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Epigenetic Influence on Apoptosis and Necrosis: Mechanisms, Interplay, and Therapeutic Potential

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ABSTRACT

Epigenetic mechanisms profoundly influence cellular fate by regulating gene expression without altering DNA sequence. Among these cellular fates, apoptosis and necrosis represent distinct modes of cell death—programmed and unprogrammed, respectively—whose dysregulation underlies numerous pathological conditions including cancer, neurodegenerative diseases, and ischemic injuries. This paper explores the molecular basis through which epigenetic modifications such as DNA methylation, histone modifications, and non-coding RNAs modulate apoptotic and necrotic pathways. It further examines the intricate interplay between these two death mechanisms and the emerging concept of necroptosis as an epigenetically controlled, regulated necrotic process. Finally, the study evaluates the therapeutic potential of epigenetic modulators in restoring cellular homeostasis and selectively inducing cell death in diseased tissues. The findings suggest that targeted manipulation of epigenetic regulators can reprogram cell fate decisions, opening new avenues for translational therapies in oncology and regenerative medicine.

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1. INTRODUCTION

Epigenetics refers to changes in gene activity that do not alter the DNA sequence but still affect how cells function. These changes include DNA methylation, modifications of histone proteins, and regulation by non-coding RNAs. They are important in many processes, including how cells live or die. Two major forms of cell death are apoptosis and necrosis. Apoptosis is a controlled process that safely removes unwanted or damaged cells without causing inflammation. Necrosis, which can also occur in a regulated form called necroptosis, is usually linked to inflammation, tissue injury, or infection. While they act differently, both apoptosis and necrosis are essential for development, immune defense, and disease progression.

Epigenetic mechanisms strongly influence these processes. Genes such as TP53 and BAX promote apoptosis, while RIPK3 and MLKL are central to necroptosis. Epigenetic changes can turn these genes on or off, shifting whether a cell survives or undergoes death. When this regulation is disrupted, it can contribute to cancer, neurodegenerative conditions, or autoimmune diseases.

However, most studies examine apoptosis and necrosis separately, without fully exploring how epigenetics controls both together. Likewise, therapies that target epigenetic changes are still rarely applied to influence these pathways at the same time.

This paper will review how epigenetic mechanisms affect apoptosis and necrosis, compare their roles in deciding cell fate, and consider how targeting these processes might open new paths for disease treatment.

2. EPIGENETIC MECHANISMS RELEVANT TO CELL DEATH

2.1 DNA Methylation

DNA methylation, predominantly occurring at CpG islands within promoter regions, is a central epigenetic modification that regulates gene expression by recruiting methyl-CpG-binding proteins and repressing transcription. In apoptosis, hypermethylation of tumor suppressor genes such as TP53, BAX, and CASP8 results in transcriptional silencing, thereby impairing programmed cell death and facilitating uncontrolled cellular proliferation. For example, hypermethylation of TP53 disrupts its ability to activate downstream apoptotic cascades, while methylation of CASP8 impedes the extrinsic

apoptotic pathway. Conversely, global DNA hypomethylation may activate oncogenes, indirectly suppressing apoptosis. In necroptosis, aberrant methylation of RIPK3 has been reported to reduce necroptotic sensitivity in cancer cells, conferring resistance to therapeutic strategies. Thus, DNA methylation is a dynamic determinant of cell fate, tilting the balance between survival and programmed death.

2.2 Histone Modifications

Histone proteins undergo diverse post-translational modifications, such as acetylation, methylation, phosphorylation, ubiquitination, and SUMOylation, which alter chromatin structure and influence transcriptional outcomes. Histone acetylation typically relaxes chromatin, allowing transcription of pro-apoptotic genes. Conversely, histone deacetylation condenses chromatin and silences these genes. Aberrant recruitment of histone deacetylases (HDACs) has been observed in multiple cancers, suppressing BAX, PUMA, and CASP9, thereby diminishing apoptosis. Histone methylation has dual roles: H3K4 methylation correlates with active transcription of apoptotic mediators, while H3K27 trimethylation is associated with repression. In necroptosis, histone modifications regulate the transcription of RIPK1, RIPK3, and pro-inflammatory cytokines such as TNF-α. The therapeutic relevance is underscored by the use of HDAC inhibitors (e.g., vorinostat) which restore apoptotic sensitivity in resistant cancer cells.

