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Review

Mitochondrial DNA Alterations in HPV-Related Cancers: Emerging Insights and Future Directions

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Abstract

Human papillomavirus (HPV) infection is a leading cause of cervical cancer and a significant contributor to anogenital and oropharyngeal malignancies worldwide. While the oncogenic functions of HPV oncoproteins E6 and E7 in disrupting nuclear tumor suppressor pathways are well established, their influence on mitochondrial biology has only recently emerged as a critical facet of HPV-driven carcinogenesis. This review synthesizes current evidence on the qualitative and quantitative alterations of mitochondrial DNA (mtDNA) and their functional consequences in HPV-associated cancers. We discuss how E6 and E7 modulate mitochondrial dynamics, bioenergetics, and redox balance, contributing to metabolic reprogramming, resistance to apoptosis, and adaptation to tumor microenvironmental stress. We also examine the clinical significance of mtDNA mutations, deletions, and copy number variations as potential biomarkers for diagnosis, prognosis, and therapy response. Advances in multi-omics approaches, high-throughput sequencing, and patient-derived organoid models have accelerated the exploration of mitochondria as therapeutic targets. Integrating mitochondrial profiling into HPV-related cancer research holds promise for identifying novel metabolic vulnerabilities and guiding the development of mitochondria-directed treatment strategies.

Keywords: Human Papillomavirus (HPV); mitochondrial DNA (mtDNA); mitochondrial dysfunction; E6 oncoprotein; E7 oncoprotein; oxidative phosphorylation; mitochondrial dynamics; reactive oxygen species (ROS); metabolic reprogramming; cervical cancer (CC)

1. Introduction

Human papillomavirus (HPV) is a double-stranded DNA virus that infects epithelial cells and is recognized as a major etiological factor in several human malignancies, most notably cervical cancer, which remains the fourth most common cancer among women worldwide [1]. According to the Global Cancer Observatory (GLOBOCAN) 2022 estimates, cervical cancer accounted for over 600,000 new cases and 340,000 deaths globally, with the highest burden in low- and middle-income countries [2]. Beyond the cervix, high-risk HPV types, particularly HPV-16 and HPV-18, are also implicated in the development of anogenital cancers (including vulvar, vaginal, penile, and anal cancers) and a growing proportion of oropharyngeal squamous cell carcinomas (OPSCC), particularly in high-income countries [3,4].

The oncogenic potential of high-risk HPV is largely driven by the persistent expression of viral oncoproteins E6 and E7, which disrupt host tumor suppressor pathways. E6 promotes degradation

of the tumor suppressor p53 via the E6AP ubiquitin ligase, while E7 inactivates the retinoblastoma protein (pRb), leading to uncontrolled cell cycle progression and inhibition of apoptosis [5,6]. These viral-mediated mechanisms contribute to genomic instability, deregulation of the DNA damage response, and accumulation of somatic mutations that drive carcinogenesis [7]. While the nuclear genomic consequences of HPV infection have been extensively studied, emerging evidence suggests that mitochondrial dysfunction and alterations in mitochondrial DNA (mtDNA) may also play a critical role in HPV-associated tumorigenesis [8,9].

Mitochondria are essential organelles involved in oxidative phosphorylation (OXPHOS), ATP production, regulation of apoptosis, calcium signaling, and reactive oxygen species (ROS) generation [10]. Unlike nuclear DNA, mitochondrial DNA is a circular, double-stranded molecule that encodes 13 essential protein subunits of the electron transport chain, along with 22 tRNAs and 2 rRNAs [11]. mtDNA is particularly vulnerable to damage due to its proximity to the inner mitochondrial membrane where ROS are generated, the absence of protective histones, and limited DNA repair mechanisms [12]. Alterations in mtDNA such as point mutations, large deletions, copy number changes, and transcriptional dysregulation—have been increasingly associated with various cancers, including breast, colorectal, and head and neck cancers [13,14].

Recent studies have begun to reveal a link between HPV infection and mitochondrial dysfunction. HPV oncoproteins have been shown to interact with mitochondrial pathways, leading to increased ROS production, metabolic reprogramming, and resistance to apoptosis [15–17]. Notably, transcriptomic and proteomic analyses of HPV-positive cancers have identified significant changes in mitochondrial gene expression profiles, suggesting a potential role for mtDNA alterations in HPV-mediated oncogenesis [8,18,19]. These findings align with the broader concept that mitochondrial dysfunction contributes to cancer progression through the Warburg effect, redox imbalance, and evasion of cell death [20].

Given the central role of mitochondria in cellular homeostasis and stress responses, understanding mtDNA alterations in HPV-related cancers offers a promising yet underexplored avenue for biomarker discovery and therapeutic targeting. mtDNA mutations and copy number variations may serve as indicators of mitochondrial stress and tumor aggressiveness, while altered expression of mitochondria-encoded genes could inform patient stratification or predict treatment responses [21]. Furthermore, with the advent of high-throughput sequencing and advanced model systems such as 3D organoids and patient-derived spheroids, it is now feasible to investigate mtDNA changes in a biologically relevant context [22].

This review aims to summarize current knowledge on mitochondrial DNA alterations in HPV-related cancers, with a focus on their biological consequences, clinical implications, and future potential as therapeutic targets. By integrating recent findings from transcriptomics, mitochondrial biology, and HPV research, we seek to provide a comprehensive perspective on this emerging field and highlight opportunities for translational research.

2. HPV and Mitochondrial Function

Human papillomavirus (HPV) oncoproteins, particularly E6 and E7, exert multifaceted effects on mitochondrial function that contribute to carcinogenesis [18]. Beyond their role in oxidative phosphorylation (OXPHOS) and ATP production, mitochondria are central regulators of apoptosis, redox homeostasis, and metabolic adaptation. By targeting these organelles, HPV reshapes cellular metabolism, survival capacity, and stress responses to support persistent infection and malignant transformation. HPV oncoproteins' interaction with mitochondrial function are given in Table 1.

