BIOCELL

Tech Science Press

http://doi.org/10.32604/biocell.2026.081268

REVIEW

The Metabolic-Epigenetic Crosstalk: Mitochondrial Retrograde Signaling in Telomere Homeostasis

Michele Manganelli*

Department of Precision and Regenerative Medicine and Ionian Area, University of Bari-Aldo Moro, Bari, Italy
*Corresponding Author: Michele Manganelli. Email: m.manganelli1991@gmail.com

Received: 27 February 2026; Accepted: 07 May 2026; Published: 22 September 2026

ABSTRACT: Telomere homeostasis is intrinsically integrated into the cellular metabolic network through a complex mito-nuclear communication system. Telomeric chromatin acts as a sensitive sensor of mitochondrial flux, where the stability of telomeres depends on mitochondrial-derived metabolites essential for epigenetic remodeling. Three primary axes govern this control: (1) Acetyl-CoA-mediated histone acetylation necessary for human Telomerase Reverse Transcriptase (hTERT) expression; (2) the competitive balance between α-ketoglutarate/succinate, modulating Jumonji-C (JmjC)-demethylases and Ten-eleven translocation (TET) enzymes; (3) the mitochondrial NAD^+/NADH ratio, governing sirtuin 6 (SIRT6) fidelity. The bidirectional non-coding RNA shuttling, TERC-53 fragment, acts as a retrograde signal of mitochondrial distress. A shift in these metabolic ratios—often induced by succinate dehydrogenase (SDH) deficiency or NAD^+ depletion—leads to epigenetic hardening, characterized by telomeric hypermethylation and repressive chromatin state. Sustained metabolic failure triggers the extranuclear translocation of hTERT, generating a mitohormetic trade-off that prioritizes mitochondrial repair over nuclear replicative capacity. This review aims to provide a comprehensive overview of the functional pathways through which mitochondrial dysfunctions act as a primary driver of genomic instability, providing a comprehensive roadmap to restore epigenetic integrity and cellular homeostasis in age-related pathologies.

KEYWORDS: Mitochondria; nucleus; human telomerase reverse transcriptase; succinate dehydrogenase (SDH); Acetyl-CoA; sirtuins; epigenetics; senescence; genomic instability

1 Introduction

The maintenance of telomeric integrity has historically been framed within the context of the mitochondrial free radical theory of aging (MFRTA) [1,2], where mitochondria are the primary sources of reactive oxygen species (ROS) that induce direct DNA damage and genome attrition [3–5]. However, emerging evidence is shifting this paradigm toward a more complex mito-nuclear communication network, known as mitochondrial-nuclear signaling [6–8].

This communication involves two distinct pathways: anterograde signaling, through which the nucleus regulates mitochondrial biogenesis, and retrograde signaling, a surveillance pathway by which mitochondria communicate their functional status to the nucleus to trigger compensatory responses [9]. Retrograde signaling is activated under conditions of mitochondrial stress and operates through several conserved mechanisms, including the Mitochondrial Unfolded Protein Response (UPRmt) and the Integrated Stress Response (ISR) [10,11]. These pathways rely on a diverse array of signaling molecules, such as ROS, mitochondrial DNA (mtDNA) fragments, the AMP-activated protein kinase (AMPK) as an energy sensor,

and key intermediates of the Tricarboxylic Acid (TCA) cycle [12]. While retrograde signaling influences multiple cellular processes, its role in epigenetic regulation represents a sophisticated layer of genome control [13].

Mitochondria represent dynamic metabolic hubs that actively influence the nuclear epigenetic landscape [14–16]. At the heart of this metabolic-epigenetic wiring lies the observation that epigenetic modifiers—including histone acetyltransferases (HATs) and DNA methyltransferases (DNMTs), function not as autonomous effectors, but as metabolic sensors [17–19]. HATs add an acetyl group to histone tails (H3K9, H3K27, H3K56, H4K16), which neutralizes their positive charge and weakens their interaction with negatively charged DNA. Acetylation acts as a molecular opener, promoting a relaxed, transcriptionally active euchromatin state [20]. Methylation and demethylation involve the addition or removal of methyl groups to DNA or histones (H3K9, H3K4). Unlike acetylation, the effect of methylation is context-dependent: while it can facilitate gene silencing through compact heterochromatin formation, it is also important to maintain structural boundaries within the genome. Demethylation, conversely, serves to reset these marks, allowing for dynamic plasticity [21]. The cell reads its energetic status through the availability of mitochondrial metabolites to decide which genes to turn on or off. Their catalytic activity is strictly dependent upon the availability of specific mitochondrial-derived substrates and co-factors, particularly Acetyl-CoA, α-ketoglutarate (α-KG), and NAD^+ [22,23]. Consequently, fluctuations in mitochondrial Tricarboxylic Acid (TCA) cycle act as a metabolic signal that ripples beyond bioenergetics, extending their influence into alterations of the epigenetic code [24–26].

Telomeric chromatin is particularly sensitive to metabolic fluctuations (Fig. 1) [27,28]. Indeed, the sensitivity of telomeres to mitochondrial fluctuations is not universal, but rather a tunable function of the cell differentiation status and specific bioenergetic demands. In pluripotent and adult stem cells, where mitochondrial metabolism is often primed toward glycolysis and telomere reverse transcriptase (hTERT) constitutive activation, the metabolic-nuclear flux serves as a permissive signal for self-renewal [25,29]. Conversely, in highly oxidative differentiated cells, the gradual decline in mitochondrial efficiency acts as a signal for telomere regulation and replicative senescence [30–32]. This is particularly evidenced when the mitochondrial-nuclear metabolite flux is disrupted—as occurs in succinate dehydrogenase (SDH) deficiency or NAD^+ depletion—as the cell undergoes a metabolic-epigenetic imbalance. This uncoupling leads to the loss of the protective chromatin architecture, leaving the telomere vulnerable to premature shortening and instability [33–35]. It becomes clear that telomere homeostasis is a function of mitochondrial health.

This review aims to address the functional pathways through which mitochondrial metabolites govern telomeric stability, highlighting that mitochondrial dysfunction is a primary driver of genomic instability through the disruption of the metabolic-epigenetic signaling axis, providing a comprehensive roadmap to restore epigenetic integrity and cellular homeostasis in age-related pathologies.

2 Molecular Landscape of the Mito-Nuclear Communication

The metabolic-epigenetic crosstalk is a complex regulatory network where mitochondria act as environmental sensors for the nucleus. This communication relies on a diverse set of intermediates, including TCA cycle metabolites, non-coding RNAs, and transiently translocating proteins that function as molecular messengers. Table 1 provides a comprehensive overview of these actors, their associated metabolites, and their specific roles in maintaining telomeric homeostasis.

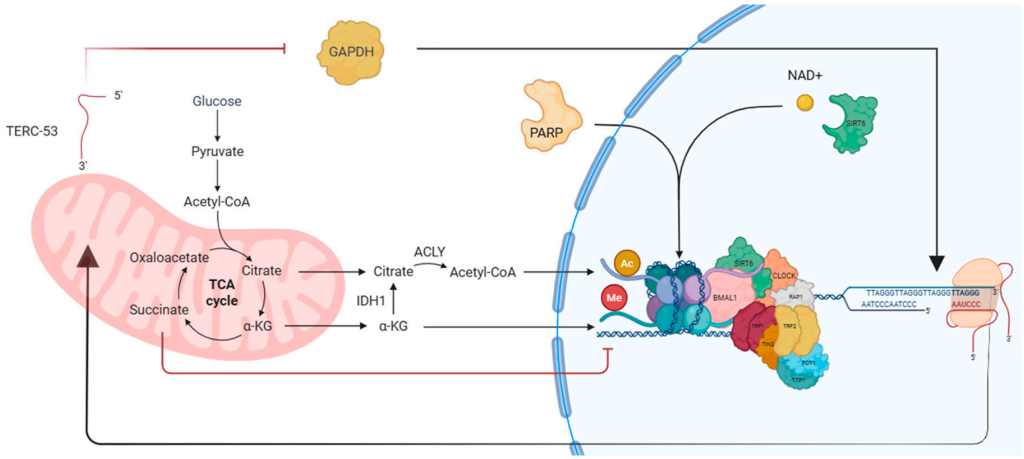

Figure 1: Mitochondrion-nucleus feedback loop. The picture illustrates the crosstalk between cellular metabolism and the structural integrity of nuclear DNA. Within the mitochondrion, the TCA cycle generates key metabolites such as citrate and α-KG. Once transported into the cytosol, citrate is converted into Acetyl-CoA by the enzyme ACLY, providing acetyl groups (Ac) for histone acetylation, while α-KG acts as an essential cofactor for demethylation (Me) modifications, directly influencing the epigenetics of telomeric DNA. In parallel, the NAD^+ pool regulates the activity of crucial nuclear enzymes: SIRT6, which promotes telomere deacetylation and stability, and PARPs, involved in DNA damage repair. The Shelterin complex interacts with circadian clock proteins to protect the TTAGGG telomeric repeat sequences. A retrograde signal is represented by TERC-53, a non-coding RNA fragment that bridges mitochondrial distress to nuclear response. The disruption of this homeostatic balance compromises genomic stability and accelerates cellular decline. Abbreviations: TCA, Tricarboxylic Acid; α-KG, α-Ketoglutarate; ACLY, ATP Citrate Lyase; Acetyl-CoA, Acetyl Coenzyme A; Ac, Acetylation; Me, Methylation; NAD^+, Nicotinamide Adenine Dinucleotide; SIRT6, Sirtuin 6; PARPs, Poly(ADP-ribose) Polymerases; TERC-53, Telomerase RNA Component 53-nt fragment; TRF1/2, Telomeric Repeat-binding Factor 1/2; TIN2, TRF1-interacting Nuclear Protein 2; RAP1, Repressor/Activator Protein 1; POT1, Protection of Telomeres 1; TPP1, TIN2-interacting Protein 1; BMAL1, Brain and Muscle ARNT-Like 1; CLOCK, Circadian Locomotor Output Cycles Kaput. This figure was created with BioRender.com.

Table 1: Molecular mediators of the Mitochondrial-Telomere retrograde signaling axis.