2.3 Non-Coding RNAs (ncRNAs)

Non-coding RNAs (ncRNAs) encompass microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), all of which regulate cell death-related pathways post-transcriptionally. miRNAs such as miR-34a promote apoptosis by targeting anti-apoptotic BCL2, while miR-21 exerts an anti-apoptotic role by suppressing pro-apoptotic proteins like PTEN. Dysregulation of lncRNAs, such as HOTAIR and MALAT1, influences chromatin remodeling complexes, thereby indirectly regulating apoptotic and necrotic gene expression. In necroptosis, miR-155 has been implicated in modulating RIPK1 and MLKL, linking ncRNAs with inflammatory cell death. This regulatory layer highlights the adaptability of epigenetic networks in determining cell fate decisions.

3. EPIGENETIC MODULATION OF APOPTOSIS

3.1 Intrinsic Pathway

The intrinsic (mitochondrial) pathway of apoptosis is primarily governed by the BCL2 family of proteins, mitochondrial membrane permeability, and cytochrome c release. Epigenetic silencing of APAF1, BAX, or PUMA through DNA hypermethylation leads to impaired apoptosome assembly and reduced caspase-9 activation. Histone modifications further fine-tune transcriptional activity; H3K9 methylation represses pro-apoptotic gene expression, while H3 acetylation enhances transcription. miRNAs such as miR-125b inhibit p53-mediated apoptosis, blocking intrinsic pathway activation. Thus, epigenetic dysregulation in the intrinsic pathway often contributes to chemoresistance in malignancies.

3.2 Extrinsic Pathway

The extrinsic pathway is initiated via death receptors such as Fas, TRAIL-R, and TNF-R. Epigenetic repression of FAS, FADD, and CASP8 by promoter methylation prevents receptor-mediated apoptosis, frequently observed in colorectal, gastric, and lung cancers. Histone deacetylation of extrinsic pathway genes further decreases transcription, whereas HDAC inhibition restores their activity. miRNAs such as miR-196b have been shown to downregulate FAS, impairing apoptosis. Therefore, epigenetic alterations at multiple levels converge to weaken the extrinsic apoptotic machinery, favoring tumor cell survival.

3.3 Therapeutic Implications

Epigenetic therapies hold significant promise in reactivating apoptotic pathways. DNA methyltransferase inhibitors (DNMTi) like decitabine and azacitidine demethylate promoters of silenced pro-apoptotic genes, restoring apoptosis. HDAC inhibitors (HDACi), including vorinostat and romidepsin, induce transcriptional activation of apoptotic genes and sensitize cancer cells to chemotherapy or radiotherapy. Additionally, epigenetic reprogramming with ncRNA-based therapies, such as miR-34a mimics, is being explored. Combination therapies (e.g., DNMTi + HDACi + checkpoint inhibitors) are under investigation to overcome resistance and enhance therapeutic efficacy.

4. APOPTOSIS AND NECROSIS

4.1 Necroptosis Pathway Regulation

Necroptosis represents a form of programmed necrosis that bridges the gap between apoptosis (controlled, non-inflammatory death) and classical necrosis (uncontrolled, inflammatory death). It is primarily orchestrated by the RIPK1–RIPK3–MLKL signaling axis, and increasing evidence shows that epigenetic regulation strongly influences each step of this pathway.

Core Pathway Components and Epigenetic Control

RIPK1 (Receptor-Interacting Protein Kinase 1):
RIPK1 acts as a molecular switch between survival, apoptosis, and necroptosis.

Epigenetic silencing of RIPK1 via promoter methylation has been reported in several tumor types, resulting in impaired necroptotic potential and enhanced tumor cell survival.

Conversely, histone acetylation at the RIPK1 promoter enhances transcription, sensitizing cells to necroptotic triggers such as TNF-α under caspase inhibition.ncRNAs such as miR-24-3p have been shown to target RIPK1 mRNA, reducing its expression and thus blocking necroptotic signaling.

RIPK3 (Receptor-Interacting Protein Kinase 3):
RIPK3 phosphorylates MLKL, committing cells to necroptosis.In multiple cancers (e.g., breast, colorectal), hypermethylation of the RIPK3 promoter suppresses necroptotic capacity, allowing tumor cells to evade immunogenic death.

HDAC activity has also been implicated in repressing RIPK3 transcription, while HDAC inhibition restores expression and necroptotic competence. miRNAs like miR-155 and miR-499 regulate RIPK3 levels post-transcriptionally, fine-tuning necroptotic activation in both cancer and inflammatory disorders.

MLKL (Mixed Lineage Kinase Domain-Like protein):
MLKL is the final effector of necroptosis. Once phosphorylated by RIPK3, MLKL oligomerizes and disrupts plasma membrane integrity.Histone modifications, especially H3K4me3 (active mark), are associated with upregulation of MLKL.Conversely, ncRNAs such as miR-181b have been reported to downregulate MLKL expression, reducing necroptotic execution.

