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Autophagy in Human Papillomavirus

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Abstract: Human papillomavirus (HPV), a prevalent oncovirus, contributes significantly to global cancer burden, particularly cervical and head and neck cancers. Despite the availability of prophylactic vaccines, HPV-related malignancies remain a growing concern, underscoring the need to understand its molecular interactions. Autophagy, a cellular degradation process, plays a dual role in tumorigenesis, acting as both a tumor suppressor and promoter. This review examines the intricate relationship between HPV and autophagy, highlighting how the virus exploits autophagic pathways to enhance infectivity, evade immune responses, and promote oncogenesis. Key HPV oncoproteins, such as E5, E6, and E7, manipulate distinct stages of autophagy to facilitate viral persistence and tumor progression. Emerging evidence suggests that targeting autophagy, particularly the fusion of autophagosomes with lysosomes, could offer therapeutic potential. This paper explores autophagy's role in HPV pathogenesis and its implications for developing antiviral and anticancer strategies.

Keywords: Autophagy; Human papillomavirus; HPV16; Oncoviruses; Tumorigenesis; Viral oncogenes

INTRODUCTION

Oncovirus infection is one of the primary contributors of cancer globally, contributing for almost 12% of the worldwide cancer burden [1]. Human papillomavirus (HPV) infection is responsible for around 2% and 7% of the overall cancer burden in developed and emerging nations, respectively [2]. Higher risk (HR) Human papillomaviruses, which include HPV16, are the leading source of cervical carcinoma and are also linked to other anogenital malignancies, non-melanoma skin cancers, and head and neck cancer (HNC) [3]. Even though vaccinations targeting common tumor-causing HPVs have been developed, the prevalence of HPV-related carcinomas, notably HNC, is rapidly rising [4]. Against these causes, and in the lack of specific therapeutics for HPV-tumors, a thorough knowledge of the molecular pathways driving HPV carcinogenesis is critical.

Autophagy is an intracellular degradation system that uses lysosomal activity to break down cellular components of various origins. It plays a critical role in degrading long-lived proteins and organelles, such as mitochondria (via mitophagy) and the endoplasmic reticulum (via ER-phagy). Additionally, it eliminates aggregate-prone proteins, like α-synuclein, mutant huntingtin, and tau (via aggrephagy), and disposes of intracellular pathogens, such as bacteria and viruses, through xenophagy [1]. Based on the delivery route of materials to lysosomes, autophagy is classified into chaperone-mediated autophagy, microautophagy, and macroautophagy. In chaperone-mediated autophagy, molecular chaperones engage with lysosome-associated membrane protein (LAMP) type 2A, which functions as a receptor, to transport unfolded proteins from the cytosol into lysosomes [2]. Microautophagy is identified by direct rupture of the lysosomal membrane and engulfment of cytoplasmic substances [3]. In macroautophagy (also known as autophagy), a double-membraned organelle called the autophagosome retains cytosolic molecules before fusing with a lysosome to form an autolysosome, where molecules undergo digestion by lysosomal hydrolases [4]. Autophagy is a highly intricate cellular process that can be categorized into three key phases: the initiation of the phagophore, its

elongation, and subsequent fusion with lysosomes. In mammalian cells, the initiation phase is orchestrated by the unc-51 like autophagy activating kinase 1 (ULK1) complex. This complex includes ULK1 (or its homolog ULK2), autophagy-related protein 13 (ATG13), FAK family kinase-interacting protein of 200 kDa (FIP200), and ATG101. The ULK1 complex is recruited to specific cellular membranes, such as the endoplasmic reticulum (ER)-mitochondrial junction [5] or the ER-Golgi intermediate compartment [6]. This recruitment and subsequent activation of the ULK1 complex are tightly regulated by the mammalian target of rapamycin (mTOR), a key sensor of nutrient availability [7].

Under conditions of nutrient deprivation, energy deficits in the cell are detected by AMP-activated protein kinase (AMPK), which phosphorylates mTOR and inactivates the mTOR complex 1 (mTORC1). The inactivation of mTORC1 allows its dissociation from the ULK1 complex, enabling the activation of ULK1. Once activated, ULK1 phosphorylates mammalian ATG13 (mATG13) and FIP200, triggering the initiation of phagophore formation. This process involves the sequential recruitment of autophagic factors and membrane components, resulting in the formation of the phagophore, which is a double-membrane structure that originates from a donor membrane and subsequently detaches.

The elongation phase of autophagy is mediated by the class III phosphatidylinositol 3 kinase (PI3K) complex, which comprises the vacuolar protein sorting 34 (VPS34) PI3K, its regulatory components ATG14L, VPS15, and Beclin 1. During this stage, the dissociation of Beclin 1 from the anti-apoptotic protein B-cell lymphoma/leukemia-2 (Bcl-2) activates the PI3K complex. This activation facilitates the recruitment of two ubiquitin-like conjugation systems, which are responsible for the attachment of phosphatidylethanolamine (PE) lipid molecules to microtubule-associated protein 1 light chain 3 (LC3) [8]. The lipidated form of LC3, referred to as LC3-II, is associated with both sides of the forming autophagosome and serves as a widely recognized marker for autophagosome formation. LC3-II plays a pivotal role in membrane elongation and the maturation of the autophagosome [9].

