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Chapter

Epi-Regulation of Cell Death in Cancer

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Abstract

How do organisms regulate the correct balance between the production of "new" cells and the elimination of the "old" ones, remains an important biology issue under investigation. Cell(s) death represents a fundamental process involved in organism development and cell homeostasis, whose alteration is considered one hallmark of cancer and lead to drug resistance and consequently treatment failure. The recent re-classification of cell death has identified new molecular programs in which several proteins have a pivotal role. Several studies have highlighted a direct link between epigenetic modifications and cell death mechanisms. Different epi-modifications have been described, capable of regulating diverse key players implicated in cell death, leading to uncontrolled proliferation of cancer cells. Scientific efforts are focused on the understanding the epigenetic regulation of cell death mechanisms by developing tools and/or new epi-molecules able to overcome cell death resistance. The development of new epi-molecular tools can overcome cell death deregulation thus potentially improving the sensitivity to the anti-tumor therapies. This chapter focuses on the main epigenetic deregulations in cell death mechanisms in cancer.

Keywords: epigenetics, cell death, cancer, apoptosis, necroptosis pyroptosis, Immunogenic cell death, NETosis, parthanatos

1. Introduction

Epigenetics is the study of functionally heritable changes in the genome that occur without structural changes in the DNA sequence [1], characterizing cellular phenomena and molecular mechanisms responsible of the remodeling of a phenotype starting from a fixed structure that is determined by the genotype [2]. Epigenetic mechanisms can regulate gene expression through covalent chemical modifications, histone posttranslational modifications (PTMs), several RNA species or also through chromosomal superstructure modifications in which DNA is packaged without making any change in the DNA (in its) basic structure [3, 4]. During the past years, different types of epigenetic mechanisms have been identified (i) DNA methylation, (ii) histone modifications, and (iii) non-coding RNA (ncRNA),

able to modulate gene and protein expression [3]. Epigenetic changes are the results of the action of three different enzymatic classes, (i) *writers*, able to add chemical groups on DNA, histones and proteins; (ii) *readers,* which read and identify several "signals" through their structural domains, and (iii) *erasers* involved in the removal of chemical groups.

DNA methylation is one of the most known epigenetic modifications able to repress gene transcription and expression, especially when located near the transcription start sites of genes [5]. Well-known is the crucial role of both hypermethylation of tumor suppressor and global hypomethylation of oncogenes in tumor initiation and progression [6]. PTMs, changing the histone structure, are also able to alter gene expression. [7]. These alterations, mediated by the addition of chemical groups at the N-terminal tail of histones are covalent, reversible, and redundant creating a real "histone code" that regulates the chromatin structure, gene expression and the recruitment of different enzymes. These changes can include (i) acetylation of lysine residues; (ii) methylation of lysine and arginine residues; (iii) phosphorylation of serine residues; (iv) the binding of one or more monomers of ubiquitin (ubiquitination), (v) the binding of several polypeptide (SUMOylation), (vi) citrullination, consisting in the conversion of arginine residues into citrulline residues by specific enzymes [8]. Much progress has been made in understanding the roles of both microRNAs (miRNAs) and long noncoding RNAs (lncRNAs) in gene regulation which play an important part in several biological processes such as proliferation, differentiation, apoptosis [9].

Epigenetic changes are often associated to the genesis of many pathologies with a "high social impact" such as cancer. These modifications induce the blocking or definitive silencing of many cellular signal transduction pathways, the restoration of which today represents a promising therapeutic perspective. Particularly
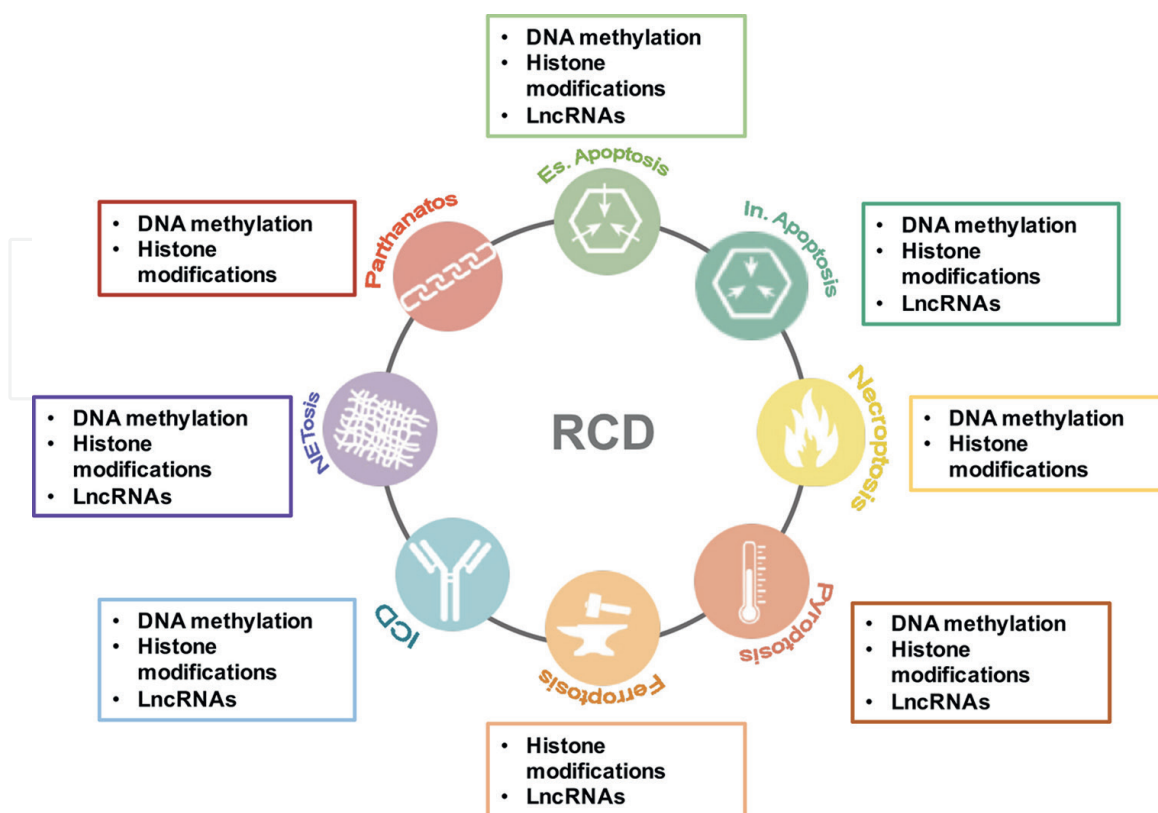