Abbreviation	Full Name	Associated Metabolite	Functional Role in Telomere Homeostasis	References
ACLY	ATP Citrate Lyase	Acetyl-CoA	Converts mitochondrial citrate into Acetyl-CoA, fueling histone acetylation (H3K9ac, H3K27ac) at the hTERT promoter to maintain its expression.	[36–38]
AMPK	AMP-activated Protein Kinase	ATP/AMP ratio	Master energy sensor; triggers mitochondrial retrograde signaling and activates PGC-1α to promote TERRA expression under metabolic stress.	[30,39,40]
ATRX	Alpha-Thalassemia/ X-linked	N/A	Chromatin remodeler that maintains telomeric heterochromatin; its loss is a hallmark of the Alternative Lengthening of Telomeres (ALT) pathway.	[41–43]

Table 1: *Cont.*

Abbreviation	Full Name	Associated Metabolite	Functional Role in Telomere Homeostasis	References
EZH2/SUZ12	PRC2 Complex subunits	SAM	Methyltransferases that interact with TERRA to deposit repressive H3K27me3 marks using SAM as a methyl donor, ensuring telomeric silencing.	[44,45]
hTERT	Telomerase Reverse Transcriptase	N/A	Under oxidative stress, it translocates to mitochondria to protect mtDNA and respiratory function.	[46–48]
ISR/UPRmt	Integrated Stress Response	Mito-stress signals	Signaling cascades that communicate mitochondrial proteotoxic stress to the nucleus to modulate cellular lifespan and adaptation.	[10,11]
JHDMs	JmjC-domain Demethylases	α-KG/Succinate	α-KG-dependent enzymes that remove repressive marks (H3K9me3) to maintain telomere plasticity. Competitively inhibited by succinate.	[49–51]
NAMPT	Nicotinamide phosphoribosyl -transferase	NAD^+	Rate-limiting enzyme in NAD^+ metabolism; links the circadian clock to SIRT6-mediated telomere protection.	[52,53]
NRF1	Nuclear Respiratory Factor 1	N/A	Transcription factor that coordinates mitochondrial biogenesis and promotes TERRA transcription during physiological stress.	[54,55]
SDH	Succinate Dehydrogenase	Succinate	Complex II enzyme; its deficiency causes succinate accumulation, leading to epigenetic hardening and telomeric instability.	[34,35,56]
SIRT6	Sirtuin 6	NAD^+	NAD^+-dependent deacetylase; ensures T-loop stability and prevents R-loop formation.	[57,58]
TERC-53	Telomerase RNA Component (fragment 53)	Mito-stress signals	A cytoplasmic fragment of TERC that shuttles to the nucleus as a retrograde signal of mitochondrial distress, bypassing canonical telomerase roles.	[59]
TERRA	Telomeric Repeat RNA	N/A	Long non-coding RNA acts as a scaffold for chromatin modifiers (PRC2 and LSD1) and interacts with TERC-53 for mito-nuclear signaling.	[44,60]

Note: N/A: not applicable.

The complexity of this communication lies in its hierarchical decision-making logic. As illustrated in Fig. 2, the cell translates mitochondrial functional states (energetic, oncometabolite, and redox status) into specific nuclear fates. This stepwise transduction ensures that telomere stability is dynamically tuned to the bioenergetic capacity of the cell, transitioning from a permissive state of self-renewal under optimal conditions to epigenetic hardening and senescence when mitochondrial distress signals predominate.

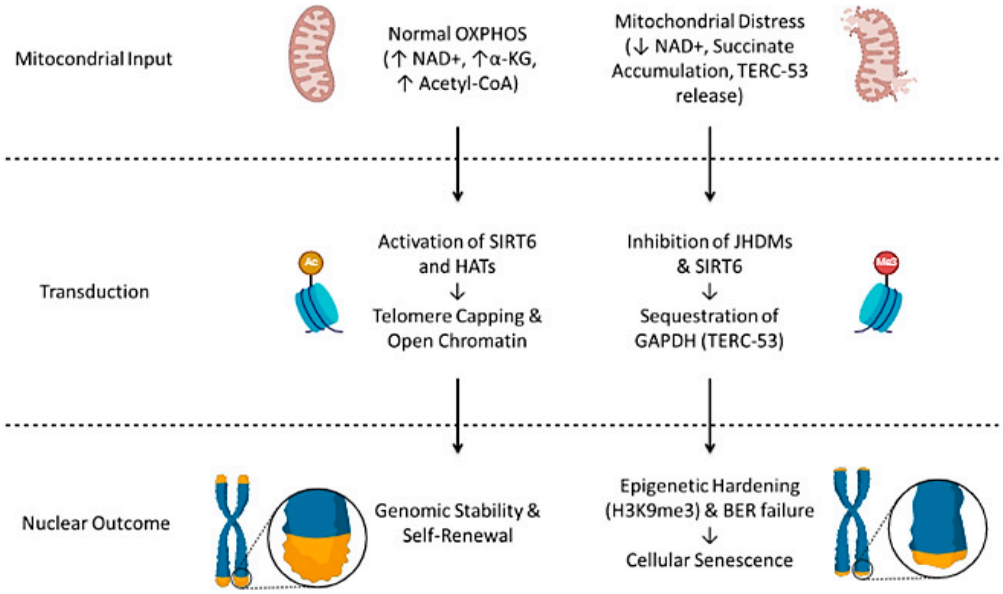

Figure 2: Stepwise functional roadmap of mitochondrial-telomere retrograde signaling. The picture illustrates the causal hierarchy of the mito-nuclear crosstalk, moving from metabolic inputs to genomic outcomes. (Top) Mitochondrial Input: Normal oxidative phosphorylation (OXPHOS) (left) maintains high levels of nicotinamide adenine dinucleotide (NAD^+), α-ketoglutarate (α-KG), and Acetyl-CoA, whereas Mitochondrial Distress (right) leads to NAD^+ depletion, succinate accumulation, and telomerase RNA component fragment 53 (TERC-53) release. (Middle) Transduction: These metabolic states are sensed by epigenetic modifiers. In homeostatic conditions, sirtuin 6 (SIRT6) and histone acetyltransferases (HATs) ensure telomere capping and an open chromatin state. Conversely, mitochondrial distress triggers the inhibition of histone demethylases (JHDMs) and SIRT6, alongside GAPDH sequestration by TERC-53. (Bottom) Nuclear Outcome: The signaling axis dictates the cellular fate, leading to genomic stability and self-renewal (left) or the epigenetic hardening (H3K9me3), base excision repair (BER) failure, and cellular senescence (right). This figure was created with BioRender.com.

3 The Energetic Axis: Acetyl-CoA and Telomeric Chromatin Accessibility

3.1 Acetyl-CoA Production and Compartmentalization

Acetyl-CoA is the key metabolic intermediate produced by the catabolism of carbohydrates, lipids, and amino acids [61]. The acetyl group is transported out of the mitochondria through an indirect shuttle system: acetyl-CoA inside the mitochondrion condenses with oxaloacetate to form citrate. Citrate passes into the cytoplasm across the inner mitochondrial membrane through the Citrate carrier (SLC25A1) [62]. In the cytosol, citrate is cleaved by citrate lyase (ACLY) to regenerate acetyl-CoA [36]. The cytosolic pool of citrate is also sustained by the reductive carboxylation of α-KG mediated by IDH1. Under conditions of mitochondrial impairment or metabolic shift, IDH1 reverses the canonical flux to generate isocitrate and subsequently citrate, which ACLY then cleaves into Acetyl-CoA [63].

Seminal evidence highlighted that ACLY can translocate into the nucleus, providing a compartmentalized nuclear pool of Acetyl-CoA for histone acetylation [64,65]. Accordingly, ACLY nuclear translocation in fibroblasts upon fibrotic stimulation, facilitating TGF-β-mediated myofibroblast activation by promoting H3K27ac at fibrotic gene loci [37]. On the other hand, in cisplatin-resistant hepatocellular carcinoma cells, the stabilization of nuclear ACLY by NAT10-mediated acetylation at K468 prevents its degradation through SQSTM1-mediated proteasomal pathways. This enhances the nuclear acetyl-CoA levels, increasing H3K27ac at chemoresistance-related genes like CYP2C9 and PIK3R1 [38,66].

Interestingly, in most somatic cells, the hTERT promoter (the on/off switch for telomerase) is typically embedded in a nuclease-resistant, closed chromatin structure that silences gene expression. However, an adequate bioenergetic supply facilitates a switch to an accessible euchromatin state, characterized by markers such as H3K9ac, H3K27ac, and H3K4me2/3, allowing key transcription factors like c-Myc and Sp1 to initiate transcription [67,68]. c-Myc binds to specific E-box sequences (5′-CACGTG-3′) within the hTERT promoter [69]. The convergence of c-Myc/Sp1 serves as a metabolic sensor by recruiting HATs, such as TRRAP and p300/CBP [70,71]. TRRAP is essential for this selectivity, as it bridges nuclear ACLY activity directly to the c-Myc cluster. This process acts as a metabolic sensor: during G1-S phases, the nucleus requires enormous amounts of acetyl-CoA for histone acetylation. While ACLY maintains a basal level of acetylation, translocation of the pyruvate dehydrogenase complex (PDC) produces acetyl-CoA directly from pyruvate within the nucleus, providing a high-flux, spatiotemporal boost of acetyl-CoA directly to chromatin during the high-stress window of DNA replication [64,72,73].

3.2 Metabolic Sensing and hTERT Promoter Regulation

This spatial substrate channeling ensures that Acetyl-CoA is utilized *in situ* to catalyze the acetylation of surrounding histones, effectively opening the hTERT chromatin while other genomic regions remain unaffected [74]. This is particularly evident in the context of hTERT promoter mutations [75]. Cytosine-to-thymine (C > T) transitions at positions -124 bp (C228T), and -146 bp (C250T) are the most frequent genetic alterations within the hTERT promoter in medulloblastomas [76], hepatocellular carcinomas (HCC) [77], urothelial carcinomas of the bladder [78], melanomas [79], and primary glioblastomas (GBM) [80]. These mutations result in the generation of *de novo* binding sites (consensus sequence 5′-CCGGAA-3′) for the ETS family of transcription factors [81]. Specifically, the transcription factor GABPA selectively recognizes and binds to the mutated promoter, whereas it shows no affinity for the wild-type sequence [82]. This specific binding recruits the transcriptional machinery, leading to the overexpression of hTERT and subsequently promoting cellular immortalization. Therefore, the oncogenic potential of hTERT mutations is functionally dependent on the bioenergetic state [83,84].