Epigenetic Integration with Upstream Signals
TNF-α, Fas, and Toll-like receptor (TLR) pathways converge on RIPK1. Epigenetic repression of these upstream mediators, such as FADD methylation, reduces necroptotic initiation.
Non-coding RNAs act as epigenetic rheostats, dynamically controlling the balance between apoptosis and necroptosis, depending on cellular context.

Pathological and Therapeutic Relevance
In cancers, silencing of RIPK3 and MLKL via methylation confers resistance to necroptotic stimuli, contributing to immune evasion.In neurodegenerative diseases, upregulation of necroptotic mediators through histone acetylation and pro-inflammatory ncRNAs exacerbates neuronal damage.

Epigenetic drugs, such as DNMT inhibitors (e.g., decitabine) and HDAC inhibitors, can restore RIPK3 expression, reinstating necroptosis in resistant tumor cells.

Targeted ncRNA therapies (e.g., anti-miR-155) are being investigated to modulate necroptosis in autoimmune and inflammatory disorders.

4.2 Inflammatory Consequences

Necrosis and necroptosis often release damage-associated molecular patterns (DAMPs) such as HMGB1 and ATP, which trigger inflammation. Epigenetic regulation of cytokines (TNF-α, IL-6) and DAMPs modulates the intensity of the immune response. For example, histone acetylation at promoters of inflammatory cytokines enhances their expression, while ncRNAs like miR-223 suppress DAMP-induced inflammation. Dysregulated epigenetic control of necroptosis can therefore contribute to chronic inflammation in autoimmune diseases or excessive tissue injury during ischemia-reperfusion.

5. INTERPLAY BETWEEN APOPTOSIS AND NECROSIS: EPIGENETIC CONTROL POINTS WITH A FOCUS ON SIRT1

1) The decision logic: stress intensity, energy state, and chromatin context
Cells integrate stress intensity with bioenergetic state and epigenetic marks to choose between apoptosis (ATP-sufficient, caspase-driven, immunologically quiet) and necrosis/necroptosis (often ATP-poor, lytic, inflammatory). Low–moderate insults typically allow caspase-8–mediated apoptosis; severe DNA damage or oxidative bursts can hyperactivate PARP1,

deplete NAD^+/ATP, block caspases, and tilt toward necrosis.

Epigenetic gating (DNA methylation, histone acetylation/deacetylation of death-regulatory loci) sets the thresholds for these outcomes—for example, methylation-driven repression of RIPK3 blunts necroptosis, while permissive chromatin at TP53 targets favors apoptosis.

2) SIRT1 as the NAD^+-sensing epigenetic rheostat
SIRT1 is a class III histone/non-histone deacetylase whose activity tracks NAD^+ availability. When active, it deacetylates key death regulators and transcription factors, thereby raising the apoptosis threshold and restraining inflammatory necrosis. Conversely, PARP1 hyperactivation during genotoxic stress consumes NAD^+, suppressing SIRT1 and predisposing to energetic collapse and necrosis.

3) SIRT1–p53 axis: tuning the apoptotic program
SIRT1 deacetylates p53 (notably at Lys382), weakening p53's transcriptional activation of pro-apoptotic genes (PUMA, NOXA, BAX) and thereby raising the apoptotic threshold. In multiple settings, enforced SIRT1 activity attenuates p53-dependent apoptosis; loss or inhibition of SIRT1 permits p53 acetylation and facilitates apoptosis. Beyond chromatin, SIRT1 also modulates mitochondrial apoptosis through Ku70–Bax control: SIRT1 deacetylates Ku70, strengthening Ku70–Bax binding and preventing Bax translocation to mitochondria. Acetylation of Ku70 releases Bax and promotes mitochondrial permeabilization. This provides a non-transcriptional route by which SIRT1 restrains apoptosis.

Net effect: Active SIRT1 generally suppresses p53-driven apoptosis (nuclear arm) and sequesters Bax (mitochondrial arm). Under extreme stress with NAD^+ depletion, SIRT1 activity falls, removing these brakes.

4) SIRT1–NF-κB axis: restraining inflammatory death
SIRT1 directly deacetylates RelA/p65 at K310, dampening NF-κB transcriptional output. Because NF-κB drives inflammatory mediators and survival factors (e.g., c-FLIP, cIAPs), SIRT1's repression can both reduce inflammation and alter death mode selection: reduced NF-κB activity lessens pro-survival signaling, potentially allowing apoptosis when caspases are competent, while concurrently lowering the cytokine milieu that amplifies necrotic/necroptotic inflammation.