Figure 1.
Epigenetic regulation in cell deaths.

studied are the cell death pathways, complex and finely regulated processes whose deregulation alters the correct cell homeostasis, responsible of the excessive cell proliferation. Cell death *phenomena* alteration represents one of the main markers of oncogenic cell transformation responsible for resistance to cancer and drug therapies failure [10]; indeed, a tumor cell still retains the ability to proliferate and/or to go into apoptosis but the pathways of regulation of these signals can be silenced and therefore inactive.

The aim of this chapter is to shed light on the epigenetic regulation of the molecular players involved in cell death pathways, whose alteration has a pivotal role in carcinogenesis. Considering the reversibility of the epigenetic modifications, they represent a promising target for anticancer therapy (**Figure 1**).

2. Cell death mechanisms

For a long time, cell death was considered an inexorable event for cells, an indispensable cellular mechanism which allows the cell to die when it is damaged, altered or simply aged [11]. Cell death is to be considered not only as a destructive process for the organism but also as a defensive process that the cells put in place to preserve homeostasis [12]. Several studies have shown that cell death mechanisms not only allow the cell to die when it has reached the end of its life cycle, but they are useful events both during prenatal and the development for the removal of excess, damaged or altered formed cells [13]. Based on the severity of the insults, on the morphology and on the biological events that can be activated during the cell death process, we distinguish an accidental death cellular process (ACD), and a regulated cell death (RCD) [14].

Necrosis, a type of ACD, is an unordered and unscheduled death mechanism that cells puts in place in response to stimuli such as radiations, toxins, osmotic variations, viral or bacterial infections followed by a large immunogenic and inflammatory response. Some enzyme systems involved in this process are lytic enzymes called calpain and cathepsins as well as damage-associated molecular patterns (DAMPs) which can be DNA fragments, ATP, uric acid, inflammatory cytokines including High Mobility Group Box 1 (HMGB1), an inflammatory cytokine of great importance in the necrosis process [15].

On the other hand, RCD, is a controlled death process that can be genetically or pharmacologically regulated which is involved in two different scenarios. It acts as the main process in tissue development responsible for the cell's turnover in the absence of exogenous environmental perturbations [16, 17]. RCD can be also the result of prolonged intra and extracellular perturbations [18] and does not alter tissue homeostasis or cell development. When it occurs in physiological conditions it is called programmed cell death (PCD) [19–21]. Considering only morphological characteristics, it has been proposed a classification of several forms of cell death including: type I or apoptosis, type II or autophagy, type III or necrosis [14, 19].

In this last decade, a new subdivision of the various cell deaths has been proposed through essential and mechanistic aspects that distinguish them. Twelve types of cell deaths have been identified which are Necroptosis, Ferroptosis, Pyroptosis, Parthanatos, Entotic cell deah, NETotic cell death, Lysosome-dependent cell death (LDCD), Autophagy-dependent cell death (ADCD), Immunogenic cell death (ICD), Intrinsic apoptosis, Extrinsic apoptosis, Mithocondrial permeability transition-driven necrosis (MPT).

2.1 Epigenetic regulation in apoptosis

Apoptosis, or type I PCD, is a finely regulated "molecular assisted suicide" mechanism, necessary for maintaining cellular homeostasis processes. It is the response to DNA damage (spontaneous apoptosis), or different conditions such as hypoxia, lack of growth factors and action of chemotherapeutic agents (induced apoptosis). It is also involved in physiological processes such as embryogenesis and differentiation. It is defined as a "clean" death mechanism since there is no release of waste elements: the apoptotic bodies - which contain cell fragments - are eliminated through the action of the immune system and more specifically through the action of macrophages [22]. The loss of apoptotic regulation causes uncontrolled cell proliferation leading to several human diseases such as cancer [23]. Apoptosis is the result of extrinsic or intrinsic signals, coming from outside and inside the cell, respectively. A pivotal role, in this pathway, is played by initiator and effector caspases synthesized as inactive zymogens and activated by a proteolytic cut [24]. The extrinsic apoptosis pathway is triggered by the link between death receptors of the Tumor Necrosis Factor (TNF)-family with their specific pro-apoptotic ligands resulting in the activation of different molecular adapter able to cleave initiator caspases which in turn cleave and activate effector caspases [25] while the intrinsic pathway is triggered by mitochondrial dysfunction caused by cellular stress [26]. The main event is the release of cytochrome c from complex, called apoptosome, with other cytosolic proteins Apoptotic protease activating factor-1 (Apaf-1) and activates initiator and effector caspases [27].

Several epigenetic modifications have been identified as responsible for the evasion of the apoptotic process and carcinogenesis. As result of an alteration of DNA methyltransferases (DNMTs) functions, in cancer cells diffused events of hyper- and hypo-methylation, contributes to apoptosis resistance [28].

In several cancers, hypermethylation of the promoter region of tumor suppressor genes involved in the regulation of apoptotic processes leads to an uncontrollable proliferation contributing to apoptosis resistance of cancer cells [29].

Hypermethylation on FAS promoter region, is responsible of the suppression of its expression, leading to a Cutaneous T-cell lymphoma and neoplastic transformation of epithelial cells into colon cancer [30, 31]. In neuroblastoma, melanoma and ovarian cancer cells, the resistance to TRAIL-induced apoptosis is due to hypermethylation of the DR4 and DR5 promoters [32–34]. In other cancer types, such as hepatocellular carcinoma, bladder cancer, small-cell lung carcinoma, glioblastoma, retinoblastoma, and neuroblastoma, caspases 8 and 10 are silenced by the methylation on their promoters resulting in a block of apoptotic pathway [35–39]. Silencing of Apaf-1, as result of the block of intrinsic apoptotic pathway, is observed in leukemia and melanoma, as well as bladder and kidney cancers and is associated with therapeutic resistance [40–43].