3.3 TERRA Modulation and the Bioenergetic Checkpoint

Consistently, in mammalian cells, the Telomeric Repeat-containing RNA (TERRA) transcript is essential for cis/trans telomere capping to protect the T-loop architecture [44,85,86]. TERRA interacts with H3K9me3 and HP1 (heterochromatin protein 1) proteins [87], the histone methyltransferase SUV39H1 [88], and with chromatin remodeling complexes such as NoRC (nucleolar remodeling complex) [89], MORF4L2 (a component of the NuA histone acetyltransferase complex), and ARID1A [90]. NuA4 is responsible for the acetylation of histone H4 (H4Ac). This specific modification neutralizes the positive charge of the histone tails, reducing DNA torsional tension and favouring chromatin to open. Thus, RTEL1 helicases could remove G-quadruplexes and allow DNA polymerase to complete its work [91,92]. Without this dual-input

of Acetyl-CoA, the TERRA-bound MORF4L2 cannot maintain the requisite chromatin flexibility of the subtelomeric region during S-phase [93].

Evidence suggests that telomere length (TL) itself can modulate metabolic signaling, establishing a retrograde feedback loop [94]. The telomere acts as a physical sensor that feedback-regulates the cell's enzymatic capacity to maintain its own length through the Telomere Position Effect over Long Distance (TPE-OLD) or the non-telomeric binding of TRF2 to the hTERT promoter [95–97]. In cases of severe bioenergetic failure, the lack of substrates for the epigenetic machinery triggers a cascade of genomic instability [57,98]. The loss of histone acetylation results in replication fork stalling and the formation of DNA secondary G-quadruplexes [99,100]. These unresolved stalls result in persistent double-strand breaks (DSBs) at telomeric repeats [101]. In this context, the cell is forced to utilize the existing DSBs as substrates for homology-directed repair (HDR), effectively bypassing the need for telomerase through aberrant template switching [102–104]. Consequently, the Acetyl-CoA flux serves as a fundamental checkpoint: when the fuel for acetylation is exhausted, the cell is propelled toward senescence or aberrant genomic survival strategies.

4 The Control Axis: α-KG/Succinate and Telomeric Stability

4.1 Competitive Inhibition of 2-OGDD Enzymes by Succinate

Beyond acetylation, the mitochondrial-nuclear axis exerts a second layer of epigenetic control through the α-ketoglutarate (α-KG)/succinate ratio [49]. α-KG, produced in the mitochondrial matrix by isocitrate dehydrogenase (IDH), is the obligatory co-substrate for the 2-oxoglutarate-dependent dioxygenase (2-OGDD) superfamily [50]. This family includes TET (Ten-Eleven Translocation) DNA demethylases, which convert 5-methylcytosine (5-mC) to 5-hydroxymethylcytosine (5-hmC), and JmjC-domain-containing histone demethylases (JHDMs), such as KDM4B/C, which remove repressive marks like H3K9me3 and H3K27me3 [105–107]. An accumulation of succinate acts as a potent competitive inhibitor of 2-OGDDs. Specifically, succinate competes with α-KG for binding to the highly conserved Fe^{2+}-containing active site of TET and JmjC enzymes, thereby blocking their catalytic activity [108].

Mitochondrial α-KG is exported to the cytosol through the oxoglutarate carrier SLC25A11 (OGC) in exchange for malate. On the other hand, mitochondrial succinate is exported to the cytosol through the dicarboxylate carrier SLC25A10. Once in the cytosol, their availability in the nucleus directly depends on the cytosolic α-KG/succinate ratio [62]. The α-KG/succinate ratio thus dictates the global methylome: a high ratio (high α-KG) promotes a permissive, hypomethylated state, whereas a low ratio (high succinate) triggers a hypermethylator phenotype. This low-ratio state, often termed CpG Island Methylator Phenotype (CIMP), leads to the hypermethylation of DNA and histones across the genome [109].

At telomeric and subtelomeric regions, this axis is critical for structural plasticity, although through distinct substrates. While subtelomeric regions are regulated by DNA methylation at CpG islands, the telomeric core—which lacks CpG sites—relies exclusively on histone marks [110,111]. TET and JmjC enzymes utilize α-KG to maintain these regions in a metabolically responsive state, facilitating the dynamic turnover of shelterin proteins and fine-tuning the transcription of TERRA [44,86,112,113].

4.2 SDH Deficiency and the Epigenetic Lock

Consistently, TERRA transcripts associate with the histone methyl transferase Polycomb Repressive Complex 2 (PRC2), through a direct interaction with the PRC2 components EZH2 and SUZ12 [44]. Furthermore, TERRA G-quadruplex acts as a scaffold for other telomere-binding proteins, such as the translocated in liposarcoma/fused in sarcoma protein (TLS/FUS) and TRF2 [114,115]. These interactions

through the activity of Suv4-20h2, which associates with TLS/FUS, can promote H4K20me3 modification at telomeres [116]. Without this RNA scaffold, the telomere loses its ability to manage and organize its own heterochromatin, leading to structural fragility.

While a systemic lack of S-adenosylmethionine (SAM) could potentially leave methyltransferases catalytically starved, the pathological accumulation of succinate exerts a dominant inhibitory effect on the 2-OGDD family. This disruption shifts the telomeric landscape from a dynamic state to one of epigenetic inertia, leading to replication fork stalling and instability [104]. Mitochondrial compromises, such as loss-of-function mutations in succinate dehydrogenase (SDH), cause a massive accumulation of succinate, leading to an epigenetic silencing of the 2-OGDD family [117]. This process occurs not through mere energy depletion, but through the induction of a state of biochemical pseudohypoxia [118]. The pathological accumulation of succinate, acting as an oncometabolite, inhibits prolyl hydroxylases (PHDs) in the cytosol, leading to the constitutive stabilization of Hypoxia-Inducible Factor 1-alpha (HIF1α) even under normoxic conditions [117,119–121]. This stabilization triggers a profound biological paradox that explains the genomic instability observed in SDH-deficient tumors and chronic metabolic diseases. On one hand, stabilized HIF1α translocates to the nucleus and directly binds to the hTERT promoter, attempting to upregulate telomerase expression as an evolutionary rescue mechanism to counteract mitochondrial-induced cellular stress [122,123]. On the other hand, the succinate surplus that stabilizes HIF1α simultaneously functions as a competitive inhibitor of the TET and JmjC enzymes required to maintain telomeric chromatin accessibility [45]. Consequently, the cell faces a metabolic-epigenetic mismatch: it attempts to activate hTERT within a genomic environment that is physically inaccessible. This is driven by subtelomeric DNA hypermethylation and, crucially, by the persistence of H3K9me3 at the telomeric core due to JHDM inhibition [124–126]. This epigenetic lock prevents the functional translation of the HIF1α signal into effective telomere repair. Instead, the compromised binding of the shelterin complex to hypermethylated repeats—coupled with the inability of telomerase to access the T-loop—accelerates telomere attrition and favors aberrant DNA template switching [125,127], triggering a transition toward aberrant survival pathways such as the alternative lengthening of telomeres (ALT) pathway [128–130]. Moreover, this transition is significantly favored by the loss of ATRX, a chromatin remodeler frequently mutated in SDH-deficient tumors [41,42]. This epigenetic instability promotes the formation of extra-chromosomal telomeric circles (C-circles) and facilitates homology-directed repair (HDR), providing the genetic and metabolic ground for ALT [43,131].

4.3 Mitochondrial Cofactors: Pyrimidine Synthesis and FAD-Dependent Demethylation

Furthermore, the failure of the SDH-CoQ axis disrupts the *de novo* synthesis of pyrimidines via dihydroorotate dehydrogenase (DHODH), creating a localized depletion of dNTPs that further cripples any residual telomerase-mediated repair [132–134].

Complementary to the α-KG-dependent family, telomeric heterochromatin is further fine-tuned by Lysine-specific demethylase 1 (LSD1). Unlike JmjC enzymes, LSD1 does not require α-KG, but is strictly dependent on Flavin Adenine Dinucleotide (FAD) as a catalytic cofactor [61]. LSD1 orchestrates the oxidative demethylation of mono- and di-methylated H3K4 and H3K9, a process that reduces FAD to FADH2. Consequently, in case of ETC compromise, a decline in the mitochondrial FAD/FADH2 ratio limits LSD1 enzymatic turnover [135]. This metabolic bottleneck leads to the aberrant persistence of H3K4 methylation marks, which effectively opens the telomeric chromatin, facilitating the pathological transcription of TERRA and predisposing the locus to the formation of DNA-damaging R-loops [136,137].

5 The Surveillance Axis: NAD$^+$ Bioavailability and SIRT6 Fidelity

5.1 SIRT6 as a Metabolic Sensor of NAD$^+$

The NAD$^+$/SIRT6 axis constitutes the third critical pillar of mitochondrial-nuclear communication. Nicotinamide adenine dinucleotide (NAD$^+$) is the central redox cofactor for the mitochondrial electron transport chain (ETC), facilitating the transfer of electrons to generate the proton gradient necessary for ATP synthesis [138]. Functional mitochondria maintain a high NAD$^+$/NADH ratio, which is essential for maintaining the catalytic activity of NAD$^+$-dependent enzymes [52]. While acetyl-CoA and α-KG provide the building blocks and signals for chromatin remodeling, NAD$^+$ serves as a real-time sensor of bioenergetic integrity that activates nuclear surveillance enzymes. These include the so-called longevity sirtuin, SIRT6 deacetylase, often referred to as the guardian of telomere stability [139,140].

The biochemical fidelity of SIRT6 is strictly governed by NAD$^+$ bioavailability [58,141]. Unlike other sirtuins, SIRT6 possesses a low Kd (~27 μM) and high Km (~270–800 μM) for NAD$^+$, making SIRT6 a true metabolic sensor due to its catalytic activity sensitive to fluctuations in the nuclear NAD$^+$ pool and capable of adapting gene expression and DNA repair based on energy availability [142].