The final stage involves the activity of another class III PI3K complex, termed complex II, which includes VPS34, VPS15, Beclin 1, and UV radiation resistance-associated gene protein (UVRAG). This complex stimulates the small GTPase Rab7, enhancing its GTPase activity. This activation facilitates the fusion of the mature autophagosome with late-stage lysosomes, forming autolysosomes [10]. These autolysosomes possess degradative capabilities due to the enzymes contained within lysosomes, enabling the breakdown and recycling of cellular macromolecules and organelles.

Historically, autophagy was believed to function primarily as a cellular response to starvation and as a mechanism for the degradation and recycling of cellular components. However, research has revealed that autophagy exerts broad influences on various cellular processes in both physiological and pathological contexts. For instance, it plays significant roles in the pathogenesis of muscular disorders, neurodegenerative diseases, aging, and inflammatory conditions (reviewed in [4]). Dysregulation of autophagy is also implicated in cancer, where it can act as a double-edged sword. In the early stages of tumor development, autophagy functions as a tumor suppressor by curbing inflammation, reducing intracellular reactive oxygen species (ROS), and maintaining genomic stability. Conversely, in the later stages of tumor progression, autophagy can promote tumor survival by enabling cancer cells to endure nutrient-deprived and hypoxic conditions [11]. Consequently, many cancers exhibit suppressed autophagy in precancerous cells but heightened autophagic activity in established tumors.

Additionally, autophagy's extensive regulatory roles make it a target for exploitation by certain pathogens, which have evolved strategies to manipulate the autophagic machinery to their advantage. Viruses, in particular, can evade autophagy by inhibiting its induction, blocking autophagosome maturation, or subverting autophagy components to enhance their own survival and replication [12]. This review focuses on the interplay between autophagy and human papillomavirus (HPV) infection and tumorigenesis. It also explores how autophagy might serve as a therapeutic target for developing novel antiviral and anticancer strategies, while drawing comparisons with mechanisms employed by other oncoviruses to modulate host autophagic responses.

1. Overview - Autophagy

Autophagy is a fundamental catabolic process found in eukaryotes, where intracellular components are broken down within lysosomes to maintain metabolic balance [13]. This process enables cells to eliminate various elements, ranging from macromolecules to organelles. Discovered over five decades ago and named by Belgian biochemist Christian de Duve in 1963, the understanding of autophagy continues to advance. Autophagy depends on a conserved, intricate system of autophagy-related (ATG) proteins, initially identified in yeast by scientists like Yoshinori Ohsumi, Michael Thumm, and Daniel Klionsky. In recognition of his groundbreaking work, Yoshinori Ohsumi was awarded the 2016 Nobel Prize in Physiology or Medicine. Initially considered a non-selective

process, autophagy is now understood to be highly selective, targeting specific structures, organelles, or macromolecules [14].

1.1 Autophagy-related genes (ATG)

Autophagy-related genes (ATG) are critical for orchestrating the various stages of autophagy, from its initiation to the degradation phase. These genes, first identified in yeast, are conserved across eukaryotes and encode proteins central to the autophagy machinery. The process starts with the initiation phase, where the ULK1 complex—comprising ATG1 (ULK1/2), ATG13, FIP200, and ATG101—is activated by nutrient signals to form the phagophore, a cup-shaped isolation membrane [15]. The subsequent nucleation phase involves forming the phagophore at specific locations, often linked to the endoplasmic reticulum (ER). This step requires the class III phosphatidylinositol 3-kinase (PI3K) complex, which includes VPS34 (PI3KC3), Beclin-1 (ATG6), ATG14, and p150, responsible for generating phosphatidylinositol-3-phosphate (PI3P) to recruit additional ATG proteins to the phagophore. During the expansion stage, the phagophore enlarges to create the autophagosome. This process relies on two ubiquitin-like conjugation systems: the ATG12-ATG5-ATG16L1 complex and the LC3 (ATG8) conjugation system. The ATG12-ATG5-ATG16L1 complex functions as an E3 ligase, aiding in conjugating LC3-I to phosphatidylethanolamine (PE), forming LC3-II, which integrates into the autophagosomal membrane. After the autophagosome forms completely, it matures and fuses with lysosomes, resulting in an autolysosome, where lysosomal enzymes degrade the encapsulated cargo. Fusion involves various SNARE proteins and other membrane fusion elements [16]. The degraded materials within the autolysosome are then recycled into the cytoplasm for reuse. Besides the core components, other ATG proteins play essential regulatory roles to ensure autophagy adapts appropriately to cellular needs. Studying the functions of ATG genes and proteins enhances understanding of autophagy's mechanisms and its implications for health and disease [17].