Promoter hypermethylation of BAX, BAK, and PUMA in multiple myeloma and Burkitt's lymphoma cells, is responsible for the silencing of these genes and so of the abrogation of related death pathway while in prostate cancer patients, despite the hypermethylation of the Bcl-2 promoter, apoptotic pathways, particularly the extrinsic pathway, are largely preserved [44–46].

However, also a global genomic hypomethylation has a role for carcinogenesis [47]. In a variety of human cancers, including metastatic tumor, B-cell chronic lymphocytic leukemia, cervical, colorectal, hepatocellular and bladder cancer hypomethylation determine chromosomal instability and cancer transformation [48–52]. In addition to DNA methylation, other epigenetic modifications, such as

histone modification and miRNA regulation, can alter apoptotic pathway. In Burkitt's lymphoma, a well-known repressive chromatin mark, the trimethylation of lysine 27 of histone H3 (H3K27me3), affects the expression levels of proapoptotic BIM protein [53]. In medulloblastoma patients, abnormal H3 and H4 acetylation patterns at the promoter region of DR4 gene expression, alter apoptosis [54]. Similarly, increased H3 and H4 acetylation induced by HDAC inhibitors affect the amounts of proapoptotic Bax protein in human colon cancer cells leading to cell cycle arrest and apoptosis [55].

An alteration of the balance between Histone Acetyltransferases (HATs) and Histone Deacetylases (HDACs) contributes to cancer promotion modulating the acetylation levels of several non-histone proteins involved in apoptotic cell death pathway such as Rb, E2F and ku70. Indeed, the involvement of Ku70 in promoting apoptosis, is strictly regulated by its acetylation level. Ku70, inhibits BAX activation, preventing its translocation to the mitochondrial membrane and suppressing apoptosis. Ku70 acetylation promoted by CBP and PCAF on two different lysine residues (K539 and K542), blocks Ku70-BAX connection and promotes apoptosis [56]. Acetylation of E2F1 is essential for the recruitment of several proteins that control the apoptotic response to DNA damage. In response to DNA damage, acetylated E2F1 interacts with Rb influencing the cellular response driven transcription of the proapoptotic target gene p73 [57, 58].

Through the regulation of gene expression, miRNAs are considered key regulators of several cellular processes such as apoptosis and have a pivotal role in cancer progression. A function in tumorigenesis was described for miR15/16 as well as for some miR-34 family members. In pituitary adenoma, B-cell chronic lymphocytic leukemia and prostate cancer, miR15/16 miRNAs down regulated or deleted led to overexpression of antiapoptotic BCL-2, as well as cyclin D1, MCL1, and WNT3A at the post-transcriptional level inducing cancer cell proliferation and invasiveness [59–62]. Further investigation indicated a positive feedback loop between p53 and miRNAs. P53 regulates miRNA expression at numerous levels and, as a transcription factor, p53 can affect the expression of individual miRNAs [63, 64].

MiR-34a and miR-34b/c, three members of the mir34 family, are direct p53 targets. MiR-34 family regulated SIRT1 mRNA leading to an increase in p53 acetylation levels which regulate cell-cycle and apoptosis [65]. MiR-34a is repressed via hypermethylation in different types of cancer such as gastric cancer, chronic lymphocytic leukemia, pancreatic, breast, colon, kidney cancer, and Burkitt's lymphoma [66], while miR-34b/c was down regulated in sarcoma, colon, and ovarian cancer [62]. Another miRNA, the miR-29b, able to target DNMT3b and MCL1 is significantly reduced in several cancers such as lung, pancreatic and ovarian [67–70]. An hypermethylation of miR-127 is characterized in cancers of the bladder, prostate, breast, and lung, as well as lymphoma [71]. This epi-modification is responsible of the miR-127 silencing, which in turn determines the hyperactivity of one of its molecular targets, the proto-oncogene BCL-6, in these cancers [72]. Other examples are miR-106b and miR-93, which are known to alter TGF-induced apoptosis in gastric cancer cells by inhibiting BIM expression while MiR-135a inhibits JAK2, resulting in a decrease in antiapoptotic Bcl-xL expression [73, 74]. MiR-135a expression is reduced in ovarian cancer, Hodgkin lymphoma, Acute Myeloid Leukemia (AML) (**Table 1**) [75, 76].

2.2 Epigenetic regulation in necroptosis

Necroptosis, a form of regulated cell death independent from caspase activation, is regulated by specific death receptors, including (but not limited to) FAS/APO-1

Cell death	Epigenetic modification	Targets	Cancers	References
Apoptosis	DNA hypermethylation	FAS receptor	CTCL, CRC	[30, 31]
		DR4, DR5	NB, Melanoma, OC	[32–34]
		Caspase 8 and Caspase 10	HCC, TCC, SCLC, GBM, Rb, NB	[35–39]
		Apaf-1	AML, Melanoma, TCC, RCC	[40–43]
		BCL-2	PDAC	[44]
		BAX, BAK, PUMA	MM, BL	[45, 46]
		miRNA 34a	GC, CLL, PDAC, BC, CRC, RCC, BL	[66]
		miRNA 34b/c	SARC, CRC, OC	[62]
		miRNA 127	TCC, PC, BC, LC, Lymphoma	[71]
	DNA hypomethylation	Chromosomal stability	CLL, CC, CRC, HCC, TCC	[48–52]
	Histone methylation	BIM	BL	[53]
	Histone acetylation and deacetylation	DR4	MB	[54]
		BAX	CRC	[55]
		Rb, E2F and Ku70	Cancer progression	[56–58]
	miRNA 15/16	BCL2, Cyclin D1, MCL1, WNT3a	Pituitary adenomas, CLL, PC	[59–62]
	miRNA 29b	DNMT3b, MCL1	NSCLC, PDAC, OC	[67–70]
	miRNA 106b and miRNA 93	BIM	GC	[73, 74]
	miRNA 135a	JAK2	OC, HL, AML	[75, 76]

Table 1.
Epigenetic regulation in apoptosis.