5.2 T-Loop Stability and TERRA Repression

Unlike other members of the sirtuin family, SIRT6 is constitutively tethered to chromatin and is indispensable for telomere stability [58]. Under metabolic homeostasis, mitochondrial Complex I maintains the NAD$^+$/NADH balance, fueling SIRT6 to orchestrate telomeric protection through three primary NAD$^+$-coordinated mechanisms. SIRT6 mediates H3K9 and H3K56 deacetylation to promote a stable heterochromatic structure. This specific deacetylation is a prerequisite for stabilizing the protective T-loop architecture, preventing the formation of aberrant telomeric DNA circles (t-circles) and suppressing illegitimate recombination [143,144]. Moreover, SIRT6 acts as a molecular scaffold for the recruitment of the shelterin complex TRF2 and the coordination of DNA repair machinery. It facilitates the recruitment of the DNA-dependent protein kinase catalytic subunit (DNA-PKcs), ensuring that DBSs at telomeric ends are addressed by non-homologous end joining (NHEJ) [145–147]. Finally, in somatic contexts, SIRT6 prevents uncontrolled cellular proliferation and transcriptional leakage of TERRA, thereby protecting telomeres from inappropriate DNA damage response (DDR) activation [148,149]. Mechanistically, the H3K9 residue can be either acetylated or methylated, but never both simultaneously. When SIRT6 is active, it removes the acetyl group (H3K9Ac → H3K9). Thus, SUV39H1 can deposit the methylation mark (H3K9 → H3K9me3). Finally, HP1 binds to the H3K9me3 signal. In this state, TERRA transcription is maintained at basal, physiological levels. Without SIRT6, lysine 9 remains engaged by the acetyl group (H3K9Ac). Consequently, SUV39H1 is unable to act, H3K9me3 fails to form, HP1 is not recruited, and the telomere fails to compact. As a result, RNA polymerase II produces an excessive amount of TERRA. These transcripts then form R-loops (three-stranded DNA: RNA hybrids) on the telomeric DNA. During the S-phase, these structures block the replication fork, leading to double-strand breaks (DSBs) and the subsequent activation of the DDR [150,151].

5.3 The Bioenergetic-Telomeric Trap and PARP-1 Competition

When mitochondrial bioenergetics fail, the resulting reduction in NAD$^+$ bioavailability compromises SIRT6 fidelity. Without sufficient NAD$^+$, SIRT6 can no longer function as an epigenetic brake, leading to the deregulation of metabolic genes through the p53-mediated repression of PGC-1α and PGC-1β [152]. Consequently, the impaired HAT activity due to the localized Acetyl-CoA depletion may lead to reduced histone acetylation, potentially contributing to a transition toward a repressive, closed chromatin state.

Without α-KG, TET/JmjC demethylases become blocked (hypermethylation). This bioenergetic-telomeric trap propels the cell toward a point of no return where replicative senescence becomes the inevitable outcome of systemic metabolic exhaustion [57,153]. This vulnerability is exacerbated by the competition for the same NAD^+ pool with Poly(ADP-ribose) polymerase 1 (PARP-1) [154]. Activated by DNA damage—often a byproduct of mitochondrial ROS—PARP-1 acts as a metabolic sink, depleting nuclear NAD^+ levels due to its higher affinity for the substrate [155]. This creates a lethal vicious cycle: the accumulation of telomeric damage recruits PARP-1, which further starves SIRT6 of NAD^+, thereby accelerating telomeric uncapping and preventing efficient DNA repair [156,157].

6 The Extranuclear Translocation of hTERT: Translational Perspectives

6.1 Stress-Induced Nucleocytoplasmic Shuttling of hTERT

Beyond its canonical role within the nucleus, the catalytic subunit hTERT possesses a nucleocytoplasmic shuttling characteristic [46].

In homeostatic conditions, hTERT is predominantly nuclear. However, in response to oxidative stress (i.e., H_2O_2 exposure), hTERT is transiently exported to the cytosol. This process is mediated by the CRM1 (Exportin 1) pathway and the Ran-GTPase system [47,158]. hTERT possesses an evolutionarily conserved Nuclear Export Signal (NES) located within its C-terminus reverse transcriptase domain (residues 701–900). This signal is conditionally accessible: under basal conditions, the NES is sequestered within the protein tertiary structure. Upon oxidative stress, phosphorylation at specific residues (Tyr707) by Src-kinase or Abl-tyrosine-kinase induces a conformational change that exposes the NES for CRM1 recognition. This mechanism ensures that hTERT export is not a random process but a tightly regulated rescue strategy to protect hTERT from nuclear degradation and to prevent telomerase-induced *de novo* addition at fragile genomic sites during stress [159].

6.2 Mitochondrial TERT (mtTERT) and the Mitohormetic Trade-Off

Once in the cytosol, hTERT could also be directed to the mitochondria through a specific 20-amino acid amphipathic alpha-helix Mitochondrial Targeting Sequence (MTS), located at the N-terminus (residues 1–20) [160]. Here, it functions as a mitochondrial chaperone (mtTERT) through several integrated mechanisms. While initial studies focused on mtTERT binding to the ND1 and ND2 regions, more extensive mapping has revealed that mtTERT interacts with a broad array of mitochondrial loci, including 12S and 16S rRNA, ND4, ND5, COX I, COX III, and ATP synthase subunits 6 and 8, enhancing its resistance to oxidative damage and reducing the local production of ROS [161]. A compelling hypothesis proposes that mtTERT actively participates in mtDNA replication by utilizing mitochondrial tRNAs as primers. By favoring alternative origins of replication (mt-tRNA genes), mtTERT may limit the traditional strand displacement mode, which is notoriously prone to deletions [162]. Furthermore, mtTERT interacts with the RNA component of mitochondrial RNA processing (RMRP) and improves the activity of the electron transport chain (ETC), particularly Complex I, stabilizing membrane potential and ATP production [163,164]. Finally, mtTERT acts as a protein scaffold for mitochondrial transcripts, stabilizing mitochondrial ribosome function and ensuring efficient translation of respiratory proteins [165].

This movement represents a strategic metabolic pivot where hTERT transitions from a genomic enzyme to a mitochondrial protector. This mitohormetic strategy creates a functional trade-off designed to prioritize immediate cellular survival and bioenergetic maintenance at the direct expense of long-term replicative capacity [48,166]. The pharmacological modulation of this axis offers a promising therapeutic frontier.

Molecules capable of stabilizing nuclear hTERT or, conversely, promoting its mitochondrial translocation could be used to fine-tune the balance between genomic stability and metabolic efficiency [167].

6.3 TERC-53 and the Retrograde Signaling of Mitochondrial Distress

The regulatory hierarchy between the nucleus and mitochondria is not a one-way round. The mitochondrial compartment is capable of incorporating and processing non-coding RNAs [168]. The telomerase RNA component (TERC) facilitates this bidirectional feedback loop. TERC-53 is a 53-nucleotide fragment derived from the 5′-end of TERC, and its cytosolic accumulation is dynamically regulated by mitochondrial function [59]. Under conditions of mitochondrial distress, TERC-53 accumulates in the cytosol, acting as a molecular decoy that traps glyceraldehyde 3-phosphate dehydrogenase (GAPDH) in the cytosol, thus preventing its translocation to the nucleus [59]. Nuclear GAPDH is essential for the stabilization and catalytic efficiency of Uracil-DNA Glycosylase (UNG), the primary enzyme responsible for removing pro-mutagenic uracil residues from DNA for the Base Excision Repair (BER) machinery. The resulting failure of the BER pathway leads to the accumulation of single-strand breaks [169]. This finding adds a critical layer to the metabolic axes previously discussed: the mitochondrial-telomere crosstalk is not only mediated by protein translocation (hTERT) or metabolite flux (Acetyl-CoA, NAD^+), but also by non-coding RNA signals (TERC-53) that dictate the transition toward replicative arrest [59,169–171].

7 Spatiotemporal Regulation and Circadian Clock

The entire system is not static, but it follows a biological circadian rhythm. Telomere maintenance is finally dynamically synchronized within the circadian clock. It regulates the rhythmic availability of NAD^+ through the rate-limiting enzyme NAMPT (Nicotinamide phosphoribosyltransferase). NAMPT expression is directly governed by the CLOCK: BMAL1 heterodimer, creating a 24-h oscillation in nuclear NAD^+ levels. This temporal fluctuation implies that the surveillance capacity of SIRT6—and consequently the stability of the telomeric T-loop—is subject to a circadian window of vulnerability [53]. However, it should be mentioned that current literature regarding the direct circadian control of telomere-mitochondria crosstalk remains extremely limited. This knowledge gap is due to the significant methodological challenges in chronobiology research.

Finally, under Caloric Restriction (CR), a physiological state of low nutrient intake without malnutrition that shifts cellular priority toward survival and repair, the activation of the AMPK/PGC-1α pathway recruits Nuclear Respiratory Factor 1 (NRF1) to subtelomeric promoters, directly promoting TERRA expression, to ensure that the chromatin environment remains responsive [55,172].

8 Conclusion

In conclusion, the telomere acts as a metabolic antenna, sensing the state of the mitochondria to decide the cell fate. The transition towards cellular aging is not only a matter of physical DNA wear, but an epigenetic hardening due to the failure of mitochondrial signaling. Deciphering the language of this communication is essential for the generation of therapies in age-related pathologies. Consistently, age-related pathologies would require a holistic approach that views genomic stability as a direct reflection of mitochondrial health.

Acknowledgement: Not applicable.

Funding Statement: The author received no specific funding for this study.

Availability of Data and Materials: Not applicable.

Ethics Approval: Not applicable.

Conflicts of Interest: The author declares no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

MFRTA	Mitochondrial Free Radical Theory of Aging
ROS	Reactive Oxygen Species
DNMTs	DNA Methyltransferases
TCA	Tricarboxylic Acid (cycle)
SLC25A1	Citrate Carrier (Solute Carrier Family 25 Member 1)
IDH1	Isocitrate Dehydrogenase 1
NAT10	N-acetyltransferase 10
CYP2C9	Cytochrome P450 Family 2 Subfamily C Member 9
PIK3R1	Phosphoinositide-3-Kinase Regulatory Subunit 1
TRRAP	Transformation/Transcription Domain Associated Protein
PDC	Pyruvate Dehydrogenase Complex
GABPA	GA Binding Protein Transcription Factor Subunit Alpha
HP1	Heterochromatin Protein 1
SUV39H1	Suppressor Of Variegation 3-9 Homolog 1
NoRC	Nucleolar Remodeling Complex
ARID1A	AT-Rich Interaction Domain 1A
RTEL1	Regulator of Telomere Elongation Helicase 1
TL	Telomere Length
TPE-OLD	Telomere Position Effect over Long Distance
DSBs	Double-Strand Breaks
HDR	Homology-Directed Repair
2-OGDD	2-Oxoglutarate-Dependent Dioxygenase
TET	Ten-Eleven Translocation
SLC25A11 (OGC)	Oxoglutarate Carrier
SLC25A10	Dicarboxylate Carrier
CIMP	CpG Island Methylator Phenotype
PRC2	Polycomb Repressive Complex 2
TLS/FUS	Translocated in Liposarcoma/Fused in Sarcoma
SAM	S-Adenosylmethionine
PHDs	Prolyl Hydroxylases
HIF1α	Hypoxia-Inducible Factor 1-alpha
ALT	Alternative Lengthening of Telomeres
DHODH	Dihydroorotate Dehydrogenase
dNTPs	Deoxynucleotide Triphosphates
LSD1	Lysine-specific Demethylase 1
ETC	Electron Transport Chain
DNA-PKcs	DNA-dependent Protein Kinase catalytic subunit
NHEJ	Non-Homologous End Joining
DDR	DNA Damage Response
PGC-1α/β	Peroxisome proliferator-activated receptor Gamma Coactivator 1-alpha/beta
PARP-1	Poly(ADP-ribose) Polymerase 1
CRM1	Chromosome Region Maintenance 1 (Exportin 1)
NES	Nuclear Export Signal
MTS	Mitochondrial Targeting Sequence
mtTERT	Mitochondrial hTERT