1.2 Types of Autophagy

Autophagy is classified as either non-selective or selective, depending on the cargo. In non-selective autophagy, large portions of the cytoplasm are engulfed by phagophores, typically during starvation to maintain nutrient levels in cells. Conversely, selective autophagy targets specific intracellular cargo with the help of selective autophagy receptors (SARs). These receptors interact with ATG8 family proteins on the inner phagophore membrane, facilitating the delivery of specific cargo and recruiting the autophagic machinery [18] [19]. In addition to preserving the quantity and integrity of cellular organelles, selective autophagy plays a role in pathogen clearance. A specific type of selective autophagy, virophagy, targets and degrades viral components or entire virions [20]. This process also aids in viral antigen processing and subsequent presentation on major histocompatibility complex (MHC) class I and II molecules, triggering adaptive immunity [21].

In mammals, autophagy is categorized into three main types: microautophagy, macroautophagy, and chaperone-mediated autophagy (CMA). Although morphologically distinct, all three pathways converge on delivering cargo to the lysosome for degradation and recycling [22]. In microautophagy, cargo is captured through invaginations or protrusions of the lysosomal membrane [23]. The uptake occurs directly at the lysosome's limiting membrane and can involve intact organelles. CMA differs in that it bypasses membranous structures, using chaperones to identify and deliver substrate proteins containing a specific pentapeptide motif. These proteins are unfolded and directly translocated across the lysosomal membrane [24]. In contrast, macroautophagy sequesters cargo away from the lysosome by forming double-membrane autophagosomes through de novo synthesis, which then transport the cargo to the lysosome [25]. Of these types, macroautophagy is the most extensively studied. It occurs at low levels under normal conditions but can be induced during stress, such as nutrient or energy deprivation, to break down cytoplasmic material into metabolites for biosynthesis or energy production, supporting cell survival [25]. Under normal conditions, macroautophagy maintains cellular health by selectively degrading damaged or unnecessary organelles [26]. While primarily cytoprotective, excessive autophagy can be harmful. Dysregulated autophagy has been linked to numerous human diseases, including lung, liver, and heart conditions, neurodegeneration, myopathies, cancer, aging, and metabolic disorders like diabetes [27].

1.2.1 Microautophagy

Microautophagy involves the direct entry of cytoplasmic materials into the lysosome through invagination or deformation of the lysosomal membrane [28]. An early study using electron microscopy demonstrated that isolated rat liver lysosomes engulf Percoll particles in vitro via protrusions or cup-like invaginations of the lysosomal membrane, which form vesicles inside the lysosome. Some of these particles were observed freely within the lysosomal lumen, likely due to rupture or lysis of the vesicles [29]. A recent study introduced evidence of a microautophagy-like process called endosomal microautophagy, which facilitates the transport of soluble cytosolic proteins to vesicles in late endosomal multivesicular bodies

[30]. Due to the scarcity of research tools, our understanding of microautophagy, including its regulation and role in human health and disease, remains limited [23].

1.2.2 Chaperone-Mediated Autophagy (CMA)

Chaperone-mediated autophagy (CMA), observed only in mammalian cells, differs from microautophagy and macroautophagy by being highly specific. CMA substrates share a pentapeptide targeting motif similar to KFERQ [31], and approximately 30% of cytosolic proteins contain this sequence based on sequence analysis and immunoprecipitation studies [32]. Proteins with the KFERQ motif are unfolded by cytosolic chaperones and transported directly across the lysosomal membrane for degradation in the lysosomal lumen [33]. CMA targets include glycolytic enzymes, transcription factors, calcium and lipid-binding proteins, proteasome subunits, and proteins involved in vesicular trafficking [34].

During CMA, the KFERQ motif is recognized by HSPA8/HSC70 and cochaperones [35]. HSPA8 delivers the substrate to the lysosomal membrane and aids in its unfolding [36]. At the lysosomal membrane, the substrate binds to the monomeric CMA receptor LAMP2A, triggering LAMP2A multimerization [37]. HSP90 stabilizes the multimeric translocation complex on the lumenal side [38], and lumenal HSPA8 facilitates substrate translocation. Cytosolic HSPA8 actively disassembles the translocation complex, reverting LAMP2A to its monomeric state for another cycle [39].

Regulation occurs mainly at the substrate binding stage, a rate-limiting step [40]. LAMP2A levels on the lysosomal membrane, influenced by degradation and membrane organization, modulate CMA activity [41]. Some evidence suggests redistribution of LAMP2A within the lysosomal membrane affects its degradation [42]. CMA activity increases under oxidative stress [43], protein-damaging toxins [44], and prolonged nutrient deprivation, but the underlying intracellular signaling pathways remain poorly understood [39].

HSPA8 and LAMP2A are also implicated in chaperone-assisted selective autophagy, a type of macroautophagy, where chaperones assist in clearing selectively ubiquitinated organelles and protein complexes. This process involves receptors like SQSTM1/p62 and enzymes such as HDAC6, allowing recognition by the macroautophagy machinery [45] [46] [47].