2.1. Modulation of Mitochondrial Dynamics

Mitochondrial dynamics, namely the coordinated balance between fission and fusion, is essential for maintaining mitochondrial morphology, distribution, and function. These processes are regulated by GTPases such as dynamin-related protein 1 (DRP1) and fission protein 1 (FIS1) for fission, and mitofusins (MFN1, MFN2) and optic atrophy protein 1 (OPA1) for fusion [23,24]. Evidence from HPV-positive models indicates that infection can alter mitochondrial function and homeostasis, including changes in bioenergetic efficiency and apoptotic susceptibility, potentially

affecting the balance of mitochondrial fission and fusion [18]. While the detailed molecular connection between E6 and the fission–fusion machinery remains unresolved, E6's capacity to destabilize mitochondrial integrity indirectly through p53 degradation and suppression of mitochondrial biogenesis regulators like PGC-1 α suggests a plausible mechanism of influence [9,25]. In this context, studies in cervical cancer cells have shown that pharmacological modulation of mitochondrial dynamics, like silibinin treatment, can induce excessive mitochondrial fragmentation, upregulate DRP1 expression without altering FIS1, and promote mitochondrial dysfunction, including reduced ATP production, loss of mitochondrial membrane potential, and increased ROS generation [26]. These mitochondrial changes were accompanied by G2/M cell cycle arrest, and DRP1 knockdown was able to reverse both the mitochondrial fragmentation and cell cycle effects, underscoring the central role of DRP1-mediated fission in regulating cervical cancer cell proliferation and survival. E7 exerts its effects more clearly through degradation of pRb and activation of E2F-responsive genes, which can alter the expression of nuclear-encoded mitochondrial proteins and regulators of organelle morphology [27]. Notably, E2F1 has been shown to bind to the promoter of MFN2 and activate its transcription, with transcription factor SP1 also binding to the same promoter region. E2F1 and SP1 can form a complex at the MFN2 promoter, and E2F1-mediated regulation of MFN2 appears to influence both mitochondrial fusion and mitophagy, potentially linking E7-driven transcriptional reprogramming to the control of mitochondrial quality and turnover [28]. In some settings, E7 has also been associated with increased mitophagy, leading to selective removal of mitochondria and reshaping of the cellular mitochondrial pool [29]. Together, these alterations create a fragmented and metabolically reprogrammed mitochondrial network that supports the energetic and biosynthetic demands of HPV-transformed cells.

2.2. Impact on Reactive Oxygen Species (ROS) Generation and Oxidative Stress

Disruption of mitochondrial dynamics in HPV-positive cells is closely linked to altered redox homeostasis, with fragmented mitochondria and compromised electron transport chain (ETC) integrity, particularly at complexes I and III, increasing electron leakage and driving excessive reactive oxygen species (ROS) production [30]. While physiological ROS levels act as secondary messengers that activate pro-survival and pro-proliferative pathways, including NF- κ B and HIF-1 α signaling, chronic overproduction of ROS imposes sustained oxidative stress that damages nuclear DNA, mitochondrial DNA (mtDNA), lipids, and proteins, thereby fostering genomic instability [31]. The E6 oncoprotein exacerbates this oxidative environment by impairing p53-mediated transcription of antioxidant enzymes such as superoxide dismutase 2 (SOD2) and catalase, weakening the cell's ability to neutralize ROS [32]. E7 contributes indirectly, as its dysregulation of cell cycle progression and metabolic flux increases mitochondrial workload, further promoting electron leakage [33]. Persistent oxidative stress not only accelerates mutagenesis but also reinforces malignant progression by activating redox-sensitive transcription factors and survival pathways, creating a tumor-favorable oxidative environment that supports both HPV persistence and oncogenic transformation [34].

2.3. Links Between HPV Infection, Metabolic Reprogramming, and Mitochondrial Dysfunction

HPV-induced mitochondrial alterations are closely intertwined with metabolic reprogramming, a hallmark of HPV-associated cancers. Both E6 and E7 promote a shift away from oxidative phosphorylation toward aerobic glycolysis, enabling rapid ATP production while redirecting metabolic intermediates toward biosynthetic pathways that support proliferation [35,36]. This metabolic shift is reinforced by oxidative stress-mediated stabilization of HIF-1 α , which upregulates key glycolytic enzymes such as hexokinase 2 (HK2) and pyruvate kinase M2 (PKM2), along with glucose transporters like GLUT1, thereby increasing glucose uptake and glycolytic flux [37–39]. Reduced mitochondrial respiratory efficiency, which is stemming from structural damage to cristae, disruption of the electron transport chain, and altered expression of mitochondrial proteins, diminishes ATP yield from oxidative pathways and increases the cell's dependency on glycolysis [40]. (Hongxiang Du et al. 2025) The resulting excess lactate production acidifies the tumor microenvironment, a change that facilitates immune evasion, promotes extracellular matrix remodeling, and supports angiogenesis [41,42]. Furthermore, E6/E7-mediated modulation of

mitochondrial biogenesis regulators such as PGC-1 α and TFAM can alter mitochondrial DNA (mtDNA) copy number and transcription, exacerbating the loss of oxidative capacity and contributing to long-term mitochondrial dysfunction. Together, these changes integrate mitochondrial impairment into the broader oncogenic program of HPV, coupling metabolic flexibility with tumor-promoting adaptations in the microenvironment [25,43].

Table 1. Crosstalk Between HPV Oncoproteins and Mitochondrial Function in HPV-Associated Cancers.

