. Moreover, circHIPK3 regulated the pathogenesis of NSCLC via miR-149-mediated FOXM1 expression. Downregulation of Circ_0001776 results in high expression of miR-182 in endometrial cancer tissues and cells. Upregulation circ_0001776 significantly enhanced apoptosis [136].

4. Ferroptosis

Ferroptosis is a mode of programmed cell death characterized by the iron-dependent accumulation of lipid peroxides, which leads to membrane damage and consequently cell death. In contrast to apoptosis or autophagy, ferroptosis is initiated by a metabolic imbalance in iron and lipid metabolism and is not dependent on caspase enzymes or the formation of autophagic vesicles [137]. The molecular mechanisms behind ferroptosis are characterized by unique features, namely the suppression or reduction of glutathione peroxidase 4 (GPX4), an enzyme that mitigates lipid peroxidation, and an increased dependence on iron metabolism [138]. Dysregulation of ferroptosis through epigenetic modifications has been associated with a range of clinical disorders, such as neurological illnesses, ischemic organ damage, and cancer [137]. Available data regarding how epigenetic modifications inhibit ferroptosis and promote cancer progression is limited yet.

Table 2
ncRNAs and their involvement in cancer.

ncRNAs	Target	Cancer type
MicroRNAs regulating the intrinsic pathway of apoptosis		
miR-491	BCL-X	Colon cancer [113]
miR-133a	BCL-X_L and Mcl-1	Osteosarcoma [114]
miR-608	BCL-X_L and EGFR	Malignant chordoma [115]
miR-365	SHC1 and BAX	Pancreatic cancer [116]
miR-125b	Bcl-2 and Bak1	Breast cancer [117]
miR-15 and miR-16	Bcl-2	Chronic lymphocytic leukemia (CLL) [118]
MicroRNAs regulating the extrinsic pathway of apoptosis		
miR-221 and miR-222	p27^{kip1}	Breast cancer [119,120]
miR-21 and miR-590	FasL	Pancreatic cancer [121–123]
miR-20a		Acute myeloid leukemia
miR-25		Osteosarcoma
		Cholangiocarcinoma
miR-182 and its homologue miR96	FADD and caspase-3	Several cancer cell lines [124]
miR-145 and miR-216	TRAIL, DR4 and DR5	Several cancer cell lines [124]
miR-K10a	TWEAK receptor	Kaposi sarcoma [125]
miR-128a	FADD	Myeloid leukemia [126]

4.1. *Connection between ferroptosis and DNA methylation*

Just like autophagy and apoptosis, ferroptosis is also influenced by epigenetic changes. In lung carcinoma, DNA methylation modifier lymphoid-specific helicase (LSH), a known oncogene, interacts with WDR76, a nuclear WD protein, to inhibit ferroptosis by activating the lipid metabolic genes (*GLUT1*) and ferroptosis-related genes (*SCD1* and *FADS2*) leading to cancer proliferation [139]. Mucin 1 (MUC1) transmembrane protein is overexpressed in triple-negative breast cancer (TNBC) and modulates the glutathione (GSH) balance [140]. *MUC1* expression is regulated by both DNA methylation and histone H3 lysine 9 modification [141]. Suppression of the *MUC1* pathway induced ferroptosis and prevented the survival of TNBC cells [140].