(CD95) and TNFR1, or pathogen recognition receptors (PRRs), including TLR3, TLR4, and Z-DNA binding protein 1 (ZBP1; also known as DAI) [77]. Necroptotic signaling pathway depends on the sequential activation of the receptor-interacting serine/threonine-protein kinase 3 (RIPK3), mixed lineage kinase domain like pseudokinase (MLKL) and (at least in some settings) on the kinase activity of RIPK1, also called necrosome [19, 78]. Therefore, it is not surprising that necroptotic cell death signaling can also be regulated by epigenetic modifications at the necrosome components [79].

Necroptosis may represent a new therapeutic strategy to overcome resistance to apoptosis. In cancer, necroptosis has been defined as a *double-edged sword* for its pro- or anti-tumor effect [80]. Epigenetic alterations may modify the gene expression levels of the necroptosis regulators, affecting cancer initiation, promotion and progression [81]. Hypo- and hyper-methylation of key components of necroptosis existed in multiple tumors and could affect gene expression and prognosis of cancer patients [81]. A multi-omics approach identified promoter hypermethylation of (i)

MLKL in skin cutaneous melanoma (SKCM) and in colon adenocarcinoma (COAD); (ii) RIPK3 in adrenocortical carcinoma (ACC); (iii) RIPK1 in kidney renal clear cell carcinoma (KIRC) and kidney renal papillary cell carcinoma (KIRP). Differently, MLKL hypomethylation has been reported in low grade glioma (LGG) and uveal melanoma (UVM); RIPK3 hypomethylation in LGG, AML and KIRC; RIPK1 in LGG, thymoma (THYM), lung squamous cell carcinoma (LUSC), ACC, and SKCM [81]. Among the necrosome components, RIPK3 is often downregulated, in cancer which is why several studies focused on its epigenetic modifications, unlike RIPK1 or MLKL.

RIPK3 is normally expressed in normal tissues, but the genomic region near the *RIPK3* transcription start site (TSS) is highly methylated resulting in loss of RIPK3 expression in different types of primary cancers probably due to an adaptive process to evade necroptosis [82, 83]. In breast cancer, 85% of patients have reduced RIPK3 expression due to promoter hypermethylation [82]. However, robust re-expression of RIPK3 in recurrent breast tumor cells was unexpectedly noted. These data were confirmed by ChIP-Seq experiments in which RNA polymerase II occupies the promoter region of *RIPK3* and epigenetic histone markers, H3K9ac and H3K4me3, are enriched in the regulatory regions of the *RIPK3* gene adjacent to the RNA polymerase II binding site. Conversely, many of the cytosines in the *RIPK3* CpG island are methylated in primary tumors. However, treatment with HDAC inhibitors and/or hypomethylating agents, such as 5-azacytidine (5-AC), can restore RIPK3 expression and thus promotes sensitivity to chemotherapeutic agents in a RIPK3-dependent manner [82, 83].

As in breast cancer, RIPK3 expression is reduced also in lung cancer and this is associated with a poorer chemotherapy response. The promoter region of *RIPK3* being highly rich in CpG island is hypermethylated differently from primary human bronchial epithelial cells. The epigenetic silencing is responsible for RIPK3 and necroptotic cell death suppressions with worse response in non-small lung cancer (NSCLC) patients receiving chemotherapy. Therefore, demethylation treatments could improve the anticancer efficacy of chemotherapy [84]. A further study investigating the epigenetic landscape of necroptosis in lung adenocarcinoma (LUAD) did not identify any correlation between the levels of methylation in the *RIPK3* promoter and its mRNA expression [85].

The role of RIPK3 has also been discussed in malignant mesothelioma (MM) as downregulation at the transcriptional level consistent with epigenetic silencing via DNA methylation was observed in 62% of primary MMs. The high frequency of CpG methylation in the *RIPK3* promoter (22%) is mediated by DNA methyltransferase DNMT1 which contributes to a very poor overall survival (OS). In human pleural MM cells, *RIPK3* gene expression decrease both *in vitro* and in primary tumors, strengthening its pivotal role as tumor suppressor [86].

Some authors identified that the methylation carried out by DNMT1 in binding to the *RIPK3* promoter is stimulated by the oncometabolite in the tricarboxylic acid (TCA) cycle, 2-hydroxyglutarate (2-HG) produced by tumor-associated isocitrate dehydrogenases 1 (IDH1) mutation [86]. Tumorigenesis could be driven by IDH1 mutation at position 132 (R132) resulting in high levels of 2-HG production, which regulates DNMT1 activity by promoting its binding to specific DNA regions including the TSS of the *RIPK3* promoter. This phenomenon investigated in human brain cancers implies resistance to necroptosis and may support the survival of cancer cells, eventually leading to tumor formation [87].

Ten Eleven Translocation (TET) methylcytosine dioxygenases enzymes, using α-ketoglutarate (α-KG) as substrate, catalyze the oxidation of 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5-hmC), which is the first step for active DNA

demethylation [88]. Some intermediates of the TCA cycle, including fumarate and α-KG, can competitively inhibit the enzymatic activity of TETs [89]. In Epstein–Barr virus-encoded latent membrane protein 1 (EBV-LMP1) positive cells, high levels of fumarate and low levels of α-KG, determine *RIPK3* silencing as the result of hyper-methylation of its promoter region [89]. The oncomine database refers a significant downregulation of *RIPK3* in nasopharyngeal carcinoma (NPC), compared to naso-pharyngitis tissues, as the result from the impairment of TETs' enzymatic activity in EBV-LMP1 positive cells [89]. From an epigenetic regulation/modification point of view, RIPK3 (among the necrosome components) was the most investigated and promising mediator. For instance, very little is known about the epigenetic regulation of MLKL which is essential for the execution of necroptosis. Interestingly, in Burkitt's lymphoma cell lines, MLKL expression levels correlate with the methylation status. As a result of the activity of the new DNA hypomethylating agent SGI-110, the silenced expression of MLKL is restored [90].

In conclusion, these studies indicate RIPK3 as a critical regulator of necroptosis, which is considered a tumor suppressor gene and whose low expression, also regulated at the epigenetic level, can be associated with poor prognosis in cancer. Hence, treatment with hypomethylating agents alone or in combination with chemotherapeutic agents facilitate the activation of necroptotic signaling (**Table 2**).