Oncoprotein	Direct Mitochondrial Target / Effect	Indirect Pathway or Regulatory Mechanism	Resulting Mitochondrial or Cellular Effect	Reference(s)
E6	Bak degradation	p53 degradation → ↓ transcription of antioxidant enzymes (SOD2, catalase)	Inhibits MOMP, prevents cytochrome c release, reduces apoptosis; weakens ROS detoxification	Leverrier et al., 2007; Arash et al., 2024
E6	—	p53 loss → ↓ miR-34a → ↑ LDHA	Enhances aerobic glycolysis at expense of OXPHOS	Zhang et al., 2016
E6	—	p53 loss → ↓ PGC-1 α and ERR α	Suppresses mitochondrial biogenesis, reduces oxidative capacity	Sannigrahi et al., 2022
E6	—	Activation of Nrf2 and FoxO3a in HPV16 E6 cells	↑ Expression of antioxidant enzymes (SOD1, SOD2, catalase) → improved oxidative stress tolerance	Cruz-Gregorio et al., 2019
E7	ATP5B binding	—	↑ Mitochondrial respiration, ↑ spare respiratory capacity, ↑ ATP production	Kirschberg et al., 2020
E7	—	pRb degradation → E2F activation → altered expression of mitochondrial dynamics genes	Modifies nuclear-encoded mitochondrial protein expression; impacts mitochondrial morphology and turnover	Tian et al., 2021
E7	—	E2F1 + SP1 complex binds MFN2 promoter	Regulates mitochondrial fusion and mitophagy	Bucha et al., 2019
E7	—	—	Associated with increased	Thomas et al., 2016

			mitophagy, selective mitochondrial removal	
E2	—	Cristae disruption, ↑ ROS production, HIF- 1α stabilization	Shifts metabolism toward glycolysis, promotes angiogenesis and hypoxia adaptation	Lai et al., 2013
E2	—	Alters antisense mitochondrial RNAs (ASncmtRNAs)	Affects cell cycle regulation and nuclear transcription via miRNA sponging (e.g., miR-620 targeting PML)	Villota et al., 2012

Table 1. Crosstalk between HPV oncoproteins and mitochondrial function. Interactions include direct targeting of mitochondrial proteins and indirect modulation via nuclear transcriptional programs, microRNA regulation, or signaling pathways. Abbreviations: MOMP, mitochondrial outer membrane permeabilization; OXPHOS, oxidative phosphorylation; ROS, reactive oxygen species; MFN2, mitofusin 2; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; ERRα, estrogen-related receptor alpha; ASncmtRNA, antisense non-coding mitochondrial RNA. Reported effects may vary between HPV genotypes, cell types, and experimental conditions.

3. Qualitative and Quantitative Alterations in the Mitochondrial Genome

Susceptibility to HPV infection and progression of malignancies associated with HPV seem to rely on the mitochondrial genetic background, both qualitative and quantitative. In their study, Feng et al. (2016) stratified cervical cancer patients by both mtDNA content and the mtDNA 10398 polymorphism. The presence of the 10398 polymorphism and elevated mtDNA content exhibited the worst prognosis, relating to 5 to 8 years lower overall survival (OS). While the 10398A allele itself was not associated with OS, it was linked to increased mtDNA content, and the 10398G allele was found more frequently in HPV-positive patients. Notably, a positive correlation between HPV-18 infection and mtDNA content was found in patients aged < 45 years [44].

Guardado-Estrada et al. (2012) investigated the role of mtDNA haplogroups in CC. In the Amerindian mtDNA haplogroups, B2 conferred increased risk especially for HPV-related CC cases and A2 exerted a protective effect. This was accompanied by haplogroup-specific overexpression of mitochondrial tRNA genes and regulatory polymorphisms like 6183C and 16189C that may influence replication and transcription [45]. Likewise, Zhai et al. (2011) found that the C150T polymorphism was significantly associated with HPV infection and CC among the 90 identified polymorphic sites in the D-loop control region. The authors believe this change disrupts the origin of replication in the heavy strand of mtDNA and modifies the mitochondrial replication and OXPHOS, leading to increased malignant transformative capacity. Interestingly, for the mtDNA copy number, there was no significant relationship between CC patients. It was also found to be independent of the C150T genotype [46].

Sharma et al. (2005) also reported 55 novel mutations within the D-loop in cervical tumors, primarily base substitutions and indels, with significant correlation with HPV infection (p < 0.05). mtDNA microsatellite instability (mtMSI) was also detected in 12 out of 19 tumors, located mostly in the C-stretch in positions 303–315 (11/19), a known replication primer binding site [47]. Warowicka et al. (2013) identified a total of 62 nucleotide changes across L-SIL (n=28), H-SIL (n=30), CC (n=29), and control (n=29) tissues, where 13 mutations were uniquely present in all disease stages but absent in controls, suggesting a role in early to progressive carcinogenesis. The accumulation of a common

4,977 bp deletion was also described related with disease progression, suggesting that HPV infection may either promote mtDNA damage or choose to persist in cells with compromised mitochondrial genomes [19].

Changes in mtDNA copy number are a recurring but context-dependent feature. In cervical cancer, Sun et al. (2020) and Al-Awadhi et al. (2023) reported significantly elevated mtDNA copy numbers (mtCN), particularly in high-grade lesions (highest in SCC/HSIL cases) and HPV16-positive cases, with a dose-response relationship to cancer risk and suggesting a correlation of mtCN with lesion severity. This increase was also seen in HPV-negative lesions, suggesting oxidative stress may be an additional driver [48,49]. In contrast, Kabekkodu et al. (2014) and Mondal et al. (2013) observed mtDNA depletion in cervical and oral squamous cell carcinomas, respectively, where depletion correlated with tumor stage [50,51]. Mizumachi et al. (2008) similarly found reduced and more variable mtDNA content in HPV-transformed prostate cancer cells compared to HPV-transformed normal epithelial cells [52]. Mondal et al (2013) showed that a significant difference between the mtDNA content was present between HPV-positive & negative individuals, but the depletion of mtDNA in OSCC was associated with tumor progression and risk regardless of HPV status, similar to the mentioned findings in prostate cancer [51].

Kabekkodu et al. (2014) also revealed that 65% of mtDNA from CC samples belonged to haplogroup M, compared to 16% in non-malignant tissues. In contrast, haplogroup U was more common in controls (50% vs. 10%). The D-loop region exhibited 216 variants, including 29 novel and 4 disease-associated mutations. Alterations were predominantly base substitutions and indels, with T16172T and D310 repeat as hotspot sites. Overall mutational burden was not directly associated with HPV status, but specific variants such as A73G were significantly more common in HPV-positive samples and haplogroup M was overrepresented among HPV-positive individuals. They also reported 59 non-synonymous and 136 synonymous variants in mtDNA coding genes. Synonymous changes were common in ND5, ND4, Cytb, ND2, and ND1; while non-synonymous changes clustered in ATP6, Cytb, ND5, and ND3. These were predicted to destabilize the structure of Complex I, III, and V subunit proteins [50].