4.2. *Histone modifications influence ferroptosis*

Histone acetyltransferase lysine acetyltransferase 2B (KAT2B) induced ferroptosis by modulating GSH production. In hepatocellular carcinoma, the dissociation of KAT2B prevented HNF4A from binding to anti-ferroptosis transcription factors, allowing HIC1 to bind to ferroptosis up-regulating factors and possibly improving the prognostic outcome of patients [142]. SLC7A11 (solute carrier family 7 membrane 11) induced GSH synthesis and was upregulated in various cancer cells [143]. Histone H3 lysine 9 demethylase (KDM3B) increased SLC7A11 expression and prevented ferroptosis [144]. BRCA1-associated protein 1 (*BAP1*) is a tumor suppressor gene mutated in cancer. BAP1 mediated deubiquitination of histone 2A ubiquitination (H2Aub), while monoubiquitination of histone H2B on lysine 120 (H2Bub1) induced the expression of SLC7A11 during ferroptosis and consequently suppresses tumor growth [145]. The tumor suppressor protein p53 inhibited the histone H2B on lysine 120 (H2Bub1) expression and increased ferroptosis sensitivity in lung cancer cells [146]. Bromodomain protein (BRD4) inhibitor (+)-JQ1 induces apoptosis, however, new data shows that it can also induce ferroptosis in cancer cells. The process can be explained by the potential of (+)-JQ1 to inhibit the expression of ferroptosis-associated genes *GPX4*, *SLC7A11*, *SLC3A2,* and histone methyltransferase *G9a* or enhance histone deacetylase *SIRT1* expression [147].

4.3. *The importance of non-coding RNAs (ncRNAs) in ferroptosis*

Non-coding RNAs are key regulators of ferroptosis and depending on their activity can either induce or inhibit ferroptosis. Inducers of ferroptosis are miR-4715/miR-4715-3p, inhibiting *GPX4* expression through downregulating Aurora kinase A (AURKA). MiR-30b/miR-30b-5p downregulated the cystine/glutamate antiporter and FPN 1, affecting glutathione (GSH) and Fe^{2+} levels [148]. Among lncRNAs, *P53*RRA promoted both apoptosis and ferroptosis, inhibiting tumor growth by interacting with G3BP1 to activate the p53 signaling pathway. *GABPB1-AS1* inhibited GABPB1 expression leading to PRDX5 downregulation, and XAV939-linked lncRNA suppressed SLC7A11 [148]. On the other hand, miRNAs inhibited ferroptosis. In melanoma, miR-137 negatively regulated SLC1A5, and miR-9 targeted glutamic-oxaloacetic transaminase 1 (GOT1). MiR-103A/miR-103a-3p influenced glutaminase 2 (GLS2). In endothelial cells, miR-17HG/miR-17-92 suppressed the expression of TNFα-induced protein 3 (TNFAIP3/A20), a positive regulator of acyl-CoA synthetase long-chain family member 4 (ACSL4). ACSL4 is an enzyme implicated in the metabolism of fatty acids. It was identified as a specific biomarker of ferroptosis [143]. MiR-7-1/miR-7-5p inhibits SLC25A37/mitoferrin causing resistance to ferroptosis, while ZFP36 induced *ATG16L1* mRNA which was also associated with resistance to autophagy-dependent ferroptosis [143]. lncRNAs inhibitors of ferroptosis were: *LINC00336*, nuclear lncRNA, interacting with *ELAVL1* and reducing miR-6852 activity, which subsequently enhanced cystathionine β-synthase (CBS) expression in lung adenocarcinoma and promoted tumorigenesis [148]. CircRNAs are currently only known for their potential to inhibit ferroptosis in cancer: circ-*TTBK2* upregulated the miR-761/ITGB8 pathway in glioma cancer and circ-0008035 enhanced *EIF4A1* expression and targeted miR-599 in gastric cancer cells [148]. Taken together, the data highlight how incredibly complex cancer development is and how challenging the development of cancer therapies is, given the interconnections among the epigenetic regulators.

5. Other types of cell deaths

Necroptosis is known as programmed necrosis, characterized by the inhibition of caspase-8 activity and the formation of an intracellular complex called necrosome, by the receptor-interacting serine/threonine kinase (RIPK) 1, and RIPK3. RIPK3 activates the mixed lineage kinase domain-like pseudokinase (MLKL), which leads to membrane permeabilization and necrotic cell death [149]. Interestingly, similar to autophagy, necroptosis can either promote or suppress cancer development based on the development stage. As with other cell death types, it is also influenced by epigenetic modifications.

Hypermethylation of the *RIPK3* promoter, decreased the expression of RIPK3 through different mechanisms and was associated with poor outcome, while an increase of RIPK3 expression prevented tumor development in mice [150–153]. The HDAC inhibitor SAHA up-regulated p-RIP3 and MLKL levels in a p21-dependent manner in MCF-7 breast cancer cells, suggesting that it can induce necroptosis [154].