2.3 Epigenetic regulation in pyroptosis

Pyroptosis is a form of inflammatory RCD induced by the activation of the NF-kB pathway followed by the triggering of intracellular sensors / receptors such as NLRP3, NLRC4 and AIM2, in response to DAMPs, Pathogen-associated molecular pattern (PAMPs) or different cytotoxic stimuli [91, 92]. Assembly of the inflammasome leads to pyroptotic cell death mediated by the cleavage of Gasdermin-D (GSDM-D), by caspases (caspase1 or caspase-4/5/11) and to the release of Interleukin-1β *(Il-1β)* and Il-18 in the microenvironment [93]. Pyroptosis can also occur with an alternative mechanism by which caspase-3 activates GSDM-E [94]. Recent studies have identified an epigenetic modulation of the pyroptotic process in cancer [95]. Among the

Cell death	Epigenetic modification	Targets	Cancers	References
Necroptosis	DNA hypermethylation	MLKL	SKCM, COAD, BL	[81, 90]
		RIPK3	ACC, BC, NSCLC, MESO, NPC	[81, 82, 84, 86, 89]
	DNA hypomethylation	RIPK1	KIRK, KIRP, LGG, THYM, LUSC, ACC, SKCM	[81]
		RIPK3	LGG, KIRK, AML	[81]
		MLKL	LGG, UVM	[81]
	Histone methylation	RIPK3	BC	[82]
	Histone acetylation	RIPK3	BC	[82]

Table 2.
Epigenetic regulation in necroptosis.

proteins involved in the pyroptosis, epigenetic modification related to NLRP3, the sensor ASC, caspase-1 and GSDMs are the best characterized [96].

In gastric carcinoma, the loss of caspase-1 gene expression, which appears to be related to the worsening of the patient's prognosis, could be associated with methylation phenomena [97]. Indeed, anticancer therapy with the 5-aza-C hypomethylating agent, activates transcriptional mechanisms with expression of caspase-1 and the conclusion of the pyroptotic program [97]. In gastric, NPC and breast cancer, the hypermethylation at the promoter of the tumor suppressor ZDHHC1, induces pyroptosis by increasing the activation of caspase-1 in response to accumulated oxidative damage [98]. DNA methylation plays a crucial role in NLRP3-inflammasome activation in human monocytes, where, under physiological conditions, Cas-1a, ASC and Il-1β promoters are hypermethylated [95]. Furthermore, NF-kB and the demethylase TET2 are responsible for the hypomethylation and reactivation of ASC and Il-1β genes in differentiated monocytes and macrophages [95]. In lung, gastric and renal cancers, the hypermethylated state of ASC increased tumor growth and is associated with poor prognosis [99], indeed some studies report ASC demethylation as a possible strategy to induce selective cell death in cancer cells [100]. Conversely, reduced methylation in the ASC promoter, often associated with migration and invasion which are the basis of the metastatic process, is reported in patients with glioblastoma and squamous cell carcinoma [101, 102]. NLRP3-acetylation is fundamental for the assembly of the ASC domain and for its activation in response to exogenous stimuli in aging-associated inflammatory diseases as cancer; thus, the NLRP3 deacetylation mediated by SIRT2 represses its activity and inflammasome formation [103]. These evidences were confirmed in Aged SIRT2-deficient mice with a high-fat diet, which showed an increase in plasma Il-18 followed by an increase in NLRP3-inflammasome activity [103]. The epigenetic regulation of pyroptosis may also depend on the action of small non-coding RNAs. It is known that several miRNAs bind to 3′-untranslated NLRP3 gene region and degrade it [104]. To confirm these evidences, it was demonstrated that during myeloid differentiation, low levels of miR-233 increases NLRP3 inflammasome transcription, accompanied by the release of pro-inflammatory cytokines in activated macrophages [105]. In addition, XLOC_000647 overexpression, an intergenic lncRNA, reduces the expression of NLRP3 in pancreatic cancer cells, playing a protective role against the starting of endothelial-mesenchymal transition (EndoMT), proliferation and metastasis formation, identifying a novel epigenetic mechanism involving the NLRP3-inflammasome in tumor progression of pancreatic cancer [106]. Additional research demonstrated the direct regulation of pro-caspase-1 by Neat1. This lncRNA can stabilize mature caspase-1 tetramers (p20: p10)2 and (p33: p10)2, promoting the assembly of the NLRP3-AIM2-inflammasomes, inducing a caspase-1-dependent pyroptosis [107]. The best characterized member of the GSDMs family, GSDM-D, appears to play a key role in NSCLC and can be regulated by methylation processes [108]. Elevated GSDM-D levels have been associated with unfavorable prognosis in lung cancer but favorable in skin cutaneous melanoma and its expression is regulated by the binding of Foxo1 on its promoter [109]. The hypermethylating activity of DNMT was also found at the GSDM-D promoter in lymphocytes natural killer, NK92 cells, in which it appears to be a critical checkpoint for the inhibition of the pyroptosis mechanism [110]. An indirect regulation occurs in colorectal cancer, where the rp1-85f18.6 knockout, a lncRNA highly expressed in CRC patients, leads to an increased pyroptosis through the cleavage of GSDM-D, suggesting a possible application of epigenetic modulators of inflammosomes for cancer therapy [111]. GSDM-E is found to be silenced in gastric, colorectal and breast cancer due to hypermethylation

of CpG islands within its promoter and appears to be related to an increased risk of metastasis [112]. Epigenetic regulation of GSDM-E may also depend on small non-coding RNA activity such as miR-155-5p, which can bind 3'-UTR reducing GSDM-E expression [113]. A further regulation takes place thanks to the presence of lncRNA which have been shown to be involved in pathological processes of various diseases including cancer by regulating directly or indirectly proteins involved in the main pyroptotic pathways [113]. Recent discoveries have identified new molecules, which in turn can activate or inhibit the expression of GSDMs, regulating pyroptosis at the epigenetic level [114]. One of the most important is Decitabine (DAC), a DNMT inhibitor used in hematological cancers therapy combined with chemotherapy, which can regulate the expression of several genes. In particular DAC treatment in several tumor cell lines induces DFN5 gene up-regulation leading to an increase of GSDM-E protein expression followed by pyroptosis activation. [115]. Moreover, treatment with methyltransferase inhibitors (e.g. 5-aza-C) increases the expression of GSDM-E in cancer cell lines and also improves the efficacy of chemotherapeutic agents (e.g. doxorubicin) to trigger pyroptosis [116]. Furthermore, anti-inflammatory drugs such as dimethyl fumarate (DMF) and monomethyl fumarate (MMF) have shown the ability to increase transcription levels of DNMT3a and DNMT3b, leading to GSDM-D silencing via its promoter hypermethylation (**Table 3**) [108].