In addition, Hao et al (2019) identified somatic mtDNA mutations in all six HPV-positive recurrent recurrent respiratory papillomatosis (RRP) tissue samples, averaging 1.8 mutations per sample (all heteroplasmic). Among the nine total mutations two were previously unreported, nonsynonymous mutations: A336T in COI and G215D in ND5. The authors claim these could be functionally significant due to the evolutionary conservation of the affected residues [53]. Likewise, Warowicka et al. (2020) detected 12 somatic point mutations in the mitochondrial ND1 gene in HPV-positive precancerous and cancerous cervical tissues. No mutations were observed in control tissues and were present only in HPV+ cases. 8/12 mutations were missense, altering protein function (p.T67A, p.V11A, p.M156K). All mutations were homoplasmic, suggesting complete dominance of mutated mtDNA in affected cells. A novel mutation, p.M156K, was identified in the transmembrane domain IV [54].

In a case study of HPV53-positive bilateral multinodular oncocytic hyperplasia (MNOH) of the parotid glands, Kurelac et al (2014) revealed the bilateral presence of a novel homoplasmic mtDNA mutation located in the ND2 subunit of complex I, m.4561T>A [55]. These observations suggest that the mtDNA copy number and qualitative mtDNA alterations such as base substitutions, indel mutations, and haplogroups are interconnected and may contribute to persistent HPV infection and disease progression. Findings on the changes in mtDNA in HPV-related cancers is summarized in Table 2 and illustrated in Figure 1.

Table 2. Qualitative and Quantitative mtDNA Alterations in HPV-Related Cancers.

Alteration Type	Gene / Region	Specific Mutation / Variant	HPV Status Association	Cancer Type / Lesion Stage	Functional Impact / Proposed Mechanism	Reference (s)
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Point mutation	ND1	p.M156K	HPV+ only	Precancerous & cervical cancer	Alters Complex I subunit, reduces proton pumping efficiency	Warowicka et al., 2020
Point mutation	ND4	T170P	HPV+	Cervical cancer	Complex I destabilization	Kabekkodu et al., 2014
Point mutation	ND2	V31E	HPV53+	Multinodular oncocyctic hyperplasia (parotid)	Complex I destabilization	Kurelac et al., 2014
Point mutation	COI	A336T	HPV+	Recurrent respiratory papillomatosis	May disrupt ETC function due to conserved residue change	Hao et al., 2019
Point mutation	ND5	G215D	HPV+	Recurrent respiratory papillomatosis	May disrupt ETC function due to conserved residue change	Hao et al., 2019
D-loop polymorphism	Control region	C150T	HPV+	Cervical cancer	Alters replication origin, modifies OXPHOS	Zhai et al., 2011
D-loop mutations	Control region	55 novel mutations	HPV+	Cervical cancer	May disrupt replication & transcription regulation	Sharma et al., 2005
D-loop mutations	Control region	216 variants (29 novel)	Mixed HPV status	Cervical cancer	Multiple substitutions & indels; T16172T & D310 repeat hotspots	Kabekkodu et al., 2014
mtDNA deletion	Multiple genes	Common 4.977 bp deletion	HPV+	LSIL → HSIL → CC progression	Loss of ETC genes; ↑ ROS & genomic instability	Warowicka et al., 2013
Copy number ↑	—	—	HPV16+ (highest in SCC/HSIL)	High-grade lesions & SCC	Possible compensatory mechanism for OXPHOS despite mutations	Sun et al., 2020; Al-Awadhi, 2023; Warowicka et al., 2013
Copy number ↓	—	—	Mixed HPV status	CC, OSCC, HPV-transformed prostate cancer	Favors glycolysis; reduced oxidative capacity	Kabekkodu et al., 2014; Mondal et al., 2013; Mizumac

Haplogroup association	mtDNA haplogroups	Haplogroup B2 ↑, A2 protective	HPV+	Cervical cancer	Influences mitochondrial tRNA gene expression & replication	hi et al., 2008 Guardado-Estrada et al., 2012
Haplogroup association	mtDNA haplogroups	Haplogroup M ↑, Haplogroup U ↓	HPV+	Cervical cancer	Overrepresentation of M in HPV+ cases; associated with specific variants (e.g., A73G)	Kabekkodu et al., 2014

Table 2. Summary of qualitative and quantitative mitochondrial DNA alterations reported in HPV-associated cancers. Abbreviations: CC, cervical cancer; OSCC, oral squamous cell carcinoma; HSIL, high-grade squamous intraepithelial lesion; L-SIL, low-grade squamous intraepithelial lesion; mtCN, mitochondrial DNA copy number; mtMSI, mitochondrial microsatellite instability; MNOH, multinodular oncocytic hyperplasia; OXPHOS, oxidative phosphorylation. Reported effects reflect associations observed in clinical samples or experimental models; causality between HPV infection and specific mtDNA alterations should be interpreted with caution due to potential confounding factors such as oxidative stress and host genetic background.