Additionally, necroptosis-related lncRNAs have the potential to predict survival outcome in patients with different types of cancer [155–160].

Parthanatos, a mitochondrial-related programmed cell death, is characterized by hyperactivation of PARP-1 and translocation of apoptosis-induced factor (AIF) into the nucleus [149]. The mechanisms through which parthanatos prevents tumor development have not yet been fully clarified. Parthanatos can be induced by N-methyl-N0-nitro-N0-nitrosoguanidine (MNNG) through the activation of PARP1 or the sodium–hydrogen antiporter inhibitor HMA (5-N, N-hexamethylene amiloride) through acid L-DNAse II [161]. Lysine demethylase 6B (KDM6B), a key regulator of parthanatos, could be used as a biomarker to predict the therapeutic efficacy of alkylating agents on cancer cells. KDM6B regulated O^6-methylguanine-DNA methyltransferase (MGMT), downregulation of KDM6B, and subsequent upregulation of MGMT leading to resistance to parthanatos after treatment with alkylating agents [162]. Additionally, YK-4-279, an inhibitor of the small-molecule E26 transformation-specific (ETS) factor, induced hyperphosphorylation of histone H2A.x in P53 knock-out RKO cells and activated the parthanatos pathway [163]. This represents an interesting mechanism requiring further investigation on its role in cancer.

6. Conclusion

The current review undertakes a journey through the epigenetic modifications that take place in different types of cell death and their role in cancer. The enumerated cell death types are all being controlled through highly regulated mechanisms, often interacting with each other. Epigenetic modifications can deregulate the normal processes and lead to tumor progression. As seen in the case of autophagy, apoptosis, and necroptosis, cell death modes can either suppress cancer development or promote it depending on the tumor development stage and the mechanism activated. In various types of cancer, epigenetic changes either directly suppress ferroptosis or increase the resistance of cancer cells to ferroptosis and consequently tumor progression. Both HDAC and DNMT inhibitors exemplify how targeting epigenetic alterations can be a powerful strategy in cancer therapy. By reversing the epigenetic silencing of crucial genes and tumor suppressors governing cell survival and death (including autophagy, apoptosis, or ferroptosis), these inhibitors can reactivate the body's natural mechanisms for controlling and eliminating cancer cells. Certain HDACi and DNMTi are already in clinical trials or approved and being used in combination with other therapies (chemotherapy, immunotherapy) with promising results. The use of epigenetic drugs in cancer therapy not only prevents cancer resistance but can help to develop personalized therapies based on the individual epigenetics. Additionally, certain histone modification (H3K9, H3K27) and ncRNAs (*HOTTIP, HOTAIR MALAT1* and *TODL*) have already been tested as prognostic biomarkers, making them valuable assets in cancer therapy. Further studies will be needed to uncover the mechanisms and interconnections between these cell death types and cancer.

7. Future perspectives

Our understanding of how epigenetic modifications influence cell processes in cancer is limited, but new insights provide valuable information on how these pathways work in cancer. Although new drugs have been developed due to the heterogeneity of cancer and interconnection between cellular processes, it is still challenging to link specific epigenetic modifications to one cell death type. However, new emerging technologies using CRISPR/Cas9 or artificial intelligence-driven predictive models can help understand the complexity behind the surviving mechanisms of tumor cells and how epigenetic modifications affect cell death processes. Furthermore, because of their potential as biomarkers epigenetic modifications could be used in the future in cancer prevention and early detection, as well as predictive biomarkers for treatment response and prognosis. Moreover, the new drugs targeting specific epigenetic modifications together with other treatments (immunotherapy, chemotherapy) can pave the way to personalized medicine and overcoming cancer resistance, because these drugs target multiple cell death pathways.

CRediT authorship contribution statement

R. Damiescu: Writing – original draft, Conceptualization. **T. Efferth:** Writing – review & editing, Conceptualization. **M. Dawood:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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