1.2.3 Macroautophagy

Unlike microautophagy and CMA, macroautophagy is characterized by cytosolic vesicle formation away from the lysosome. Autophagosomes, the vesicles unique to macroautophagy, form de novo through expansion rather than budding from an existing organelle (Figure 1) [39]. In yeast, autophagosome formation begins at a perivacuolar site known as the phagophore assembly site (PAS) [48], while in mammals, it occurs at multiple cytoplasmic locations [48] [49]. Studies suggest mammalian omegasomes, ER-associated structures, may initiate autophagosome formation [50] [51].

During autophagosome development, the membrane, called the phagophore, expands, eventually forming a double-membrane spherical autophagosome [52]. Sources of the membrane remain debated, with possibilities including the plasma membrane [53] [54], ER [50] [51], Golgi complex [55], and mitochondria [56] [57] [58]. The autophagosome encloses cargo and fuses with lysosomes (or vacuoles in yeast and plants) for degradation. In mammals, the product is an autolysosome [59], and the degraded materials are recycled back into the cytoplasm for biosynthesis or energy production [25]. Macroautophagy often intersects with the endocytic pathway, with autophagosomes fusing with endosomes to form amphisomes before lysosomal fusion [60] [61].

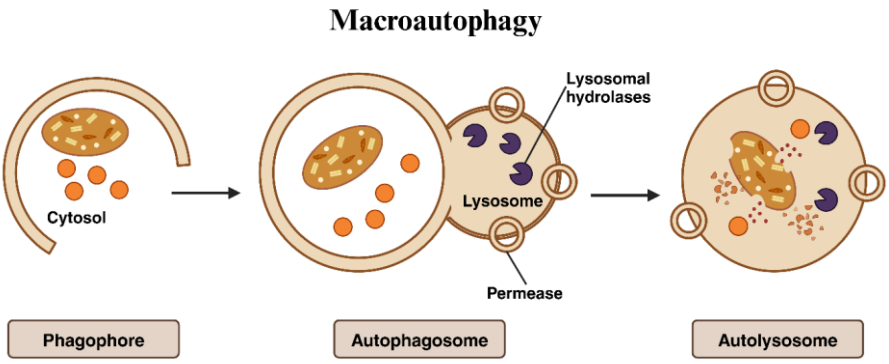

Figure 1. Macroautophagy depends on the formation of new double-membrane vesicles, known as autophagosomes, in the cytosol. These structures are responsible for isolating and transporting cellular cargo to lysosomes for degradation and recycling.

2. HPV Manipulation of Host Autophagy

During recent times, a tight relationship linking autophagy and HPV has founded. HPV, like a variety of viruses, relies on the autophagic mechanism to strengthen its lifespan within host-infected cells. Furthermore, oncogenic HPVs use cellular autophagy to promote the growth of infected epithelial cells, which greatly contributes to cancer development. In the next parts, we will look at how autophagy impacts HPV pathogenesis as well as how the virus uses this mechanism to increase its longevity in the host.

2.1. Autophagy Inhibition Promotes HPV Infectivity

HPV, a double-stranded DNA virus with a circular genome, encodes early genes—E1, E2, E4, E5, E6, and E7—that are essential for processes like replication, transcription, and cellular transformation, along with late genes, L1 and L2, which code for viral capsid proteins. The replication cycle of HPV is intricately linked to the differentiation process of infected epithelial tissue. Initial infection occurs exclusively in the basal keratinocytes at microtrauma sites, often resulting from sexual activity. In contrast, viral protein production and the assembly of new virions are restricted to the upper differentiated layers of the epithelium.

Within the wounded basal layer, HPV particles first interact with the basement membrane, primarily through heparan sulfate proteoglycans (HSPGs), facilitated by contacts with the L1 capsid protein. This interaction then enables the binding of HPV to HSPGs on the surface of basal keratinocytes. Such binding induces conformational changes in the L2 capsid protein, exposing a specific cleavage site at the N-terminus of L2. Cleavage at this site enhances further interaction between the viral capsid and secondary receptors on the keratinocyte membrane. Once bound, HPV is typically internalized via clathrin-mediated endocytosis, a process dependent on actin-rich cell protrusions that guide the virus through the endocytic pathway [62].

The processes of HPV binding and internalization are intricately linked to the manipulation of host autophagy. Interaction with HSPGs rapidly activates host cell signaling pathways that favor HPV infection. Notably, HPV entry suppresses autophagy by activating the mTOR pathway. Upon binding to HSPGs, HPV16 interacts with epidermal growth factor receptors (EGFRs) present on the plasma membrane of target cells [63]. This interaction triggers phosphorylation of Protein Kinase B (Akt) and inactivation of the phosphatase and tensin homolog (PTEN), ultimately leading to phosphorylation and activation of mTOR [64]. Activated mTOR phosphorylates and activates mTOR complex 1 (mTORC1) components, such as 4E-BP1 (eukaryotic initiation factor 4E-binding protein 1) and S6K1 (ribosomal protein S6 kinase 1) [14]. These components are essential for protein synthesis. Concurrently, mTOR phosphorylates and deactivates ULK1, a kinase involved in autophagosome formation, thereby inhibiting autophagy [65].