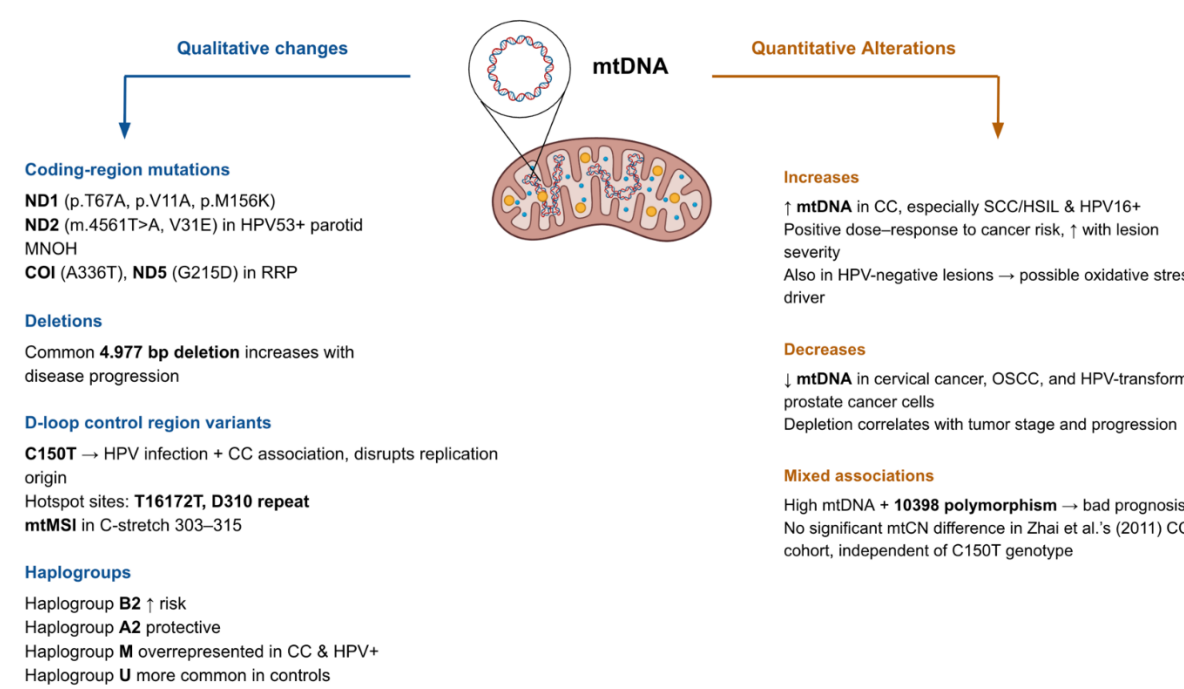


Figure 1. Qualitative and Quantitative Alterations of mtDNA in HPV-Associated Cancers.

Coding-region mutations (e.g., ND1, ND2, COI, ND5), deletions (such as the common 4.977 bp deletion), D-loop variants (C150T, T16172T, D310 repeat), and haplogroup associations contribute to HPV-driven carcinogenesis. Quantitative alterations include both increases and decreases in mtDNA copy number, with changes correlating with cancer risk, tumor stage, and progression. Mixed associations, such as the 10398 polymorphism, further highlight the prognostic complexity of mtDNA alterations in HPV-related disease.

4. Functional Consequences of mtDNA Alterations

4.1. Effects on Oxidative Phosphorylation (OXPHOS) and Cellular Energy Metabolism

Mitochondrial DNA (mtDNA) alterations in HPV-associated disease often affect genes encoding key components of the electron transport chain (ETC), disrupting oxidative phosphorylation.

Pathogenic coding-region mutations such as ND1 p.M156K, ND4 T170P, and ND2 V31E impair structural stability of Complex I subunits, leading to reduced proton pumping efficiency and compromised ATP synthesis. Such defects can decrease respiratory chain capacity and promote compensatory metabolic shifts [50,54,55].

Altered mtDNA copy number also impacts OXPHOS. In cervical lesions, elevated mtDNA content may represent a compensatory mechanism to maintain ATP production despite accumulating mutations or deletions [19,48,49]. In contrast, mtDNA depletion observed in cervical and oral squamous cell carcinomas, as well as in HPV-transformed prostate cancer cells, can impair oxidative capacity and favor a glycolytic phenotype [50–52].

Viral oncoproteins directly modulate mitochondrial metabolism. The E7-ATP5B interaction enhances mitochondrial respiration, spare respiratory capacity, and ATP production in HPV-positive cancers, potentially improving cellular fitness [56]. Conversely, HPV-18 E2 disrupts mitochondrial cristae, increases ROS, and promotes a shift toward aerobic glycolysis via HIF-1α stabilization [57]. E6-mediated p53 degradation reduces miR-34a, derepressing LDHA and enhancing glycolysis at the expense of oxidative metabolism [58].

Figure 2 shows how HPV oncoproteins contribute to mitochondrial metabolic dysfunction.

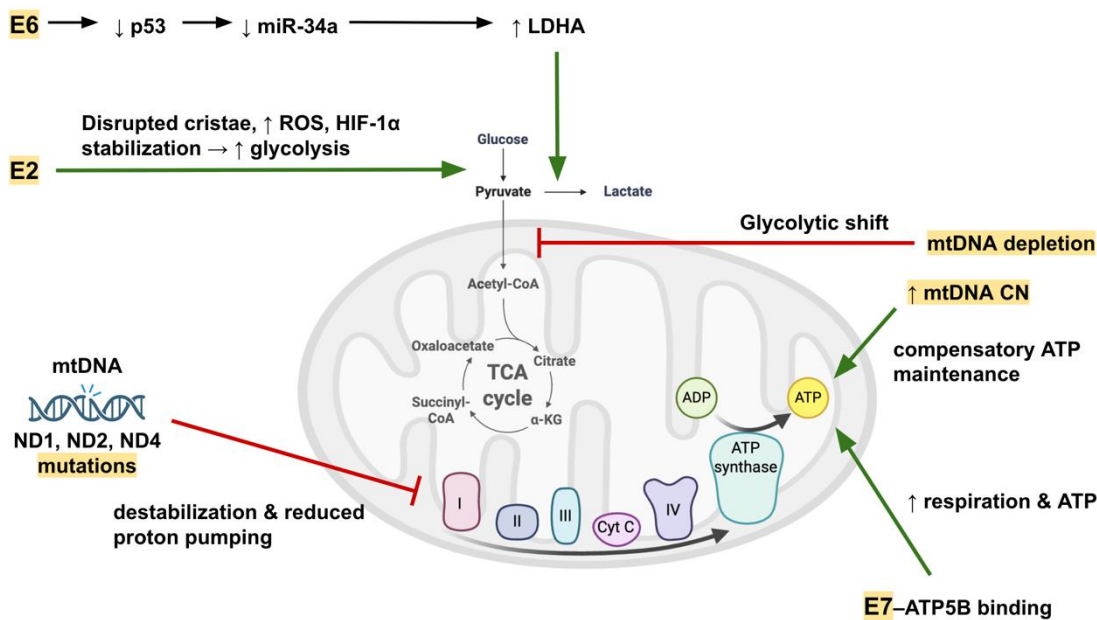


Figure 2. Pathways Linking HPV Oncoproteins to Mitochondrial Dysfunction and Metabolic Adaptations.