RMRP	RNA component of Mitochondrial RNA Processing
UNG	Uracil-DNA Glycosylase
BER	Base Excision Repair
CLOCK: BMAL1	Circadian Locomotor Output Cycles Kaput: Brain and Muscle ARNT-Like 1
CR	Caloric Restriction

References

1. Somasundaram I, Jain SM, Blot-Chabaud M, Pathak S, Banerjee A, Rawat S, et al. Mitochondrial dysfunction and its association with age-related disorders. Front Physiol. 2024;15:1384966. [CrossRef].
2. Manganelli M, Stabile G, Scharf C, Podo Brunetti A, Paolino G, Giuffrida R, et al. Skin photodamage and melanomagenesis: a comprehensive review. Cancers. 2025;17(11):1784. [CrossRef].
3. Amano H, Chaudhury A, Rodriguez-Aguayo C, Lu L, Akhanov V, Catic A, et al. Telomere dysfunction induces sirtuin repression that drives telomere-dependent disease. Cell Metab. 2019;29(6):1274–90.e9. [CrossRef].
4. Stojanovic B, Jovanovic I, Dimitrijevic Stojanovic M, Stojanovic BS, Kovacevic V, Radosavljevic I, et al. Oxidative stress-driven cellular senescence: mechanistic crosstalk and therapeutic horizons. Antioxidants. 2025;14(8):987. [CrossRef].
5. Picca A, Guerra F, Calvani R, Coelho-Júnior HJ, Leeuwenburgh C, Bucci C, et al. The contribution of mitochondrial DNA alterations to aging, cancer, and neurodegeneration. Exp Gerontol. 2023;178:112203. [CrossRef].
6. Kim KH, Lee CB. Socialized mitochondria: mitonuclear crosstalk in stress. Exp Mol Med. 2024;56(5):1033–42. [CrossRef].
7. Chen G, Dong H, Tian Y. Mito-nuclear communication: from cellular responses to organismal health. Mol Cell. 2026;86(3):522–32. [CrossRef].
8. Zhu D, Li X, Tian Y. Mitochondrial-to-nuclear communication in aging: an epigenetic perspective. Trends Biochem Sci. 2022;47(8):645–59. [CrossRef].
9. Walker EM, Pearson GL, Lawlor N, Stendahl AM, Lietzke A, Sidarala V, et al. Retrograde mitochondrial signaling governs the identity and maturity of metabolic tissues. Science. 2025;388(6743):eadf2034. [CrossRef].
10. Eckl EM, Ziegemann O, Krumwiede L, Fessler E, Jae LT. Sensing, signaling and surviving mitochondrial stress. Cell Mol Life Sci. 2021;78(16):5925–51. [CrossRef].
11. Torres AK, Fleischhart V, Inestrosa NC. Mitochondrial unfolded protein response (UPR^{mt}): what we know thus far. Front Cell Dev Biol. 2024;12:1405393. [CrossRef].
12. Meichsner A, Bader V, Winklhofer KF. Mitochondria as sources and targets of cellular signaling. Mol Cell. 2026;86(3):503–21. [CrossRef].
13. Liu YJ, Sulc J, Auwerx J. Mitochondrial genetics, signalling and stress responses. Nat Cell Biol. 2025;27(3):393–407. [CrossRef].
14. Donato L, Mordà D, Scimone C, Alibrandi S, D'Angelo R, Sidoti A. From powerhouse to regulator: the role of mitoepigenetics in mitochondrion-related cellular functions and human diseases. Free Radic Biol Med. 2024;218:105–19. [CrossRef].
15. Shyh-Chang N, Ng HH. The metabolic programming of stem cells. Genes Dev. 2017;31(4):336–46. [CrossRef].
16. Gunawan AL, Liparulo I, Stahl A. Mammalian mitohormesis: from mitochondrial stressors to organismal benefits. EMBO J. 2025;44(20):5640–61. [CrossRef].
17. Ge T, Gu X, Jia R, Ge S, Chai P, Zhuang A, et al. Crosstalk between metabolic reprogramming and epigenetics in cancer: updates on mechanisms and therapeutic opportunities. Cancer Commun. 2022;42(11):1049–82. [CrossRef].
18. Covarrubias AJ, Perrone R, Grozio A, Verdin E. NAD+ metabolism and its roles in cellular processes during ageing. Nat Rev Mol Cell Biol. 2021;22(2):119–41. [CrossRef].
19. Paciolla C, Manganelli M, Di Chiano M, Montenegro F, Gallone A, Sallustio F, et al. Valeric acid: a gut-derived metabolite as a potential epigenetic modulator of neuroinflammation in the gut–brain axis. Cells. 2025;14(22):1823. [CrossRef].
20. Zhang X, Gao Y, Zhang S, Wang Y, Pei X, Chen Y, et al. Mitochondrial dysfunction in the regulation of aging and aging-related diseases. Cell Commun Signal. 2025;23(1):290. [CrossRef].
21. Younesian S, Mohammadi MH, Younesian O, Momeny M, Ghaffari SH, Bashash D. DNA methylation in human diseases. Heliyon. 2024;10(11):e32366. [CrossRef].

22. Lee HT, Roe JS, Youn HD. Metabolic oxidoreductases: central regulators of the epigenetic landscapes in stemness. Exp Mol Med. 2026;58(4):1017–37. [CrossRef].
23. Xu Y, Jian X, Shi L, Shock LS, Chen L, Chow LT, et al. Mitochondria and epigenetic regulation: bidirectional crosstalk and emerging mitochondria-targeted degron tools. Cells. 2026;15(2):95. [CrossRef].
24. Nam H, Yu G, Ahn SI, Nam S. Mechanical regulation of metabolism, epigenetics, and their interplay. npj Biomed Innov. 2026;3:5. [CrossRef].
25. Wei P, Zhang X, Yan C, Sun S, Chen Z, Lin F. Mitochondrial dysfunction and aging: multidimensional mechanisms and therapeutic strategies. Biogerontology. 2025;26(4):142. [CrossRef].
26. Assalve G, Lunetti P, Rocca MS, Cosci I, Di Nisio A, Ferlin A, et al. Exploring the link between telomeres and mitochondria: mechanisms and implications in different cell types. Int J Mol Sci. 2025;26(3):993. [CrossRef].
27. Martini H, Passos JF. Cellular senescence: all roads lead to mitochondria. FEBS J. 2023;290(5):1186–202. [CrossRef].
28. Li Y, Tian X, Luo J, Bao T, Wang S, Wu X. Molecular mechanisms of aging and anti-aging strategies. Cell Commun Signal. 2024;22(1):285. [CrossRef].
29. Gu Z, Niu Z, Yan Z, Fan Y, Sun J, Zhao X, et al. Chain-mediating effect of interaction between telomeres and mitochondria under oxidative stress in coke oven workers. Environ Pollut. 2023;331:121855. [CrossRef].
30. Chandel NS, Jasper H, Ho TT, Passegué E. Metabolic regulation of stem cell function in tissue homeostasis and organismal ageing. Nat Cell Biol. 2016;18(8):823–32. [CrossRef].
31. Sperber H, Mathieu J, Wang Y, Ferreccio A, Hesson J, Xu Z, et al. The metabolome regulates the epigenetic landscape during naive-to-primed human embryonic stem cell transition. Nat Cell Biol. 2015;17(12):1523–35. [CrossRef].
32. Dogan F, Forsyth NR. TERT promoter methylation is oxygen-sensitive and regulates telomerase activity. Biomolecules. 2024;14(1):131. [CrossRef].
33. Gao C. Investigating the association between blood metabolites and telomere length: a Mendelian randomization study. PLoS One. 2024;19(3):e0298172. [CrossRef].
34. Li W, Quan L, Peng K, Wang Y, Wang X, Chen Q, et al. Succinate dehydrogenase is essential for epigenetic and metabolic homeostasis in hearts. Basic Res Cardiol. 2023;118(1):45. [CrossRef].
35. Wang Q, Li M, Zeng N, Zhou Y, Yan J. Succinate dehydrogenase complex subunit C: Role in cellular physiology and disease. Exp Biol Med. 2023;248(3):263–70. [CrossRef].
36. Ghisletti S, Russo M. TCA-cycle metabolites in the nucleus: drivers of chromatin and epigenetic control. BMC Biol. 2025;23(1):316. [CrossRef].
37. Lazaropoulos MP, Gibb AA, Chapski DJ, Nair AA, Reiter AN, Roy R, et al. Nuclear ATP-citrate lyase regulates chromatin-dependent activation and maintenance of the myofibroblast gene program. Nat Cardiovasc Res. 2024;3(7):869–82. [CrossRef].
38. Wang Y, Su K, Wang C, Deng T, Liu X, Sun S, et al. Chemotherapy-induced acetylation of ACLY by NAT10 promotes its nuclear accumulation and acetyl-CoA production to drive chemoresistance in hepatocellular carcinoma. Cell Death Dis. 2024;15:545. [CrossRef].
39. Mandic M, Misirkic Marjanovic M, Janjetovic K, Bosnjak M, Harhaji-Trajkovic L, Trajkovic V, et al. Multifaceted role of AMPK in autophagy: more than a simple trigger? Am J Physiol Cell Physiol. 2025;329(5):C1380–97. [CrossRef].
40. Dang K, Muhammad Umer Farooq H, Gao Y, Deng X, Qian A. The role of 5′-adenosine monophosphate-activated protein kinase (AMPK) in skeletal muscle atrophy. Biocell. 2023;47(2):269–81. [CrossRef].
41. Heaphy CM, de Wilde RF, Jiao Y, Klein AP, Edil BH, Shi C, et al. Altered telomeres in tumors with ATRX and DAXX mutations. Science. 2011;333(6041):425. [CrossRef].
42. Job S, Draskovic I, Burnichon N, Buffet A, Cros J, Lépine C, et al. Telomerase activation and ATRX mutations are independent risk factors for metastatic pheochromocytoma and paraganglioma. Clin Cancer Res. 2019;25(2):760–70. [CrossRef].
43. Aguilera P, López-Contreras AJ. ATRX, a guardian of chromatin. Trends Genet. 2023;39(6):505–19. [CrossRef].
44. Montero JJ, López-Silanes I, Megías D, F Fraga M, Castells-García Á, Blasco MA. *TERRA* recruitment of polycomb to telomeres is essential for histone trymethylation marks at telomeric heterochromatin. Nat Commun. 2018;9(1):1548. [CrossRef].