This manipulation of the PI3K/Akt/mTOR pathway by HPV binding leads to increased protein synthesis and suppression of autophagy at the early stages of the viral lifecycle, even before the virus enters target cells. These functions are critical for HPV's successful infection of human keratinocytes [65]. Supporting this, inhibition of autophagy—whether through early-stage inhibitors like 3-methyladenine (3-MA) [66] or via genetic ablation of essential autophagic genes—significantly enhances HPV16 infectivity in keratinocytes [64] [67] [68]. These findings underscore the importance of autophagy in monitoring the early stages of the HPV lifecycle.

Mechanistically, rather than affecting virus attachment or internalization, autophagy inhibition prevents the degradation of HPV16 capsids within autophagosomes [68], particularly delaying the digestion of the L1 protein [67]. This ensures that HPV16 suppresses the host autophagic response, using molecular events triggered by binding and internalization as a defensive strategy. By doing so, the virus protects incoming virions from rapid degradation and prolongs its survival within infected cells [Figure 1].

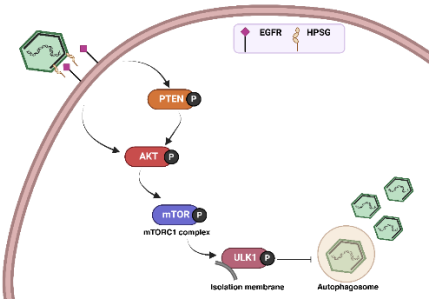

Figure 2. HPV16 binding and internalization suppresses autophagosome formation through a cascade of molecular interactions. HPV16 virions, coated with heparan sulfate proteoglycans (HSPGs), bind to epidermal growth factor

receptors (EGFRs) on the plasma membrane of target cells. This interaction triggers the phosphorylation of Akt and PTEN, subsequently activating the mTOR pathway. Activated mTOR then phosphorylates and inactivates ULK1, a key protein located on isolation membranes that initiates autophagosome nucleation. As a result, autophagosome formation is inhibited, delaying the digestion of the HPV L1 capsid protein and its degradation within autophagosomes. In the schematic representation, arrows denote activating pathways, T-bars signify inhibitory pathways, and blue lines highlight cellular and isolation membranes.

2.2. HPV16 Suppresses Autophagy to Accelerate Cancer Development

After entering basal cells, HPV traffics through the endosomal compartment, where the viral capsid proteins are degraded within acidified endosomes, allowing the viral genome to reach the nucleus. While high-risk (HR) HPV infection is a key causative factor for various cancers, its presence alone does not guarantee cancer development. This highlights the requirement for additional events, such as genomic instability or immune system failure, to trigger carcinogenesis. Among the viral factors, the E5, E6, and E7 oncoproteins play a pivotal role in driving cellular transformation. These oncoproteins interfere with cell-cycle regulation, promote the expression of human telomerase reverse transcriptase (hTERT) for telomere maintenance, and inhibit apoptosis [69]. Consequently, DNA damage and mutations accumulate, leading to the transformation of basal epithelial cells into koilocytes [70], which can progress into cancerous cells.

The E5 protein is a multifunctional oncoprotein that contributes to cellular transformation by associating with and amplifying growth factor receptor signaling pathways [71]. The E6 protein facilitates the proteasomal degradation of the tumor suppressor p53 by leveraging the ubiquitin ligase E6AP [72]. Meanwhile, E7 disrupts cell-cycle control by interacting with pocket proteins such as retinoblastoma protein (RB), p107, and p130 [73]. Beyond these interactions, HPV oncogenes also affect numerous other cellular proteins, altering their normal functions and driving the transformation of epithelial basal and parabasal cells into koilocytes [70].

Before malignant transformation occurs, persistent HPV activity leads to the formation of precancerous lesions, classified as low-grade squamous intraepithelial lesions (LSILs) and high-grade SILs (HSILs), particularly during cervical cancer progression. LSILs are characterized by abnormalities confined to the lower third of the epithelium and may either regress spontaneously or progress to HSILs. In HSILs, transformed cells are distributed throughout the epithelium, and HPV often persists in the host by integrating its DNA into the cellular genome, thereby contributing to cancer progression [74].

Autophagy plays a significant role in the carcinogenic process associated with HPV. Interestingly, the E5, E6, and E7 oncoproteins have evolved distinct mechanisms to modulate the host autophagic pathway, underscoring autophagy's importance in each step of HPV-mediated tumorigenesis [Figure 2]. For instance, ectopic expression of HPV16 E5 in HPV-negative keratinocytes reduces autophagosome marker LC3-II levels, prevents the degradation of the autophagic substrate p62, and decreases the number of autophagosomes in cells triggered by keratinocyte growth factor (KGF) or serum starvation. This indicates a failure in autophagosome assembly. Furthermore, the depletion of E5 in HPV-positive cells reverses these effects, confirming that E5 expression inhibits autophagy at early stages of the pathway. Mechanistically, HPV16 E5 downregulates the transcription of key autophagy-related genes, such as Beclin 1, ATG5, LC3, ULK1, ULK2, ATG4a, and ATG7, thus inhibiting phagophore assembly [75].