E6 promotes glycolytic shift through p53/miR-34a-mediated upregulation of LDHA, while E2 disrupts cristae integrity, increases ROS, and stabilizes HIF-1α. E7 interacts with ATP5B to influence ATP production. mtDNA mutations (ND1, ND2, ND4) destabilize Complex I and impair proton pumping, whereas mtDNA copy number changes (depletion or compensatory increase) alter ATP synthesis. These alterations collectively shift energy metabolism toward glycolysis while maintaining ATP levels.

4.2. Mitochondrial-Driven Apoptosis Resistance and Cancer Progression

HPV exploits mitochondrial pathways to inhibit apoptosis and promote cancer cell survival. E6 targets and degrades Bak, preventing mitochondrial outer membrane permeabilization (MOMP), cytochrome c release, and activation of both caspase-dependent and independent death pathways [59]. Accumulated mtDNA mutations and deletions exacerbate ROS production, creating a self-reinforcing loop of oxidative stress and genomic instability [54]. This pro-oxidant environment can activate antioxidant transcription factors such as Nrf2 and FoxO3a, with increased expression of downstream enzymes (SOD1, SOD2, catalase) in HPV16 E6 cells, enhancing stress tolerance [60]. Mitochondrial function also influences apoptosis sensitivity in a cell line-specific manner. In

oxidative stress-induced apoptosis, SiHa cells release cytochrome c and activate caspase-9/3, while CaSki cells exhibit Bax/Bcl-XL modulation without cytochrome c release, suggesting differences in mitochondrial permeabilization threshold [61]. Progressive accumulation of large deletions, such as the common 4.977 bp loss, correlates with transition from low-grade SIL to cervical cancer, implicating mitochondrial genome damage in disease progression [19].

4.3. Crosstalk Between mtDNA Changes and Nuclear Gene Expression

Mitochondrial dysfunction can trigger retrograde signaling to the nucleus, altering gene expression programs relevant to cancer progression and therapy response. ETC impairment and mtDNA mutations can activate nuclear-encoded antioxidant defenses or repress mitochondrial biogenesis regulators such as PGC-1 α and its co-activator ERR α , modulating oxidative metabolism and redox homeostasis [25,60]. ROS overproduction can stabilize HIF-1 α , driving nuclear expression of glycolytic (PDK1, CAIX) and angiogenic (VEGF) genes that facilitate adaptation to hypoxia. Viral interference with microRNA networks also connects mtDNA status to nuclear metabolism: E6-driven p53 loss downregulates miR-34a, releasing repression of LDHA and reinforcing glycolytic programming [57,58,62]. Mitochondrial non-coding RNAs participate in this crosstalk. E2-mediated downregulation of antisense mitochondrial RNAs (ASncmtRNAs) and induction of SncmtRNA-2 may influence cell cycle regulation and indirectly affect nuclear transcription through miRNA sponging (e.g., miR-620 targeting PML) [63]. Finally, mitochondrial metabolic state directly influences nuclear programs controlling therapy sensitivity: high OXPHOS activity and antioxidant capacity predict cisplatin and radiation resistance, while high full-length E6 expression suppresses these pathways, increasing sensitivity [25].

The functional consequences of mtDNA changes are presented in Table 3.

Table 3. Functional Consequences of mtDNA Alterations in HPV-Associated Cancers.

Functional Domain	Mechanism Affected	Key Examples / Alterations	Effect on Cellular Physiology	Reference(s)
Oxidative phosphorylation efficiency	Complex I subunit mutations reduce proton pumping efficiency	ND1 p.M156K, ND4 T170P, ND2 V31E	↓ ETC function, ATP depletion, impaired OXPHOS	Warowicka et al., 2020; Kabekkodu et al., 2014; Kurelac et al., 2014
Oxidative phosphorylation efficiency	mtDNA depletion in tumors	CC, OSCC, HPV-transformed prostate cancer	↓ OXPHOS capacity, ↑ glycolytic phenotype	Kabekkodu et al., 2014; Mondal et al., 2013; Mizumachi et al., 2008
Compensatory OXPHOS maintenance	mtDNA copy number increase	HPV16+ high-grade lesions, SCC	Maintains ATP production despite mtDNA mutations/deletions	Sun et al., 2020; Al-Awadhi, 2023; Warowicka et al., 2013
ROS homeostasis	mtDNA deletions and missense mutations increase ROS	Common 4.977 bp deletion, ND1 p.M156K	↑ ROS, oxidative stress loop, promotes genomic instability	Warowicka et al., 2013; Warowicka et al., 2020
Apoptosis regulation	Direct oncoprotein targeting of mitochondrial apoptosis factors	E6 → Bak degradation	Prevents MOMP, inhibits cytochrome c release, suppresses caspase activation	Leverrier et al., 2007

Apoptosis regulation	Cell line-specific mitochondrial permeabilization	Cytochrome c release in SiHa but not CaSki	Differential sensitivity to oxidative stress-induced apoptosis	Singh et al., 2008
Metabolic reprogramming	Viral oncoprotein regulation of glycolytic enzymes and transporters	E6 → p53 loss → ↓ miR-34a → ↑ LDHA; E2 → HIF-1α stabilization	Favors aerobic glycolysis (Warburg effect), ↑ lactate production	Zhang et al., 2016; Lai et al., 2013
Retrograde signaling to nucleus	Suppression of mitochondrial biogenesis regulators	PGC-1α & ERRα repression	↓ mitochondrial biogenesis, altered oxidative metabolism	Sannigrahi et al., 2022
Retrograde signaling to nucleus	Activation of nuclear antioxidant programs	Nrf2, FoxO3a activation in HPV16 E6 cells	↑ SOD1, SOD2, catalase expression, improved oxidative stress tolerance	Cruz-Gregorio et al., 2019
Angiogenesis & hypoxia adaptation	ROS-mediated HIF-1α stabilization	Induction of VEGF, PDK1, CAIX	Promotes angiogenesis, glycolysis, and tumor adaptation to hypoxia	Lai et al., 2013
MicroRNA-mediated regulation	Viral oncoproteins alter miRNA-mitochondria cross-talk	E6-mediated p53 loss → ↓ miR-34a; E2 alters ASncmtRNA	Reinforces glycolysis, affects cell cycle regulation	Zhang et al., 2016; Villota et al., 2012

