Molecular Therapy
Oncology
Review

The multilayered control of acetylation during adenovirus-based immunotherapy of cancer

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Adenoviruses are highly immunogenic agents that have shown promise first as gene delivery vectors and later as oncolytic viruses. Currently, oncolytic adenoviruses are featured in over 30% of cancer virotherapy clinical trials. Due to their effective cellular uptake and hijack of cellular machinery, replication-competent adenoviruses are promising therapeutic agents for treating a wide range of tumors. Adenoviral influence on host cell acetylome regulation has regained attention, as these viruses redirect or suppress acetylation during replication, making them potentially desirable therapeutic agents for cancers driven by epigenetic modifications. In this review, we aim to cover the viral processes influencing the acetylome of the host genome. In addition, we shall discuss the effect of differential acetylation on the antiviral defense mounted by the host immune system. Lastly, we will discuss the opportunities for combining acetylation modifiers with oncolytic adenoviruses to improve further outcomes for patients treated with viroimmunotherapy.

INTRODUCTION

Oncolytic adenoviruses have emerged as multifaceted anti-tumor therapeutic agents that successfully infect the target cancer cell and harness the host immune system to amplify their therapeutic effect. Several laboratories have exploited the interactions between adenoviral and cellular proteins to engineer therapeutic agents with selective replication in cancer cells.[1–3] For example, we have leveraged the ability of the early viral protein E1A to interact with the retinoblastoma protein (pRb), a well-established tumor suppressor. By deleting the specific residues of E1A required for binding to and inactivating pRb in normal cells, we have generated a cancer-selective replicating adenovirus that is being tested in clinical trials.[4–6]

In addition to selective oncolysis, clinical trials have shown that replication-competent adenoviruses elicit an anti-tumor immune response.[4,5] This response involves the recruitment of inflammatory immune cells and the transformation of "cold" tumors into "hot" neoplasias. Building upon this paradigm-shifting concept, current research efforts are focused on enhancing the anti-tumor immune response in virus-treated tumors.[7]

An underdeveloped area of oncology research investigates how adenoviruses induce decisive changes to the host cell epigenome during the infection process. As the viral cycle progresses from an initial interaction with the host cell to the production of virions by the host cancer cells, it architects a plethora of changes at various cellular levels, including the host epigenome.[8–11]

Without circumventing discussions on the adenoviral mechanisms, this review explores the impact of oncolytic adenoviruses on the acetylome of cancer cells. By examining these epigenetic modifications, we shall gain valuable insights into the regulation of the tumor epigenome and the complex interplay between oncolytic adenoviruses and infected tumors. These findings might inform future therapeutic strategies based on targeting post-transcriptional modifications in the field of oncolytic virotherapy.

Influence of virus-mediated acetylation changes on host epigenome

When the interior contents of the adenovirus are shuttled into the nucleus, one of the very first early viral proteins to be expressed, E1A, hijacks the host DNA replication machinery to facilitate viral genome replication.[12] It has been demonstrated that E1A binds to the lysine acetyltransferase (KAT) enzyme p300/CBP (CREB-binding protein), influencing a global loss of the histone 3 on lysine residue 18 (H3K18) acetylation in fibroblast and HeLa cells.[8] Studies in the late 1990s suggest contradictory results on the effect of E1A binding to p300 by reporting E1a-mediated inhibition of the p300 acetyltransferase activity[13,14] or an increase in the histone acetyltransferase (HAT) activity of p300/CBP by inducing phosphorylation of these enzymes.[15,16] In line with p300/CBP HAT activity maintenance upon E1A binding, works in the late 2000s demonstrate that HAT activity is retained even when p300 is bound to E1A and is capable of H3K18 acetylation *in vitro*.[8] Furthermore, chromatin immunoprecipitation sequencing (ChIP-seq) studies to decipher the distribution of H3K18ac indicate differential acetylation facilitated by the