Unlike E5, which impairs autophagosome formation, HPV16 E6 and E7 target later stages of the autophagic process, specifically the fusion of autophagosomes with lysosomes. Overexpression of E6/E7 in primary human keratinocytes results in increased levels of lipidated LC3 (LC3-II) and p62, suggesting autophagosome accumulation despite decreased degradation activity. Confocal and electron microscopy analyses confirm a reduction in autolysosome formation, identifying autophagosome-lysosome fusion as the defective step disrupted by these oncoproteins. The impairment of this late-stage autophagy is primarily linked to an E6/p53-dependent mechanism. For example, HPV16 E6 alone increases LC3-II and p62 levels, and mutants of E6 defective in p53 degradation show a reduced ability to elevate p62 levels when combined with E7 [76]. Additionally, E7 expression independently raises LC3-II levels in keratinocytes [77], reinforcing the link between HPV oncogene activity and autophagic dysfunction.

Consistent with these findings, silencing the bicistronic HPV16 E6/E7 mRNA using siRNA targeting the E7 sequence significantly increases the expression of autophagy-related genes. This also results in phenotypic evidence of autophagy activation, including the appearance of autophagosomes, punctate LC3 expression, the conversion of LC3-I to LC3-II, and reduced levels of the autophagic substrate p62 [78]. These results highlight the intricate strategies employed by HPV16

oncoproteins to manipulate host autophagy for promoting tumorigenesis.

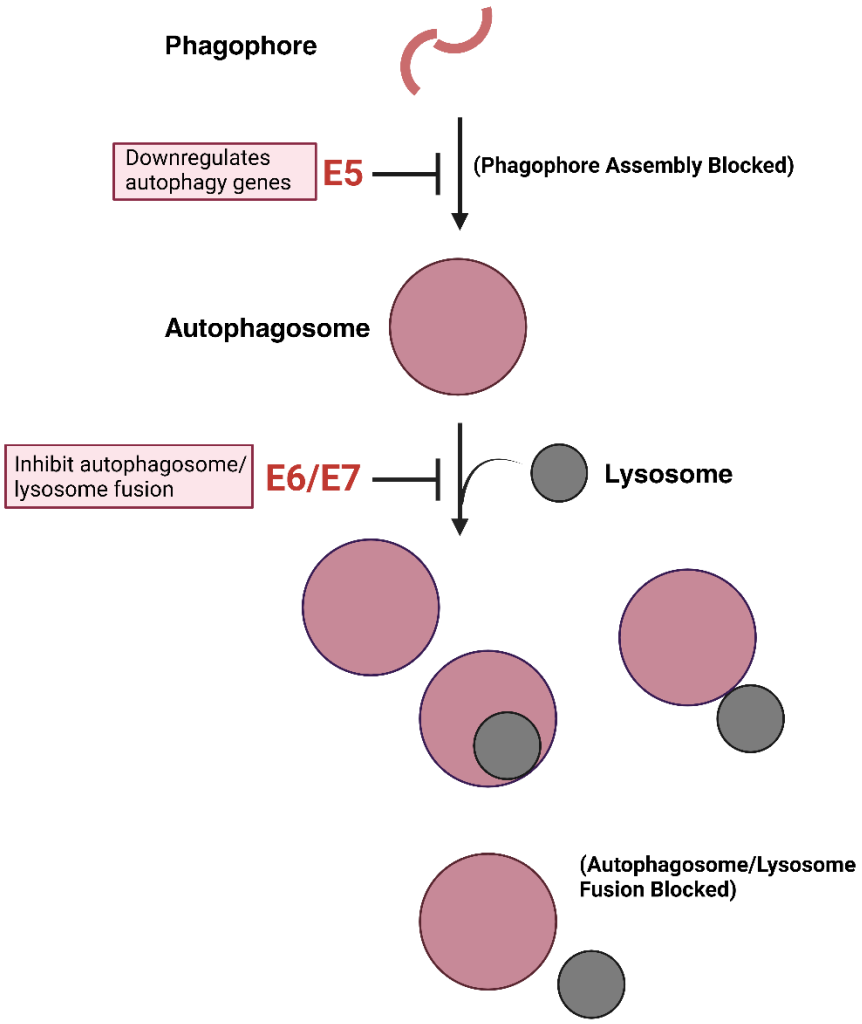

Figure 3. HPV16 oncoproteins suppress the host's autophagic response by targeting various stages of the autophagic pathway. The E5 oncoprotein disrupts the transcriptional activation of essential autophagic components, leading to the downregulation of key mRNAs, including Beclin 1, ATG5, LC3, ULK1, ULK2, ATG4a, and ATG7. This indicates an inhibition of phagophore assembly, a crucial early step in autophagy. Meanwhile, the E6 and E7 oncoproteins impair autophagosome-lysosome fusion, potentially due to the depletion of autophagy-related genes. In visual representations, arrows indicate pathways that are activated, while T-bars signify pathways that are inhibited.