45. Dogan F, Forsyth NR. Telomerase regulation: a role for epigenetics. Cancers. 2021;13(6):1213. [CrossRef].
46. Haendeler J, Hoffmann J, Brandes RP, Zeiher AM, Dimmeler S. Hydrogen peroxide triggers nuclear export of telomerase reverse transcriptase via src kinase family-dependent phosphorylation of tyrosine 707. Mol Cell Biol. 2003;23(13):4598–610. [CrossRef].
47. Marinaccio J, Micheli E, Udroiu I, Di Nottia M, Carrozzo R, Baranzini N, et al. TERT extra-telomeric roles: antioxidant activity and mitochondrial protection. Int J Mol Sci. 2023;24(5):4450. [CrossRef].
48. Ebata H, Shima T, Iizuka R, Uemura S. Accumulation of TERT in mitochondria exerts two opposing effects on apoptosis. FEBS Open Bio. 2023;13(9):1667–82. [CrossRef].
49. Bénit P, Goncalves J, El Khoury R, Rak M, Favier J, Gimenez-Roqueplo AP, et al. Succinate dehydrogenase, succinate, and superoxides: a genetic, epigenetic, metabolic, environmental explosive crossroad. Biomedicines. 2022;10(8):1788. [CrossRef].
50. Nakashima Y, Brewitz L, Tumber A, Salah E, Schofield CJ. 2-Oxoglutarate derivatives can selectively enhance or inhibit the activity of human oxygenases. Nat Commun. 2021;12:6478. [CrossRef].
51. Wang M, Xue J, Hong W, Chen S, Shi H. JMJD family proteins in cancer and inflammation. Sig Transduct Target Ther. 2022;7:304. [CrossRef].
52. Yusri K, Jose S, Vermeulen KS, Tan TCM, Sorrentino V. The role of NAD+ metabolism and its modulation of mitochondria in aging and disease. npj Metab Health Dis. 2025;3:26. [CrossRef].
53. Ramsey KM, Yoshino J, Brace CS, Abrassart D, Kobayashi Y, Marcheva B, et al. Circadian clock feedback cycle through NAMPT-mediated NAD+ biosynthesis. Science. 2009;324(5927):651–4. [CrossRef].
54. D'Souza AD, Parikh N, Kaech SM, Shadel GS. Convergence of multiple signaling pathways is required to coordinately up-regulate mtDNA and mitochondrial biogenesis during T cell activation. Mitochondrion. 2007;7(6):374–85. [CrossRef].
55. Diman A, Boros J, Poulain F, Rodriguez J, Purnelle M, Episkopou H, et al. Nuclear respiratory factor 1 and endurance exercise promote human telomere transcription. Sci Adv. 2016;2(7):e1600031. [CrossRef].
56. Bayley JP, Devilee P. Hypothesis: why different types of SDH gene variants cause divergent tumor phenotypes. Genes. 2022;13(6):1025. [CrossRef].
57. Tasselli L, Xi Y, Zheng W, Tennen RI, Odrowaz Z, Simeoni F, et al. SIRT6 deacetylates H3K18ac at pericentric chromatin to prevent mitotic errors and cellular senescence. Nat Struct Mol Biol. 2016;23(5):434–40. [CrossRef].
58. Michishita E, McCord RA, Berber E, Kioi M, Padilla-Nash H, Damian M, et al. SIRT6 is a histone H3 lysine 9 deacetylase that modulates telomeric chromatin. Nature. 2008;452(7186):492–6. [CrossRef].
59. Zheng Q, Liu P, Gao G, Yuan J, Wang P, Huang J, et al. Mitochondrion-processed TERC regulates senescence without affecting telomerase activities. Protein Cell. 2019;10(9):631–48. [CrossRef].
60. Rodrigues J, Alfieri R, Bione S, Azzalin CM. *TERRA* ONTseq: a long-read-based sequencing pipeline to study the human telomeric transcriptome. RNA. 2024;30(8):955–66. [CrossRef].
61. Wang Y, Yang H, Geerts C, Furtos A, Waters P, Cyr D, et al. The multiple facets of acetyl-CoA metabolism: energetics, biosynthesis, regulation, acylation and inborn errors. Mol Genet Metab. 2023;138(1):106966. [CrossRef].
62. Palmieri F. The mitochondrial transporter family SLC25: identification, properties and physiopathology. Mol Aspects Med. 2013;34(2–3):465–84. [CrossRef].
63. Gai C, Zeng H, Xu H, Chai X, Zou Y, Zhuang C, et al. Comprehensive exploration of isocitrate dehydrogenase (IDH) mutations: tumorigenesis, drug discovery, and covalent inhibitor advances. Eur J Med Chem. 2025;282:117041. [CrossRef].
64. Sivanand S, Viney I, Wellen KE. Spatiotemporal control of acetyl-CoA metabolism in chromatin regulation. Trends Biochem Sci. 2018;43(1):61–74. [CrossRef].
65. Yang H, Qin Y, Xu X, Chen W, Zu G, Chen X. Acetyl-CoA: an interplay between metabolism and epigenetics in cancer. Front Mol Med. 2022;2:1044585. [CrossRef].
66. Zhang Y, Jing Y, Wang Y, Tang J, Zhu X, Jin WL, et al. NAT10 promotes gastric cancer metastasis via N4-acetylated COL5A1. Signal Transduct Target Ther. 2021;6:173. [CrossRef].
67. Dong S, Li T. Metabolic reprogramming in cancer: signaling pathways and therapeutic targets. Mol Cancer. 2026;25(1):60. [CrossRef].

68. Yuan X, Larsson C, Xu D. Mechanisms underlying the activation of TERT transcription and telomerase activity in human cancer: old actors and new players. Oncogene. 2019;38(34):6172–83. [CrossRef].
69. Shou S, Maolan A, Zhang D, Jiang X, Liu F, Li Y, et al. Telomeres, telomerase, and cancer: mechanisms, biomarkers, and therapeutics. Exp Hematol Oncol. 2025;14(1):8. [CrossRef].
70. Kyo S, Takakura M, Taira T, Kanaya T, Itoh H, Yutsudo M, et al. Sp1 cooperates with c-Myc to activate transcription of the human telomerase reverse transcriptase gene (hTERT). Nucleic Acids Res. 2000;28(3):669–77. [CrossRef].
71. Luo J, Chen Z, Qiao Y, Tien JC, Young E, Mannan R, et al. Targeting histone H2B acetylated enhanceosomes via p300/CBP degradation in prostate cancer. Nat Genet. 2025;57(10):2468–81. [CrossRef].
72. Sutendra G, Kinnaird A, Dromparis P, Paulin R, Stenson TH, Haromy A, et al. A nuclear pyruvate dehydrogenase complex is important for the generation of acetyl-CoA and histone acetylation. Cell. 2014;158(1):84–97. [CrossRef].
73. Wu QJ, Zhang TN, Chen HH, Yu XF, Lv JL, Liu YY, et al. The sirtuin family in health and disease. Signal Transduct Target Ther. 2022;7:402. [CrossRef].
74. Lee JV, Carrer A, Shah S, Snyder NW, Wei S, Venneti S, et al. Akt-dependent metabolic reprogramming regulates tumor cell histone acetylation. Cell Metab. 2014;20(2):306–19. [CrossRef].
75. Shanmugam R, Ozturk MB, Low JL, Akincilar SC, Chua JYH, Thangavelu MT, et al. Genome-wide screens identify specific drivers of mutant hTERT promoters. Proc Natl Acad Sci U S A. 2022;119(3):e2105171119. [CrossRef].
76. Remke M, Ramaswamy V, Peacock J, Shih DJH, Koelsche C, Northcott PA, et al. TERT promoter mutations are highly recurrent in SHH subgroup medulloblastoma. Acta Neuropathol. 2013;126(6):917–29. [CrossRef].
77. Quaas A, Oldopp T, Tharun L, Klingenfeld C, Krech T, Sauter G, et al. Frequency of TERT promoter mutations in primary tumors of the liver. Virchows Arch. 2014;465(6):673–7. [CrossRef].
78. Kinde I, Munari E, Faraj SF, Hruban RH, Schoenberg M, Bivalacqua T, et al. TERT promoter mutations occur early in urothelial neoplasia and are biomarkers of early disease and disease recurrence in urine. Cancer Res. 2013;73(24):7162–7. [CrossRef].
79. Horn S, Figl A, Rachakonda PS, Fischer C, Sucker A, Gast A, et al. TERT promoter mutations in familial and sporadic melanoma. Science. 2013;339(6122):959–61. [CrossRef].
80. Killela PJ, Reitman ZJ, Jiao Y, Bettegowda C, Agrawal N, Diaz LA Jr, et al. TERT promoter mutations occur frequently in gliomas and a subset of tumors derived from cells with low rates of self-renewal. Proc Natl Acad Sci U S A. 2013;110(15):6021–6. [CrossRef].
81. Sharma S, Chowdhury S. Emerging mechanisms of telomerase reactivation in cancer. Trends Cancer. 2022;8(8):632–41. [CrossRef].
82. Bell RJA, Rube HT, Kreig A, Mancini A, Fouse SD, Nagarajan RP, et al. The transcription factor GABP selectively binds and activates the mutant TERT promoter in cancer. Science. 2015;348(6238):1036–9. [CrossRef].
83. Akıncılar SC, Khattar E, Boon PLS, Unal B, Fullwood MJ, Tergaonkar V. Long-range chromatin interactions drive mutant TERT promoter activation. Cancer Discov. 2016;6(11):1276–91. [CrossRef].
84. Liu M, Zhang Y, Jian Y, Gu L, Zhang D, Zhou H, et al. The regulations of telomerase reverse transcriptase (TERT) in cancer. Cell Death Dis. 2024;15:90. [CrossRef].
85. Rivosecchi J, Cusanelli E. *TERRA* beyond cancer: the biology of telomeric repeat-containing RNAs in somatic and germ cells. Front Aging. 2023;4:1224225. [CrossRef].
86. Manganelli M, Grossi I, Corsi J, D'Agostino VG, Jurikova K, Cusanelli E, et al. Expression of cellular and extracellular *TERRA*, TERC and TERT in hepatocellular carcinoma. Int J Mol Sci. 2022;23(11):6183. [CrossRef].
87. Deng Z, Norseen J, Wiedmer A, Riethman H, Lieberman PM. *TERRA* RNA binding to TRF2 facilitates heterochromatin formation and ORC recruitment at telomeres. Mol Cell. 2009;35(4):403–13. [CrossRef].
88. Porro A, Feuerhahn S, Delafontaine J, Riethman H, Rougemont J, Lingner J. Functional characterization of the *TERRA* transcriptome at damaged telomeres. Nat Commun. 2014;5:5379. [CrossRef].
89. Postepska-Igielska A, Krunic D, Schmitt N, Greulich-Bode KM, Boukamp P, Grummt I. The chromatin remodelling complex NoRC safeguards genome stability by heterochromatin formation at telomeres and centromeres. EMBO Rep. 2013;14(8):704–10. [CrossRef].
90. Scheibe M, Arnoult N, Kappei D, Buchholz F, Decottignies A, Butter F, et al. Quantitative interaction screen of telomeric repeat-containing RNA reveals novel *TERRA* regulators. Genome Res. 2013;23(12):2149–57. [CrossRef].