Table 3. Functional consequences of mitochondrial DNA alterations in HPV-associated cancers. Listed mechanisms reflect both direct effects of mtDNA mutations or copy number changes and indirect effects mediated by HPV oncoproteins. Abbreviations: ETC, electron transport chain; MOMP, mitochondrial outer membrane permeabilization; OXPHOS, oxidative phosphorylation; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor; PDK1, pyruvate dehydrogenase kinase 1; CAIX, carbonic anhydrase IX; ASncmtRNA, antisense non-coding mitochondrial RNA. Functional outcomes are based on reported experimental or clinical observations, though mechanistic pathways may overlap and vary by tumor type or cellular context.

5. Mitochondria-Directed Therapeutic Strategies and Translational Opportunities in HPV-Associated Cancers

5.1. Mitochondria-Targeted Delivery and Metabolic Modulation

Mitochondria-targeted therapeutics are emerging as a promising strategy in HPV-related and other cancers, with several delivery approaches under development. Liposomes, polymeric and organic nanoparticles that are functionalized using moieties with mitochondrial tropism like triphenylphosphonium (TPP), dequalinium (DQA), and mitochondrial penetrating peptides (MPPs), are demonstrating better pharmacological efficacy than their untargeted counterparts. Their advantage derives from being able to overcome the otherwise impermeable mitochondrial membrane [64]. A green, carrier-free nanoparticle platform was also developed by co-assembling berberine and catechin (BBR-CC NPs), which exhibited not only improved cellular uptake but also showed synergistic enhancement of ROS accumulation, mitochondrial membrane depolarization, and apoptotic signaling in HeLa cells. This highlights the potential of self-assembled phytochemical nanotherapeutics [65].

Metabolic vulnerabilities in tumors can also be exploited using complementary drugs such as sorafenib and metformin through inhibiting mitochondrial respiratory complexes, reducing ATP synthesis and inducing apoptosis, while also exerting immunomodulatory effects on the tumor

microenvironment [66]. Metabolic addictions such as glutamine, arginine, fatty acid, and glycolytic pathways can also be targeted as parallel approaches. In head and neck cancers, strategies ranging from amino acid depletion therapies to hypoxia-inducible factor (HIF) inhibitors and hypoxia-responsive nanocarriers resulted in impaired tumor growth and enhanced radiosensitivity or chemosensitivity [67]. Supporting this approach, metabolic profiling of HPV-positive and HPV-negative HNSCC cells by Li et al. (2023) revealed that HPV-positive tumors (e.g., HNSCC26) exhibit lower oxidative phosphorylation capacity compensated by glycolysis and an increased kynurenine/tryptophan ratio, implying therapeutic vulnerabilities in glycolytic and IDO pathways, whereas HPV-negative tumors displayed greater metabolic flexibility [68]. Together, these diverse interventions emphasize the importance of mitochondrial function in cancer therapy, highlighting both novel delivery technologies and metabolic pathway modulation as convergent strategies for overcoming resistance and improving therapy outcomes.

5.2. Oxidative Stress, ROS, and Mitochondria-Mediated Apoptosis

Beyond biomarkers, mitochondria are now targeted directly with a wide arsenal of natural and synthetic agents, as comprehensively summarized by Cruz-Gregorio et al. (2023), who highlighted compounds such as rotenone, berberine, curcumin, EGCG, and staurosporine, along with synthetic derivatives like TPT-benzimidazolethiol and atovaquone, all of which induce mitochondrial apoptosis through mechanisms including ROS generation, $\Delta\Psi_m$ loss, cytochrome c release, and caspase activation, while mitochondrial transplantation was suggested as a futuristic biotherapy [30]. Krishnamoorthy et al. (2024) also introduced plumbagin as a promising lead compound that disrupted mitochondrial membrane potential, induced apoptosis, blocked EMT and clonogenesis, and sensitized HPV-positive and HPV-negative cervical carcinoma cells to radiotherapy by binding stably to EGFR and attenuating EGF-driven resistance mechanisms [69]. Other small molecules, such as gamitrinibs (mitochondria-targeted HSP90 inhibitors), imipridones, and pro-oxidants like elesclomol, further disrupt mitochondrial bioenergetics or promote ROS-mediated apoptosis, offering potential to sensitize resistant glioblastoma cells to chemotherapy [70]. Findings such as these have the potential to be applied into different types of tumors. Additional evidence highlights how mitochondrial dynamics can be therapeutically manipulated in HPV-related cancers and their models. In cervical carcinoma cells, metabolic stress combined with complex I inhibition using low-dose rotenone enhanced ROS generation, stabilized p53, and shifted HeLa cells toward either senescence or apoptosis depending on glucose availability, underscoring the potential of combining metabolic restriction with mitochondria-targeting agents as a context-dependent therapeutic approach [71]. Complementing experimental plant-based mitochondrial inhibitors, Sharafabad et al. (2024) demonstrated the efficacy of *Clostridium novyi*-NT spores in HPV-positive cervical cancer models, where spore germination selectively colonized hypoxic tumor regions, triggered cytochrome c release, Bax upregulation, caspase-3 activation, and reduced HIF-1 α /VEGF expression, ultimately inducing mitochondrial apoptosis and tumor regression [72]. Adding to these findings, Mishra et al. (2025) reviewed the critical role of oxidative stress and antioxidants in the pathogenesis and treatment of cervical intraepithelial neoplasia (CIN) and cervical cancer. They demonstrated that both enzymatic (SOD, CAT, GPx) and non-enzymatic (GSH, vitamins, polyphenols) antioxidants modulate ROS homeostasis, with compounds like quercetin, resveratrol, and curcumin showing potent pro-apoptotic and anti-HPV effects via regulation of mitochondrial and signaling pathways [73]. Their findings highlight how antioxidant-rich interventions can both alleviate therapy-induced toxicity and serve as adjuvant or preventive strategies in HPV-driven malignancies. Together, these studies reinforce the multifaceted potential of mitochondria-centered ROS manipulation through synthetic mitochondrial inhibitors, phytochemicals, bacterial oncolytic agents and antioxidants as a versatile approach to promote apoptosis and overcome resistance with the aim of improving therapeutic outcomes in HPV-associated cancers.