Building on the previously mentioned in vitro findings, which collectively demonstrate that HPV16 oncoproteins interfere with autophagy via various mechanisms, additional observations from in vivo and ex vivo studies further validate that autophagy manipulation is a significant contributing factor in HPV-induced malignancies. These findings not only reinforce the importance of autophagic dysregulation in the progression of HPV-related cancers but also underscore the potential of several autophagy-associated biomarkers for diagnostic purposes and for monitoring disease progression (Table 1).

Autophagy changes in HPV-driven tumor Progression

Tumor	Altered Autophagic Proteins	Proposed Role as Biomarker
Cervical dysplasia	p62↑	Diagnosis, Progression
	Beclin 1↓	Diagnosis, Progression, Prognosis
	miR-224-3p↑, FIP200↓	Diagnosis, Progression
Anal dysplasia	LC3↑, p62↑	Diagnosis, Progression
Cervical cancer	LC3↓	HPV infection, diagnosis, prognosis
	ATAD3A↑	HPV infection, diagnosis, prognosis, therapeutic predictivity
	miR-224-3p↑, FIP200↓	Diagnosis
	miR-155-5p↓	Diagnosis

For instance, dysplastic anal tissues in HPV16 transgenic mice (K14-E6/E7) exhibit an amplified punctate expression of autophagic markers LC3 and p62. Transmission electron microscopy and immunofluorescence analyses reveal an accumulation of autophagosomes without a corresponding presence of autolysosomes in these tissues. This pattern reflects an inhibition of autophagy at late stages. Notably, this specific dysregulation of autophagic markers observed in transgenic mouse models has also been identified in human samples, firmly establishing autophagy inhibition as a critical factor in HPV-associated anal carcinogenesis [79].

Further supporting this notion, experiments involving the late-stage autophagy inhibitor chloroquine show that its administration to both wild-type (WT) and K14-E6/E7 transgenic mice significantly increases the incidence of anal cancer [79][80]. Conversely, strategies aimed at activating autophagy have been found to reduce tumor onset in these models [80]. These findings emphasize that therapeutic modulation of autophagy holds potential not only for understanding HPV-driven malignancies but also for developing targeted interventions aimed at mitigating the progression of such cancers.

2.3 Tumour Viruses Hijack Host Autophagy for Their Replication Cycle

Similar to HPV16, other oncoviruses also manipulate the host's autophagic pathways, highlighting the critical role of autophagy in maintaining oncovirus persistence and facilitating tumorigenesis. For instance, Epstein-Barr virus (EBV), a herpesvirus linked to various cancers such as Burkitt's lymphoma, nasopharyngeal carcinoma, and Hodgkin's disease, suppresses autophagy during its lytic replication phase. This suppression enhances the virus's infectivity, as evidenced by increased EBV lytic gene expression, elevated intracellular viral DNA levels, and higher production of viral progeny when autophagy is inhibited [81]. Much like HPV16 E6/E7 [82], EBV induces the accumulation of autophagosomes by hindering their fusion with lysosomes through a Rab7-dependent mechanism [83]. By obstructing this terminal step, EBV avoids autophagy-mediated viral degradation, thereby prolonging its infection and contributing to cancer progression.

Human T-cell leukemia virus type 1 (HTLV-1), a deltaretrovirus responsible for adult T-cell leukemia primarily through the action of its oncoprotein Tax [84], also manipulates autophagy to support its tumorigenic processes. HTLV-1 infection causes autophagosome accumulation via Tax, which disrupts autophagosome-lysosome fusion [85]. This disruption occurs through unique cellular mechanisms, such as the recruitment of autophagic molecules to lipid rafts, which are dependent on the NF-κB inhibitor kinase (IKK) complex [86][87]. These alterations enable HTLV-1 to enhance its persistence, promote proliferation, and suppress apoptosis in infected T lymphocytes.

Another oncogenic virus, Kaposi sarcoma-associated herpesvirus (KSHV), part of the herpesvirus family, also interferes with host autophagy. KSHV is associated with diseases like Kaposi sarcoma,

multicentric Castleman disease, and primary effusion lymphoma [88]. During its latent phase, KSHV suppresses autophagy through the viral protein FLICE-like inhibitory protein (vFLIP), which dysregulates the IKK/NF-κB signaling pathway [89]. This suppression prevents cellular senescence and promotes the proliferation of KSHV-infected cells [88]. However, during lytic reactivation, KSHV enhances autophagy via the replication and transcription activator protein (RTA). This increase in autophagic activity supports lytic gene expression and viral DNA replication, as inhibiting autophagy at this stage disrupts the completion of the KSHV replication cycle [90].