91. Mitchell L, Lambert JP, Gerdes M, Al-Madhoun AS, Skerjanc IS, Figeys D, et al. Functional dissection of the NuA4 histone acetyltransferase reveals its role as a genetic hub and that Eaf1 is essential for complex integrity. Mol Cell Biol. 2008;28(7):2244–56. [CrossRef].
92. Vannier JB, Sandhu S, Petalcorin MIR, Wu X, Nabi Z, Ding H, et al. RTEL1 is a replisome-associated helicase that promotes telomere and genome-wide replication. Science. 2013;342(6155):239–42. [CrossRef].
93. Ducker GS, Rabinowitz JD. One-carbon metabolism in health and disease. Cell Metab. 2017;25(1):27–42. [CrossRef].
94. Casagrande S, Hau M. Telomere attrition: metabolic regulation and signalling function? Biol Lett. 2019;15(3):20180885. [CrossRef].
95. Takakura M. Telomerase activation by histone deacetylase inhibitor in normal cells. Nucleic Acids Res. 2001;29(14):3006–11. [CrossRef].
96. Lewis KA, Tollefsbol TO. Regulation of the telomerase reverse transcriptase subunit through epigenetic mechanisms. Front Genet. 2016;7:83. [CrossRef].
97. Chevalier R, Murcia Pienkowski V, Jullien N, Caron L, Pinard PV, Magdinier F, et al. Telomere position effect-over long distances acts as a genome-wide epigenetic regulator through a common Alu element. Aging Cell. 2025;24(6):e70027. [CrossRef].
98. López-Gil L, Pascual-Ahuir A, Proft M. Genomic instability and epigenetic changes during aging. Int J Mol Sci. 2023;24(18):14279. [CrossRef].
99. Alabert C, Groth A. Chromatin replication and epigenome maintenance. Nat Rev Mol Cell Biol. 2012;13(3):153–67. [CrossRef].
100. Rhodes D, Lipps HJ. G-quadruplexes and their regulatory roles in biology. Nucleic Acids Res. 2015;43(18):8627–37. [CrossRef].
101. Martínez P, Blasco MA. Replicating through telomeres: a means to an end. Trends Biochem Sci. 2015;40(9):504–15. [CrossRef].
102. Lee JJ, Kim H, Park H, Lee U, Kim C, Lee M, et al. Disruption of G-quadruplex dynamicity by BRCA2 abrogation instigates phase separation and break-induced replication at telomeres. Nucleic Acids Res. 2024;52(10):5756–73. [CrossRef].
103. Sobinoff AP, Pickett HA. Alternative lengthening of telomeres: DNA repair pathways converge. Trends Genet. 2017;33(12):921–32. [CrossRef].
104. O'Sullivan RJ, Kubicek S, Schreiber SL, Karlseder J. Reduced histone biosynthesis and chromatin changes arising from a damage signal at telomeres. Nat Struct Mol Biol. 2010;17(10):1218–25. [CrossRef].
105. Tischler J, Gruhn WH, Reid J, Allgeyer E, Buettner F, Marr C, et al. Metabolic regulation of pluripotency and germ cell fate through α-ketoglutarate. EMBO J. 2019;38(1):e99518. [CrossRef].
106. Tahiliani M, Koh KP, Shen Y, Pastor WA, Bandukwala H, Brudno Y, et al. Conversion of 5-methylcytosine to 5-hydroxymethylcytosine in mammalian DNA by MLL partner TET1. Science. 2009;324(5929):930–5. [CrossRef].
107. Black JC, Van Rechem C, Whetstine JR. Histone lysine methylation dynamics: establishment, regulation, and biological impact. Mol Cell. 2012;48(4):491–507. [CrossRef].
108. Koivunen P, Lee S, Duncan CG, Lopez G, Lu G, Ramkissoon S, et al. Transformation by the (R)-enantiomer of 2-hydroxyglutarate linked to EGLN activation. Nature. 2012;483(7390):484–8. [CrossRef].
109. Figueroa ME, Abdel-Wahab O, Lu C, Ward PS, Patel J, Shih A, et al. Leukemic IDH1 and IDH2 mutations result in a hypermethylation phenotype, disrupt TET2 function, and impair hematopoietic differentiation. Cancer Cell. 2010;18(6):553–67. [CrossRef].
110. Blasco MA. The epigenetic regulation of mammalian telomeres. Nat Rev Genet. 2007;8(4):299–309. [CrossRef].
111. Wang K, Liu H, Hu Q, Wang L, Liu J, Zheng Z, et al. Epigenetic regulation of aging: implications for interventions of aging and diseases. Signal Transduct Target Ther. 2022;7:374. [CrossRef].
112. Ciccarone F, Vegliante R, Di Leo L, Ciriolo MR. The TCA cycle as a bridge between oncometabolism and DNA transactions in cancer. Semin Cancer Biol. 2017;47:50–6. [CrossRef].
113. Bettin N, Oss Pegorar C, Cusanelli E. The emerging roles of *TERRA* in telomere maintenance and genome stability. Cells. 2019;8(3):246. [CrossRef].

114. Collie GW, Haider SM, Neidle S, Parkinson GN. A crystallographic and modelling study of a human telomeric RNA (*TERRA*) quadruplex. Nucleic Acids Res. 2010;38(16):5569–80. [CrossRef].
115. Biffi G, Tannahill D, Balasubramanian S. An intramolecular G-quadruplex structure is required for binding of telomeric repeat-containing RNA to the telomeric protein TRF2. J Am Chem Soc. 2012;134(29):11974–6. [CrossRef].
116. Takahama K, Takada A, Tada S, Shimizu M, Sayama K, Kurokawa R, et al. Regulation of telomere length by G-quadruplex telomere DNA- and *TERRA*-binding protein TLS/FUS. Chem Biol. 2013;20(3):341–50. [CrossRef].
117. Chen L, Huang M. Oncometabolites in cancer: from cancer cells to the tumor microenvironment. Holist Integr Oncol. 2024;3(1):26. [CrossRef].
118. Beyoğlu D, Idle JR. Metabolic rewiring and the characterization of oncometabolites. Cancers. 2021;13(12):2900. [CrossRef].
119. Esteban-Amo MJ, Jiménez-Cuadrado P, Serrano-Lorenzo P, de la Fuente MÁ, Simarro M. Succinate dehydrogenase and human disease: novel insights into a well-known enzyme. Biomedicines. 2024;12(9):2050. [CrossRef].
120. Ősz F, Akbar M, Zsidó BZ, Hetényi C, Orbán TI, Fóthi Á, et al. The *Caenorhabditis elegans* sdhb-1(R244H) model shows characteristics of human PPGL tumor cells. Int J Mol Sci. 2025;26(20):10185. [CrossRef].
121. Atallah R, Olschewski A, Heinemann A. Succinate at the crossroad of metabolism and angiogenesis: roles of SDH, HIF1α and SUCNR1. Biomedicines. 2022;10(12):3089. [CrossRef].
122. Nishi H, Nakada T, Kyo S, Inoue M, Shay JW, Isaka K. Hypoxia-inducible factor 1 mediates upregulation of telomerase (hTERT). Mol Cell Biol. 2004;24(13):6076–83. [CrossRef].
123. Yatabe N, Kyo S, Maida Y, Nishi H, Nakamura M, Kanaya T, et al. HIF-1-mediated activation of telomerase in cervical cancer cells. Oncogene. 2004;23(20):3708–15. [CrossRef].
124. Giger OT, ten Hoopen R, Shorthouse D, Abdullahi S, Bulusu VR, Jadhav S, et al. Preferential *MGMT* hypermethylation in SDH-deficient wild-type GIST. J Clin Pathol. 2024;77(1):34–9. [CrossRef].
125. Wang J, Yuan T, Yang B, He Q, Zhu H. SDH defective cancers: molecular mechanisms and treatment strategies. Cell Biol Toxicol. 2025;41(1):74. [CrossRef].
126. Neves JB, Roberts K, Nguyen JS, El Sheikh S, Tran-Dang MA, Horsfield C, et al. Defining the origin, evolution, and immune composition of SDH-deficient renal cell carcinoma. iScience. 2022;25(11):105389. [CrossRef].
127. Gupta P, Strange K, Telange R, Guo A, Hatch H, Sobh A, et al. Genetic impairment of succinate metabolism disrupts bioenergetic sensing in adrenal neuroendocrine cancer. Cell Rep. 2022;40(7):111218. [CrossRef].
128. Flynn RL, Centore RC, O'Sullivan RJ, Rai R, Tse A, Zhou S, et al. *TERRA* and hnRNPA1 orchestrate an RPA-to-POT1 switch on telomeric single-stranded DNA. Nature. 2011;471(7339):532–6. [CrossRef].
129. Kim W, Ludlow AT, Min J, Robin JD, Stadler G, Mender I, et al. Regulation of the human telomerase gene *TERT* by telomere position effect-over long distances (TPE-OLD): implications for aging and cancer. PLoS Biol. 2016;14(12):e2000016. [CrossRef].
130. Muoio D, Fouquerel E. The alternative lengthening of telomeres pathway through a DNA repair lens: mechanism and therapeutic opportunities. NAR Cancer. 2025;7(4):zcaf056. [CrossRef].
131. Brosnan-Cashman JA, Yuan M, Graham MK, Rizzo AJ, Myers KM, Davis C, et al. ATRX loss induces multiple hallmarks of the alternative lengthening of telomeres (ALT) phenotype in human glioma cell lines in a cell line-specific manner. PLoS One. 2018;13(9):e0204159. [CrossRef].
132. Sanford SL, Welfer GA, Freudenthal BD, Opresko PL. Mechanisms of telomerase inhibition by oxidized and therapeutic dNTPs. Nat Commun. 2020;11:5288. [CrossRef].
133. Peeters MJW, Aehnlich P, Pizzella A, Mølgaard K, Seremet T, Met Ö, et al. Mitochondrial-linked *de novo* pyrimidine biosynthesis dictates human T-cell proliferation but not expression of effector molecules. Front Immunol. 2021;12:718863. [CrossRef].
134. Hubackova S, Davidova E, Boukalova S, Kovarova J, Bajzikova M, Coelho A, et al. Replication and ribosomal stress induced by targeting pyrimidine synthesis and cellular checkpoints suppress p53-deficient tumors. Cell Death Dis. 2020;11:110. [CrossRef].
135. Hino S, Sakamoto A, Nagaoka K, Anan K, Wang Y, Mimasu S, et al. FAD-dependent lysine-specific demethylase-1 regulates cellular energy expenditure. Nat Commun. 2012;3:758. [CrossRef].