2.4 Epigenetic regulation in immunogenic cell death

Immunogenic Cell Death (ICD) is a process where dying cells activate an immunogenic response mediated by the release of DAMPs into the microenvironment, recognized by different immune cells and necessary for the immunological memory [117, 118].

DAMPs and nucleic acids released from dying cells, together with the release of chemo attractive agents in the microenvironment, contribute to increase the

Cell death	Epigenetic modification	Targets	Cancers	References
Pyroptosis	DNA hypermethylation	Caspase 1	GC	[97]
		ASC	NSCLC, GC, RCC	[99]
		GSDM-D	NSCLC,	[108]
		ZDHHC1	GC, NPC, BC	[98]
		GSDM-E	GC, CRC, BC	[112]
	DNA hypomethylation	ASC	GBM, SSC	[101, 102]
	Histone deacetylation	NLRP3	Inflammatory diseases	[103]
	miRNA 233	NLRP3	Myeloid differentiation	[105]
	XLOC_000647	NLRP3	PDAC	[106]
	Neat1	Pro-caspase-1	Unknown	[107]
	Rp1-85f18.6	Inflammosomes	CRC	[111]
	miRNA 155-5p	GSDM-E	Unknown	[113]

Table 3.
Epigenetic regulation in pyroptosis.

antigenicity of dying cells leading to the recruitment of innate immunity cells such as neutrophils and dendritic [119, 120].

Different molecular mechanisms are involved in this type of cell death, such as the UPR (Unfolded Protein Response) and autophagy as well as the release of many molecular players like Annexin 1, HMGB1, Interferons (IFNs) and different chemokines [121]. Under physiological stress, the endoplasmic reticulum (ER) activates the UPR, an evolutionarily conserved mechanism thanks to which ER chaperonins, Heat Shock Proteins (HSPs) such as HSP70 and Calreticulin (CALR) are translocated on the cell surface being an "eat me" signal for recognition by dendritic cells [122, 123].

Recently, it was demonstrated that epigenetic modifications can regulate several molecular players directly involved in ICD, supporting the idea for the development of new epigenetic drugs that can be used in cancer immunotherapy [121].

Histone and DNA methylation as well as ncRNAs are the main epigenetic modifications able to regulate targets that have a pivotal role in ICD such as HSPs, CALR, Annexin 1 and HMGB1 [121]. In lung cancer, inositol-requiring enzyme-1 (IRE1), an enzyme involved in UPR activation, is silenced by methylation. Indeed, treatment with Chaetocin, an Histone Lysine Methyltransferase (HKMT) inhibitor, determines an increment of the expression of this enzyme, suggesting that its regulation could be modulated via histone methylation (126,127). In colon and pancreatic cancer cell lines, the methylation at HSP90 promoter, related to an enhanced expression of DNA methyltransferase, inhibits its expression probably altering the immune response. The treatment with epigenetic modulators such as Zebularine, a DNMT inhibitor, can restore the immune response that leads to the induction of ICD [121, 124].

Different non-coding RNAs such as ncRNA-RB1, miR-27a and nc886, can modulate epigenetically CALR expression [121]. It has been shown that in A549 cell line (adenocarcinoma alveolar basal epithelial) the knockdown of ncRNA-RB1 reduces the expression of CALR, altering its translocation on the cell surface and probably influencing the fate of ICD [125]. Downregulation of Calreticulin was observed also in colorectal cancer by miR-27a action, resulting in a blocked Major Histocompatibility Complex (MHC) class I cell surface exposure [126]. In malignant gastric cancer cell lines, such as SNU-005, SNU-484 and MKN-01, the activity of the long non-coding RNA nc886, which has anti-proliferative and tumor suppressor roles [127, 128], has been found decreased compared to the non-malignant gastric cell line HFE-145, probably due to the CpG hypermethylation at the nc886 promoter region [128]. In nasopharyngeal carcinoma cell lines, both gene and protein expression of Annexin 1 are downregulated by methylation phenomena [129]. In head and neck squamous cell carcinoma, the presence of miRNA-196a/b epigenetically regulates Annexin 1, downregulating both mRNA and protein levels [130]. At the level of epigenetic regulation, it is thought that HMGB1 could act as an epigenetic modifier able to silence Tumor Necrosis Factor-alpha (TNF-α) and Il-1β [131]. miRNA-129-2, a tumor suppressor in glioma and hepatocellular carcinoma [132, 133], can inhibit the release of HMGB1. The regulatory region of this miRNA is strongly methylated in portions of its promoter region leading to its suppression and consequent expression of HMGB1 [134, 135]. Autophagy is essential for the ICD process as it promotes the synthesis and transport of ATP from the cell which is fundamental for an optimal immunogenic response [120, 136]. In submandibular carcinomas the expression of P2RX7 receptor is controlled by the methylation of its promoter and aberrant methylation phenomena may interfere with its expression and the related pathway [137]. Hypermethylation affects other autophagy players such as the Tensin Homolog (PTEN), as demonstrated in melanoma and in breast and stomach cancer [138, 139] and the Autophagy-Related

Protein 5 (ATG5), studied in melanoma and colorectal cancer. This epi-modification leads to a downregulation of PTEN and ATG5 protein expression during cancer progression [138–141]. The expression of CXCL10 in ovarian cancer cells, may depend on the methylation of its promoter, indeed the use of demethylating agents is able to increase its expression [142]. Acetylation can also modulate ICD [143], indeed Histone Deacetylase 3 (HDAC3)-deficient macrophages, stimulated with LPS, are unable to activate several genes involved in inflammation including IFNβ, demonstrating a main role for HDAC3 in controlling IFNβ expression. [144]. Furthermore, it has been shown that the use of caloric restriction mimetics (CRMs) may have a pivotal role in anticancer immunosurveillance [145]. CRMs stimulate ATP release by influencing acetylation of histone proteins showing a potential epigenetic mechanism able to induce or not autophagy during cancer (**Table 4**) [145, 146].