5) Caspase-8/RIPK1-RIPK3-MLKL hub: the mode switch under epigenetic influence.
At the TNF/TLR/Fas hubs, caspase-8 functions as the molecular switch: active caspase-8 promotes apoptosis and cleaves RIPK1/RIPK3, preventing necroptosis; when caspase-8 is inhibited or absent and RIPK3/MLKL are expressed, cells default to necroptosis. Importantly, epigenetic silencing of RIPK3 (promoter methylation) blocks necroptosis, biasing outcomes toward apoptosis or survival despite upstream cues.

6) Energy budget as an execution constraint (integrated with SIRT1)
ATP sufficiency is a prerequisite for organized apoptosis; ATP depletion (e.g., after PARP1 overactivation) collapses apoptotic execution and diverts to necrosis. Because SIRT1 requires NAD^+ and supports mitochondrial efficiency, it indirectly stabilizes ATP levels and thereby preserves the possibility of apoptosis (or survival) instead of catastrophic necrosis.

7) How the epigenetic landscape encodes "death thresholds"
DNA methylation: Hypermethylation of RIPK3 (and sometimes MLKL) restricts necroptosis; hypomethylation reinstates it—relevant in cancers and chronic liver disease.

Histone acetylation/deacetylation: SIRT1-dependent deacetylation of p53 and RelA lowers apoptotic and inflammatory transcription; Ku70 acetylation status governs Bax release.

Non-histone PTMs: Deacetylation of Ku70 (SIRT1/SIRT6) and RelA (SIRT1) integrates metabolic state with death signaling.

8) Therapeutic implications
NAD^+/PARP axis: PARP inhibitors (or NAD^+ boosters) can restore SIRT1 activity, preserve ATP, and steer away from necrosis, enabling apoptosis or survival—useful where inflammatory lysis is harmful (e.g., ischemia-reperfusion).

SIRT1 modulators:
Activators (e.g., experimental small molecules) may suppress p53/NF-κB activity, curb inflammation, and prevent uncontrolled necrosis; context matters because excessive SIRT1 may hinder desirable apoptosis in cancer. Inhibitors could re-enable p53 or release Bax (via Ku70 acetylation), promoting apoptosis in tumors that evade cell death

through high SIRT1.

Epigenetic editing: Demethylating the RIPK3 promoter (e.g., CRISPR/dCas9-TET strategies) could restore necroptosis to overcome chemoresistance in RIPK3-silenced tumors—balanced against potential inflammatory toxicity. Checkpoint tuning at the hub: Drugs that modulate caspase-8 activity or RIPK1 kinase (necrostatins) directly cont the apoptosis–necroptosis branch point; their effects will be conditioned by SIRT1/NAD^+ status and chromatin marks.

6. CASE STUDIES

6.1 Case Study 1: RIPK3 Promoter Hypermethylation in Colorectal Cancer

Background: Colorectal cancer (CRC) is one of the leading causes of cancer mortality worldwide. Resistance to apoptosis is a hallmark of CRC progression, and necroptosis offers an alternative tumor-suppressive mechanism.

Findings:
Researchers found that in a significant subset of CRC patients, the RIPK3 gene was silenced via promoter hypermethylation.

Tumors lacking RIPK3 expression exhibited reduced necroptotic activity, correlating with poorer prognosis and higher recurrence rates.

Treatment with DNA methyltransferase inhibitors (DNMTis) such as decitabine reactivated RIPK3 transcription, restoring necroptosis sensitivity in vitro.

Implications: This case highlights how epigenetic silencing of necroptotic regulators allows tumors to evade immunogenic cell death. Therapeutically, epigenetic drugs may "re-arm" necroptotic machinery in resistant cancers, making them susceptible to immune clearance.

6.2 Case Study 2: Necroptosis Dysregulation in Alzheimer's Disease

Background: Alzheimer's Disease (AD) is characterized by progressive neuronal loss, with both apoptosis and necroptosis contributing to pathology. Recent evidence points toward necroptosis as a driver of neuroinflammation in AD.

Findings
Autopsy studies revealed elevated RIPK1 and MLKL expression in AD brain tissue, particularly in the hippocampus. Histone acetylation patterns at RIPK1 and MLKL loci were found to be upregulated, driving excessive transcription. ncRNAs such as miR-155 (a pro-inflammatory regulator) were overexpressed in AD patients, further amplifying necroptotic signaling.

Excessive necroptosis led to release of damage-associated molecular patterns (DAMPs), exacerbating microglial activation and neuroinflammation.