136. Garcia-Exposito L, Bournique E, Bergoglio V, Bose A, Barroso-Gonzalez J, Zhang S, et al. Proteomic profiling reveals a specific role for translesion DNA polymerase η in the alternative lengthening of telomeres. Cell Rep. 2016;17(7):1858–71. [CrossRef].
137. Xu M, Senanayaka D, Zhao R, Chigumira T, Tripathi A, Tones J, et al. *TERRA*-LSD1 phase separation promotes R-loop formation for telomere maintenance in ALT cancer cells. Nat Commun. 2024;15:2165. [CrossRef].
138. Pei Z, Liang F, Wang X, Li H. NAD^+ as a central metabolic hub Regulating the hallmarks of aging: mechanisms and therapeutic implications. Mech Ageing Dev. 2026;231:112174. [CrossRef].
139. Roichman A, Elhanati S, Aon MA, Abramovich I, Di Francesco A, Shahar Y, et al. Restoration of energy homeostasis by SIRT6 extends healthy lifespan. Nat Commun. 2021;12:3208. [CrossRef].
140. Kanfi Y, Naiman S, Amir G, Peshti V, Zinman G, Nahum L, et al. The sirtuin SIRT6 regulates lifespan in male mice. Nature. 2012;483(7388):218–21. [CrossRef].
141. Mishra K, Kakhlon O. The crucial role of NAD^+ in mitochondrial metabolic regulation. Biocell. 2025;49(7):1101–23. [CrossRef].
142. Chen RR, Li YY, Wu JW, Wang Y, Song W, Shao D, et al. SIRT6 in health and diseases: from molecular mechanisms to therapeutic prospects. Pharmacol Res. 2025;221:107984. [CrossRef].
143. Simeoni F, Tasselli L, Tanaka S, Villanova L, Hayashi M, Kubota K, et al. Proteomic analysis of the SIRT6 interactome: novel links to genome maintenance and cellular stress signaling. Sci Rep. 2013;3:3085. [CrossRef].
144. Tasselli L, Zheng W, Chua KF. SIRT6: novel mechanisms and links to aging and disease. Trends Endocrinol Metab. 2017;28(3):168–85. [CrossRef].
145. Lombard DB. Sirtuins at the breaking point: SIRT6 in DNA repair. Aging. 2008;1(1):12–6. [CrossRef].
146. Onn L, Portillo M, Ilic S, Cleitman G, Stein D, Kaluski S, et al. SIRT6 is a DNA double-strand break sensor. eLife. 2020;9:e51636. [CrossRef].
147. Li Y, Jin J, Wang Y. SIRT6 widely regulates aging, immunity, and cancer. Front Oncol. 2022;12:861334. [CrossRef].
148. Tennen RI, Bua DJ, Wright WE, Chua KF. SIRT6 is required for maintenance of telomere position effect in human cells. Nat Commun. 2011;2:433. [CrossRef].
149. Robin JD, Ludlow AT, Batten K, Magdinier F, Stadler G, Wagner KR, et al. Telomere position effect: regulation of gene expression with progressive telomere shortening over long distances. Genes Dev. 2014;28(22):2464–76. [CrossRef].
150. Korotkov A, Seluanov A, Gorbunova V. Sirtuin 6: linking longevity with genome and epigenome stability. Trends Cell Biol. 2021;31(12):994–1006. [CrossRef].
151. Sahin E, Colla S, Liesa M, Moslehi J, Müller FL, Guo M, et al. Telomere dysfunction induces metabolic and mitochondrial compromise. Nature. 2011;470(7334):359–65. [CrossRef].
152. Sahin E, DePinho RA. Axis of ageing: telomeres, p53 and mitochondria. Nat Rev Mol Cell Biol. 2012;13(6):397–404. [CrossRef].
153. Wang Y, Wang X, Flores ER, Yu J, Chang S. Dysfunctional telomeres induce p53-dependent and independent apoptosis to compromise cellular proliferation and inhibit tumor formation. Aging Cell. 2016;15(4):646–60. [CrossRef].
154. Lee JH, Hussain M, Kim EW, Cheng SJ, Leung AKL, Fakouri NB, et al. Mitochondrial PARP1 regulates NAD(+)-dependent poly ADP-ribosylation of mitochondrial nucleoids. Exp Mol Med. 2022;54(12):2135–47. [CrossRef].
155. Murata MM, Kong X, Moncada E, Chen Y, Imamura H, Wang P, et al. NAD+ consumption by PARP1 in response to DNA damage triggers metabolic shift critical for damaged cell survival. Mol Biol Cell. 2019;30(20):2584–97. [CrossRef].
156. Jaskelioff M, Muller FL, Paik JH, Thomas E, Jiang S, Adams AC, et al. Telomerase reactivation reverses tissue degeneration in aged telomerase-deficient mice. Nature. 2011;469(7328):102–6. [CrossRef].
157. Li D, Li W, Liao X, Jiang S, Ma M, Hu Z, et al. NAD+-dependent Sirt6 is a key regulator involved in telomere shortening of *in vitro*-cultured preimplantation embryos. Commun Biol. 2025;8:1275. [CrossRef].
158. Burkatovskii D, Bogorodskiy A, Maslov I, Moiseeva O, Chuprov-Netochin R, Smirnova E, et al. Examining transfer of TERT to mitochondria under oxidative stress. Sci Rep. 2024;14:24185. [CrossRef].

159. Lu R, Pickett HA. Telomeric replication stress: the beginning and the end for alternative lengthening of telomeres cancers. Open Biol. 2022;12(3):220011. [CrossRef].
160. Cao C, Gong W, Shuai Y, Rasouli S, Ge Q, Khan A, et al. Canonical and non-canonical functions of the non-coding RNA component (TERC) of telomerase complex. Cell Biosci. 2025;15(1):30. [CrossRef].
161. Santos JH, Meyer JN, Skorvaga M, Annab LA, Van Houten B. Mitochondrial hTERT exacerbates free-radical-mediated mtDNA damage. Aging Cell. 2004;3(6):399–411. [CrossRef].
162. Sharma NK, Reyes A, Green P, Caron MJ, Bonini MG, Gordon DM, et al. Human telomerase acts as a hTR-independent reverse transcriptase in mitochondria. Nucleic Acids Res. 2012;40(2):712–25. [CrossRef].
163. Singhapol C, Pal D, Czapiewski R, Porika M, Nelson G, Saretzki GC. Mitochondrial telomerase protects cancer cells from nuclear DNA damage and apoptosis. PLoS One. 2013;8(1):e52989. [CrossRef].
164. Fujita T, Yuno M, Okuzaki D, Ohki R, Fujii H. Identification of non-coding RNAs associated with telomeres using a combination of enChIP and RNA sequencing. PLoS One. 2015;10(4):e0123387. [CrossRef].
165. Haendeler J, Dröse S, Büchner N, Jakob S, Altschmied J, Goy C, et al. Mitochondrial telomerase reverse transcriptase binds to and protects mitochondrial DNA and function from damage. Arterioscler Thromb Vasc Biol. 2009;29(6):929–35. [CrossRef].
166. Marinaccio J, Rossi E, Micheli E, Udroiu I, Baranzini N, Marcolli G, et al. TERT translocation to mitochondria: exploring its role in mitochondrial homeostasis. PLoS Genet. 2025;21(10):e1011923. [CrossRef].
167. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: an expanding universe. Cell. 2023;186(2):243–78. [CrossRef].
168. Taylor AD, Hathaway QA, Kunovac A, Pinti MV, Newman MS, Cook CC, et al. Mitochondrial sequencing identifies long noncoding RNA features that promote binding to PNPase. Am J Physiol Cell Physiol. 2024;327(2):C221–36. [CrossRef].
169. Azam S, Jouvet N, Jilani A, Vongsamphanh R, Yang X, Yang S, et al. Human glyceraldehyde-3-phosphate dehydrogenase plays a direct role in reactivating oxidized forms of the DNA repair enzyme APE1. J Biol Chem. 2008;283(45):30632–41. [CrossRef].
170. Luhtala N, Parker R. T2 Family ribonucleases: ancient enzymes with diverse roles. Trends Biochem Sci. 2010;35(5):253–9. [CrossRef].
171. Shamloo S, Schloßhauer JL, Tiwari S, Denise Fischer K, Almolla O, Ghebrechristos Y, et al. RNA binding of GAPDH controls transcript stability and protein translation in acute myeloid leukemia. RNA Biol. 2025;22(1):1–23. [CrossRef].
172. Manganelli M, Mazzoldi EL, Ferraro RM, Pinelli M, Parigi M, Ali Mir Aghel S, et al. Progesterone receptor is constitutively expressed in induced Pluripotent Stem Cells (iPSCs). Stem Cell Rev Rep. 2024;20(8):2303–17. [CrossRef].