2.5 Epigenetic regulation in ferroptosis

Ferroptosis is a newly discovered form of RCD reliant on iron-dependent lipid peroxidation [149]. The increase in free iron and the accumulation of lipid peroxides occurs through the action of a small molecule called erastin which can induce non-apoptotic cell death in an ST (Small T oncoproteins) and RAS^{V12} (oncogenic allele of HRAS)-dependent way [150].

By the interaction with voltage-gated anion channels (VDAC), erastin can inhibit the cysteine/glutamate transport system X_c^- (SLC7A11) leading to cysteine depletion, glutathione deficiency with excessive lipid peroxidation and consequently induction of ferroptotic cell death [151].

Some evidences highlight an epigenetic regulation of ferroptosis. For instance, ncRNAs regulate the progression of NSCLC mediating ferroptosis [152]. P53RRA, a cytosolic lncRNA, by interacting with G3BP1, promotes ferroptosis trough the

Cell death	Epigenetic modification	Targets	Cancers	References
Immunogenic cell death	DNA hypermethylation	HSP90	CRC, PDAC	[121, 124]
		Annexin 1	NPC	[129]
		P2RX receptor	SGC	[137]
		CXCL10	OC	[142]
		PTEN	Melanoma, BC and SCr	[142, 143]
	Histone methylation	IRE-1	NSCLC	[147, 148]
	Histone acetylation	IFNβ, CRMs	Cancer progression	[144–146]
	ncRNA-RB1	CALR	LUAD	[125]
	miRNA 27a	CALR	CRC	[130]
	nc886	CALR	GC	[127, 128]
	miRNA 19a/b	Annexin 1	HNSC	[130]
	miRNA 129–2	HMGB1	Glioma, HCC	[132, 133]

Table 4.
Epigenetic regulation in immunogenic cell death.

activation of p53 pathway and the transcription of some metabolic genes responsible of the increased intracellular concentration of iron and ROS lipids and of the inhibition of growth induced by erastine [153].

In lung cancer, the nuclear lncRNA LINC00336 is upregulated and, through the interaction with ELAV-like-RNA-binding protein 1 (ELAVL1), acts as an inhibitor of ferroptosis by decreasing the intracellular levels of iron and ROS lipids. Moreover, LINC00336 also acts as an endogenous sponge for another microRNA (miR-6852) which is a negative regulator of cystathionine-β-synthase (CBS) that has a pivotal role in ferroptosis [154].

Treatment of NSCLC cell line NCI-H1299 with XAV939, a Wnt/−catenin pathway inhibitor, resulted in a downregulated SLC7A11 expression that controls iron concentration and the activation of ferroptosis-mediated pathways responsible of the suppression of NSCLC progression [152]. Furthermore, the deubiquitinase DUB, a tumor suppressor inactivated in many types of tumors [155], after the assembly of the polycomb repressive deubiquitanase complex (PR-DUB) is able to inhibit the ubiquitinated histone H2A (H2Aub) placement on the SLCA711 promoter whose down-regulation blocks ferroptosis through the cysteine starvation and GSH depletion [156]. The monoubiquitination of H2B on lysine 120 (H2Bub1), a marker of transcriptional activation involved in the regulation of the Warburg effect and tumorigenesis [157], regulates both the expression of SLC7A11 and of a group of ion-binding genes linked to metabolism classifying this modification as a new epigenetic regulator of ferroptosis [158]. The activity of Lysine Demethylase 3B (KDM3B) inhibits erastin-induced ferroptosis through the activation of SLC7A11, cooperating with the transcription factor ATF4 [159]. In addition, BRD family proteins, including BRD4, can also participate in the epigenetic regulation of ferroptosis. The use of BRD4 inhibitor JQ1 has been shown to induce ferroptosis through the downregulation of GPX4, SLC7A11 and SLC3A2 expression in breast and lung cancer cells classifying it as a potential therapeutic agent in cancer treatment (**Table 5**) [160, 161].

2.6 Epigenetic regulation in NETosis

NETosis is a form of cell death exclusive for neutrophils, caused by the uncontrolled production of netotic bodies, useful in physiological conditions for the neutralization of pathogens. The mechanism originates with the activation of ion channels associated with receptors able to modify the intracellular levels of calcium. Subsequent phosphorylation pathways lead to the production of mitochondrial ROS and the calcium-dependent activation of PAD4, responsible for the chromatin decondensation and the end of the NETotic process [162]. In breast cancer, the release of cancer extracellular chromatin networks (CECNs) into the microenvironment

Cell death	Epigenetic modification	Targets	Cancers	References
Ferroptosis	Histone demethylation	SLCA711, ATF4	Unknown	[159]
	Histone ubiquitination	SLCA711	Several cancers	[158-160]
	LINC00336	ELAVL1	LC	[154]
	XAV939	SLC7A11	NSCLC	[152]

Table 5.
Epigenetic regulation in ferroptosis.

appears to be related to the onset of lung metastases [163]. Among the key molecular processes of NETosis, the role played by the PAD4 enzyme is well known, which increases the levels of citrullination of histones in a calcium-dependent manner leading to chromatin decondensation and netotic nuclear collapse [164]. Several studies on patients with different tumors, such as breast, colorectal and lung cancer, have found an important increase in plasma levels of hypercitrullinated histone H3, suggesting it as a potential prognostic marker [165–167]. The hyper-citrullination of H3 is a widespread phenomenon during the formation of NETotic bodies as well as reduced levels of methylation of arginine 3 on histone H4 and high levels of acetylated lysine 16 on histone H4 as reported in breast cancer [163]. The increase in the enzymatic activity of PAD4 and in the netotic process is closely related to its epigenetic regulation. In MCF7 cancer cells, citrullination of the OKL38 promoter by PAD4 was described, suggesting a correlation between NETs formation and breast cancer [168]. Increased angiogenesis and deposition of fibrous material in malignant tumors also appears to be related to PAD4-mediated citrullination of antithrombin (cAT) [169]. In hepatocellular carcinomas, the global hypomethylated state of DNA and the hypermethylation of promoters of genes involved in tumorigenesis, such as p53 and p21, may partially depend on the reduced action of PAD4, on the expression and the enzymatic activity of DNMT3a [170].