In contrast to HPV, the Hepatitis B virus (HBV), a hepatotropic virus associated with hepatocellular carcinoma (HCC) [91], stimulates autophagy in infected liver cells, animal models, and patient tissues [92][93]. This activation facilitates HBV DNA replication. Mechanistically, the viral protein HBx interacts with VPS34, activating the PI3K complex III and promoting autophagosome formation [92]. Additionally, HBx drives Beclin-1 phosphorylation via a DAPK-dependent mechanism [94]. Despite this induction of autophagy, HBV does not enhance autophagic degradation, indicating an impairment in lysosomal function. Specifically, HBx alters Rab7 expression and inhibits the activity of the V1D subunit of the proton-pumping V-type ATPase (V-ATPase), leading to reduced lysosomal maturation and functionality [95][96]. Moreover, HBx safeguards infected cells from apoptosis by leveraging autophagy. It acts as an autophagic adaptor, facilitating the recruitment of TNFRSF10B (a death receptor) to the autophagic machinery, promoting its degradation, and thereby reducing immune recognition of infected cells. Silencing autophagic proteins such as ATG5, ATG12, and ATG16L1 significantly impairs HBV formation and release while disrupting HBV's intracellular localization. The interaction between the HBV core protein and ATG12 enables HBV to associate with cellular membranes, facilitating the production of mature viral particles [97]. These findings underscore the pivotal role of autophagy in HBV infection.

Similar to HBV, the Hepatitis C virus (HCV) also exploits autophagy to enhance viral growth and survival in host cells. HCV promotes autophagosome formation through two mechanisms: inducing time-dependent dephosphorylation of ULK1 [98] and upregulating Beclin 1 expression [99]. However, this autophagosome formation coincides with inhibited autophagosome maturation. This inhibition is mediated by the overexpression of Rubicon, a negative regulator of UVRAG, which disrupts the UVRAG-PI3KC3 complex and Rab7 [100], as well as by the mislocalization of V-ATPase [101]. HCV utilizes lipid rafts within autophagosome membranes to enhance RNA replication [102]. Since autolysosome formation would otherwise degrade these replication complexes, HCV manipulates autophagy to prevent their destruction, improving its replication. Furthermore, this manipulation facilitates HCV release from host cells, promoting viral egress and transmission [103].

CONCLUSION

Autophagy is a vital physiological process responsible for the degradation of macromolecules and damaged cellular structures. This pathway plays a crucial role in maintaining cellular homeostasis, regulating essential cellular functions, and responding to stress. Consequently, it is unsurprising that numerous viruses have evolved sophisticated mechanisms to manipulate the host's autophagic system. This manipulation allows viruses to subvert normal cellular processes and create environments that are more favorable for viral replication [65]. Among these, oncoviruses have garnered significant attention for their ability to exploit autophagy to facilitate infection, persistence, and tumorigenesis, as highlighted in recent reviews [66].

A prime example of this phenomenon is human papillomavirus type 16 (HPV16), an oncogenic virus that has been shown to redirect the autophagic machinery during its lifecycle. Evidence indicates that HPV16 employs various mechanisms to suppress the host autophagic response, targeting multiple stages of the viral infection process and carcinogenesis.

HPV16 influences autophagy at both the initial stages of infection—such as viral adhesion and entry into target cells—and later stages of infection and transformation. During the early infection stages, HPV16 suppresses autophagic digestion to prevent the clearance of viral particles. In later stages, it contributes to the transformation of infected cells, promoting carcinogenesis. Notably, the three key oncoproteins of HPV16—E5, E6, and E7—employ distinct strategies to inhibit host autophagy. This underscores the centrality of autophagy manipulation in facilitating malignant transformation.

Mechanistically, a common outcome across many oncogenic viruses, including HPV16, is the disruption of the final step of autophagy: the fusion of autophagosomes with lysosomes. This inhibition of autophagosome-lysosome fusion has emerged as a critical target of viral autophagy manipulation. Similar disruptions are observed in other oncoviruses such as Epstein-Barr virus (EBV), human T-cell leukemia virus type 1 (HTLV-1), hepatitis B virus (HBV), and hepatitis C virus (HCV). These viruses impair autolysosome formation, indicating that autophagic degradation poses a threat to their

lifecycle. HPV16 specifically targets this step, further emphasizing the detrimental role autophagic degradation plays in the progression of oncoviral infections.

Given the importance of autolysosome formation in oncovirus-driven tumorigenesis, there is significant therapeutic potential in targeting this process. Additional research is needed to elucidate the intricate relationship between HPV and autophagy and to identify novel molecular targets within the autophagic pathway. This could pave the way for the development of biomarkers (Table 1) and therapeutic strategies that leverage autophagy modulation. Recently identified autophagic inducers that promote autophagosome-lysosome fusion [67] present a promising starting point for identifying effective molecules and designing clinical treatments against HPV infections.

Furthermore, while most current evidence stems from in vitro studies utilizing HPV16 virions or oncoproteins, it is crucial to explore whether similar impacts on autophagy are observed across other high-risk HPV (HR HPV) genotypes. Investigating the role of autophagy during low-risk HPV infections could also provide valuable insights. These studies could highlight significant similarities and differences in autophagy regulation among various HPV genotypes, strengthening strategies aimed at modulating autophagy to combat HPV infections [8]. It is evident that the inhibition of autophagy is a pivotal factor in HPV's lifecycle and its role in tumor progression. Restoring autophagic function during HPV infection and carcinogenesis could play a critical role in mitigating HPV-induced diseases. Consequently, therapeutic approaches that target the autophagic pathway could hold great potential in addressing HPV-mediated pathologies.

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