5.3. Translational and Advanced Therapeutic Platforms

Recent advances continue to broaden the therapeutic and diagnostic landscape of mitochondria in HPV-related cancers. Van der Pol et al. (2023) demonstrated that circulating tumor-derived

mtDNA can be detected in plasma and that its abundance and fragmentation patterns differ from normal mtDNA, with correlations to tumor fraction and potential for improving cancer detection when combined with copy number or mutation data [74]. Likewise, on a biomarker level, a meta-analysis has confirmed that altered mtDNA copy number is associated with increased head and neck squamous cell carcinoma risk, with a non-linear dose–response pattern, supporting the use of mitochondrial genomic alterations as predictive markers for HPV-associated cancers [75]. At a broader translational level, Aminuddin et al. (2025) emphasized the significance of mtDNA alterations in HNSCC, highlighting therapeutic strategies such as metformin, dichloroacetate, melatonin, mitochondrial transplantation, and mitoCas9-based genome editing, while stressing the importance of integrating mtDNA datasets into precision oncology [76]. Preclinical models of HPV-related head and neck cancers further demonstrate that chemoradiation, while suppressing tumor volume and inflammatory cytokine expression, induces broad alterations in mitochondrial respiratory chain gene expression and hypoxia signaling in both liver and brain, suggesting systemic mitochondrial dysfunction contributes to treatment-related morbidity and could be a target for supportive therapies [77].

Organoid and tumoroid platforms derived from patient cervical tissue and Pap smear samples now provide powerful ex vivo systems to test interventions like the ones mentioned before. HPV-driven oncogenesis, viral integration, and treatment responses including resistance to platinum analogs and sensitivity to agents like gemcitabine can be monitored through these platforms, possibly serving as precision tools for mitochondrial therapy discovery [78]. Mitochondria can be viewed as both targets and indicators in HPV-related oncogenesis and therapy, bridging metabolic interventions, systemic treatment responses, and personalized organoid testing.

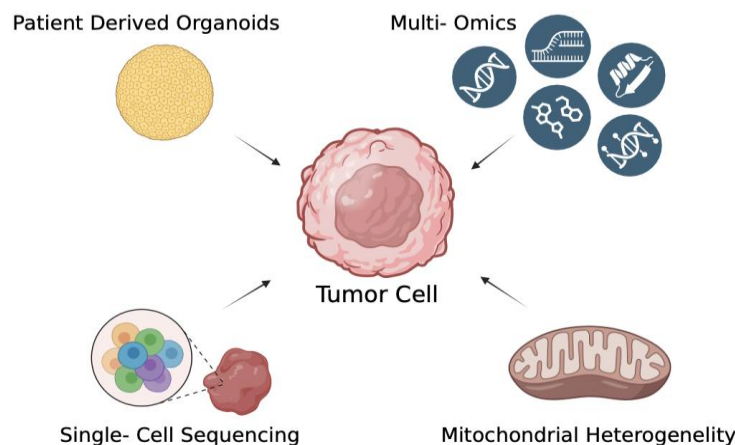


Figure 3. Advanced modeling strategies for studying mtDNA alterations in HPV-related cancers. A central tumor cell is depicted surrounded by advanced methodologies that enable in-depth characterization of cancer biology. Patient-derived organoids provide physiologically relevant three-dimensional models to recapitulate tumor architecture and microenvironment. Multi-omics strategies (including genomics, transcriptomics, proteomics, and metabolomics) allow for comprehensive profiling of tumor molecular landscapes. Single-cell sequencing resolves intratumoral heterogeneity by capturing genomic and transcriptomic variation at the single-cell level. Finally, the assessment of mitochondrial heterogeneity sheds light on metabolic diversity and mitochondrial dynamics within tumor populations. Together, these complementary approaches offer a multidimensional understanding of tumor development, progression, and therapeutic vulnerabilities.

6. Conclusions

Mitochondrial dysfunction and alterations in mitochondrial DNA are increasingly recognized as active contributors to HPV-driven oncogenesis rather than secondary byproducts of cellular stress. High-risk HPV oncoproteins E6 and E7 disrupt mitochondrial homeostasis through multiple, interconnected mechanisms through modulation of biogenesis, mitochondrial dynamics, oxidative

metabolism, and redox balance, thereby promoting metabolic reprogramming, resistance to apoptosis, and tumor adaptability. Qualitative and quantitative changes in mtDNA, including point mutations, insertion-deletions, and copy number variations further strengthen and complicate these effects, influencing both the cellular behavior of HPV-positive tumors and the clinical outcomes.

The evidence highlights the potential of mtDNA alterations as diagnostic and prognostic biomarkers, as well as therapeutic targets in HPV-associated cancers. Advances in multi-omics profiling, high-throughput sequencing, and physiologically relevant model systems such as patient-derived organoids have provided valuable opportunities for an insight into the structural link between HPV and mitochondrial dysfunction. These platforms, coupled with novel strategies to target mitochondrial bioenergetics and redox homeostasis, show promise for the development of more effective and personalized treatments.

Future research should focus on uncovering the functional consequences of mtDNA heteroplasmy, validating mitochondrial targets in clinically relevant models and integrating mitochondrial profiling into patient stratification studies. Exploiting mitochondrial vulnerabilities as a novel way of intervention in HPV-related cancers could possibly be achieved by bridging the gap between fundamental mitochondrial biology and translational oncology, with the aim of improving outcomes for patients worldwide.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/doi/s1>, Figure S1: title; Table S1: title; Video S1: title.

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