In colon cancer, miR-155 can ensure the translation of PAD4 mRNA, inducing the netotic process and the tumor progression [171]. New evidence has proved the role played by miR-505 in breast and pancreatic cancer. It negatively regulates SIRT3 by altering mitochondrial metabolism and ROS production, triggering the production of NETs (**Table 6**) [172].

2.7 Epigenetic regulation in parthanatos

Parthanatos is a type of PCD characterized by hyperactivation of poly (ADP-ribose) polymerase 1 (PARP-1) followed by PAR accumulation and mitochondrial release of apoptosis inducing factor (AIF) [173]. The molecular interaction between AIF and the macrophage migration inhibitory factor (MIF) leads to massive DNA fragmentation and cell collapse [174]. The knowledge related to the epigenetic modification involved in parthanatic process and their role in tumors is currently poorly known. In liver cancer, the damage induced by

Cell death	Epigenetic modification	Targets	Cancers	References
NETosis	DNA hypermethylation	P53, p21	HCC	[170]
	DNA hypomethylation	Global DNA	HCC	[170]
	Histone methylation	H4	BC	[163]
	Histone acetylation	H4	BC	[163]
	Citrullination	H3	BC, CRC, LC	[167, 169]
		OKL38, cAT	BC	[168, 169]
	miRNA 155	PAD4	CRC	[171]
	miRNA 505	SIRT3	BC, PDAC	[172]

Table 6.
Epigenetic regulation in NETosis.

UV rays causes the activation of PARP-1 and the PARylation of histones, with the consequent recall of ALC1 on chromatin and activation of DNA repair [175]. In fact, PARP-1 can facilitate the recruitment of repair systems through the decondensation of chromatin independently by ubiquitylation [176]. In breast cancer, the behavior and function of insulators is controlled by PARP-1, through conformational changes of chromatin. The increase in PARylation of CCCTC-binding factor (CTCF), triggers its functions as an insulator, activating mechanisms able to induce DNA hypomethylation, central feature of many forms of cancer [177, 178]. The correlation between PARP-1, chromatin opening and gene transcription activation is poorly explained in the literature. In breast cancer, PARP-1 allows chromatin access to RNA-pol II with the inhibition of demethylase activity of KDM5B by PARylation, leading to the global hypomethylation of H3K4 [179]. A very recent study identifies the lysine demethylase KDM6B as a key factor in the epigenetic control of parthanatos and in the response to antitumor therapy with alkylating agents. The reduction of KDM6B levels leads to the activation of DNA repair checkpoints mediated by MGMT, causing alkylating agents resistance. Conversely, the increase in KDM6B levels favors parthanatic cell death induced by alkylating agents [180]. These new insights open the window to understanding the epigenetic mechanisms underlying parthanatos and the epigenetic function of PARP-1 (**Table 7**).

3. Conclusions

Epigenetics regulates several processes including differentiation, development, growth and cell death. Specifically, cell death controls various physiological and pathological phenomena that are crucial for life development. A deeper knowledge of both cell death and epigenetics, and their interconnections, might be the key to better understand how different processes in life are modulated and how to exploit them therapeutically.

The fact that epi-deregulation in cancer clearly also alters the main players of the different cell death pathways has important consequences. For examples, some epi compounds (i.e. HKMT, HDAC, HMT inhibitors) might be used also for regulation of the expression of the main players involved in cell death and might, in turn, help for cell death pathways reactivation in cancer or, also into the recognition of cancer cells by the immune system. In addition, the identification of possible epigenetic biomarkers linked to cell death players deregulation could be beneficial to contrast several cancers strengthening the well-known concept of "personalized therapy".

Cell death	Epigenetic modification	Targets	Cancers	References
Parthanatos	DNA hypomethylation	H3	BC	[179]
	Histone demethylation	KDM6B	Unknown	[180]
	PARylation	Histones	HCC	[175]
		CTCF	Several cancers	[177, 178]

Table 7.
Epigenetic regulation in parthanatos.

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Conflict of interest

The authors declare no conflict of interest.

Declaration

Abbreviations

CTCL	Cutaneous T-cell lymphoma
CRC	Colorectal cancer
NB	Neuroblastoma
OC	Ovarian cancer
HCC	Hepatocellular carcinoma
TCC	Transitional cell carcinoma
SCLC	Small cell lung cancer
GBM	Glioblastoma
Rb	Retinoblastoma
AML	Acute myeloid leukemia
RCC	Renal cell carcinoma
PDAC	Pancreatic adenocarcinoma
PC	Prostate cancer
MM	Multiple myeloma
BL	Burkitt's lymphoma
GC	Gastric cancer
CLL	Cronic lymphocytic leukemia
BC	Breast cancer
CC	Cervical cancer
MB	Medulloblastoma
NSCLC	Non-small cell lung cancer
HL	Hodgkin lymphoma
SKCM	Skin cutaneous melanoma
COAD	Colon adenocarcinoma
ACC	Adrenocortical carcinoma
KIRK	Kidney renal clear cell carcinoma
KIRP	Kidney renal papillary cell carcinoma

LGG	Low grade glioma
UVM	Uveal melanoma
THYM	Thymoma
LUSC	Lung squamous cell carcinoma
STAD	Stomach adenocarcinoma
SCC	Squamous cell carcinoma
SGC	Salivary gland cancer
HNSC	Head and neck squamous cell carcinoma
LC	Lung cancer
SARC	Sarcoma
SCr	Stomach cancer
MESO	Mesothelioma

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