Implications: Epigenetic dysregulation of necroptosis contributes to neuronal death and chronic inflammation in AD. Therapies aimed at inhibiting RIPK1 (e.g., Necrostatin-1) or modulating histone acetylation may protect neurons by dampening necroptosis.

6.3 Case Study 3: Epigenetic Regulation of Necroptosis in Systemic Lupus Erythematosus (SLE)

Background: SLE is an autoimmune disease marked by overactivation of the immune system and tissue damage. Necroptosis contributes to the release of immunogenic cellular debris, perpetuating autoimmunity.

Findings
Patients with SLE demonstrated aberrant hypomethylation at the RIPK1 and RIPK3 promoters, resulting in overexpression of necroptotic mediators.

This upregulation enhanced necroptosis in immune cells, leading to higher levels of DAMPs and autoantigen exposure.

ncRNAs, including miR-223, were found to be dysregulated, further influencing RIPK3 and MLKL expression.

Epigenetic drugs and miRNA-based therapies showed promise in preclinical models by reducing necroptosis-induced inflammation.

Implications: Unlike in cancer (where necroptosis is suppressed), autoimmune conditions like SLE feature overactivation

of necroptosis via epigenetic dysregulation. Modulating these epigenetic marks could reduce disease flares and tissue injury.

Synthesis of Case Studies
Cancer (CRC): Necroptosis is silenced → tumor survival.

Neurodegeneration (AD): Necroptosis is overactive → neuroinflammation and neuronal loss.

Autoimmunity (SLE): Necroptosis is dysregulated → self-antigen exposure and immune hyperactivation.

These case studies collectively demonstrate the bidirectional role of epigenetic regulation of necroptosis:
Silencing necroptosis → cancer progression .
Overactivation of necroptosis → neurodegenerative and autoimmune damage.

7. ANALYSIS AND DISCUSSION

The analysis of epigenetic patterns across diseased tissues reveals:
A consistent silencing of apoptotic genes via methylation in tumors.
Upregulation of necrotic mediators in ischemic and inflammatory diseases.
Promising outcomes in trials using epigenetic therapy combined with immunotherapy.

8. FUTURE DIRECTIONS

Single-cell epigenomics to track cell fate decisions.
CRISPR/dCas9-epigenetic editing to target death-related genes precisely.
Development of combination therapies (epigenetic drugs + necroptosis inhibitors).
Exploring epigenetic biomarkers for predicting treatment response.

9. CONCLUSION

Epigenetics has emerged as a pivotal regulator of cell fate, intricately shaping whether cells undergo apoptosis, necrosis, or their regulated counterpart, necroptosis. By influencing the transcriptional and post-transcriptional control of key mediators such as TP53, BAX, CASP8, RIPK3, and MLKL, epigenetic mechanisms dictate the delicate balance between survival and death. Disruptions in this balance contribute to the pathophysiology of diverse diseases, including cancer, neurodegenerative conditions, and autoimmune disorders.

A central insight from this review is the duality of epigenetic modifications: while DNA methylation and histone deacetylation frequently silence pro-apoptotic and pro-necroptotic genes in tumors—promoting unchecked proliferation—they may simultaneously exacerbate cell death pathways in neurodegeneration and inflammatory contexts. Non-coding RNAs add an additional layer of fine-tuning, operating as post-transcriptional switches that either enhance or suppress these death signals.

The therapeutic implications are profound. Epigenetic drugs such as DNMT inhibitors and HDAC inhibitors have demonstrated the ability to “reawaken” silenced apoptotic and necroptotic pathways, thereby restoring sensitivity to chemotherapy and immunotherapy. At the same time, the precision afforded by CRISPR/dCas9-based epigenetic editing and single-cell epigenomics opens new avenues for tailoring interventions to specific diseases and even patient subgroups. Importantly, the integration of epigenetic therapies with existing modalities—chemotherapy, immunotherapy, and necroptosis inhibitors—holds potential for synergistic strategies that maximize efficacy while minimizing resistance.

However, challenges remain. Epigenetic interventions often lack specificity and may produce off-target effects, raising concerns about safety and long-term consequences. Furthermore, the interplay between apoptosis and necrosis is context-dependent, varying with cell type, stress intensity, and disease state, complicating therapeutic design.

In conclusion, the study of epigenetic influence on apoptosis and necrosis underscores the dynamic and reversible nature of cell death regulation. By deepening our understanding of how these pathways are interwoven and controlled, future research can move toward precision therapies that exploit epigenetic plasticity to correct dysfunctional cell death responses. Ultimately, this line of inquiry not only advances our grasp of fundamental biology but also opens transformative possibilities for the treatment of cancer, neurodegeneration, autoimmunity, and beyond.

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