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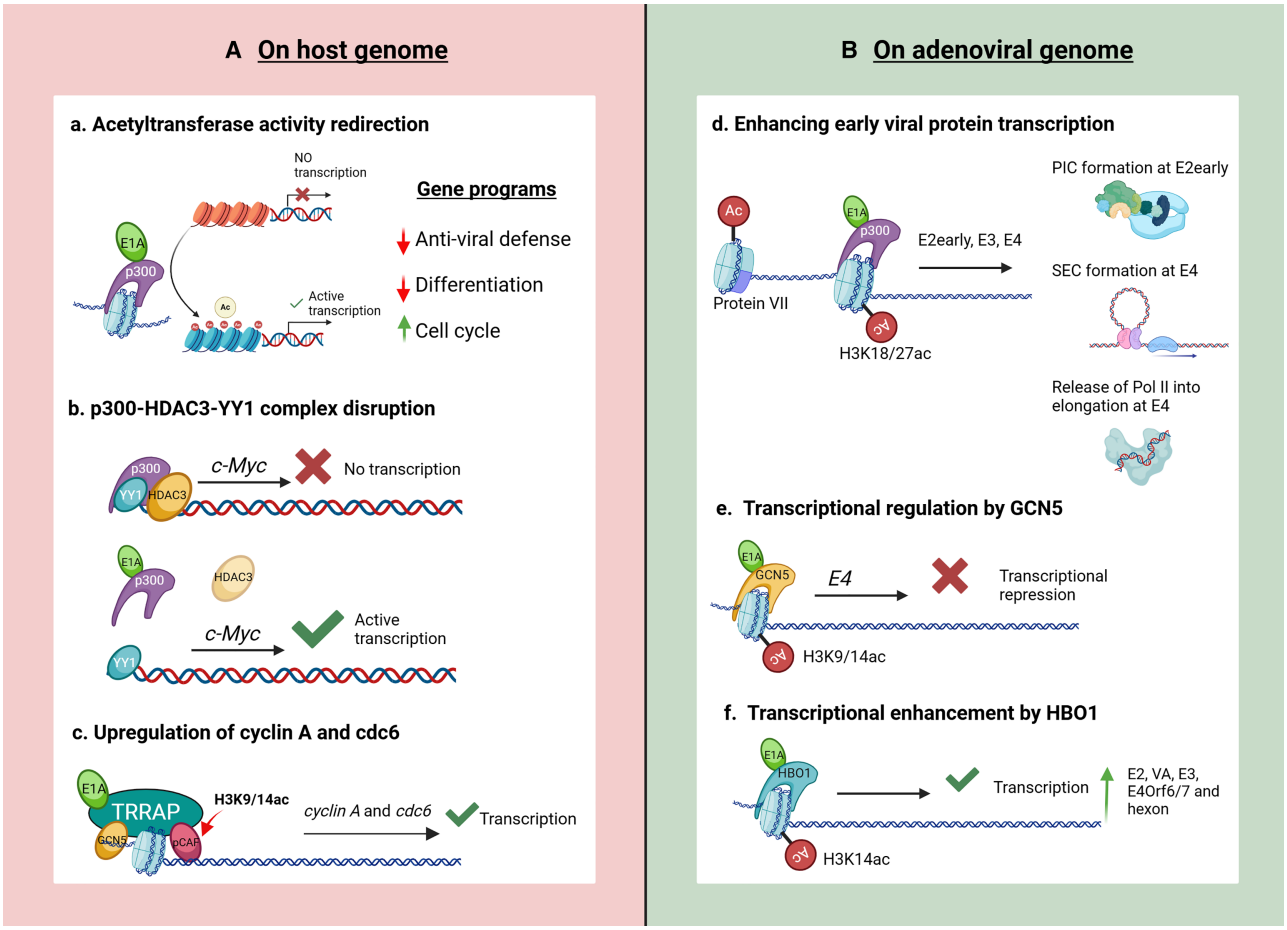

Figure 1. Adenovirus-induced alterations in acetylation and their impact on gene expression

(A) E1A protein redirects p300-mediated acetylation on the host genome to facilitate viral replication. (B) E1A disrupts the p300-HDAC3-YY1 complex, promoting c-Myc transcription. (C) E1A recruits acetyltransferases from the TRRAP complex, enhancing cyclin A and cdc6 expression. (D) E1A-p300 interaction leads to histone acetylation on adenoviral DNA in "adenosomes," facilitating transcription. (E) E1A-bound GCN5 represses adenoviral gene transcription. (F) E1A interacts with HBO1 (MYST family) to acetylate H3K14 on the viral genome, enhancing viral gene expression. This figure was created with BioRender.com.

E1A-p300 interaction.[17] The authors of this study demonstrate that the adenoviral-mediated differential p300 activity downmodulates antiviral mechanisms and differentiation pathways while upregulating S-phase-related genes, aiding in viral replication[17] (Figure 1A). ChIP-seq studies reveal a shift in H3K18ac occupancy from intergenic regions (IRs) and introns in the mock-infected cells to promoter regions in the virus-infected cells as soon as 24 h post-infection.[18] The authors of this study also note that the establishment of new H3K18ac peaks in the virus-infected cells is mainly at the promoter regions of genes involved in cell cycling. Additional work focusing on the E1A interaction with additional host proteins revealed that E1A forms a tertiary complex with pRb and p300, where E1A-bound p300 acetylates pRb. The acetyl pRb bound to E1A was shown to repress gene expression in cellular defense and differentiation.[10] The authors of this study demonstrate that differential H3K18ac occupancy in the IR influences gene expression. IRs of genes related to immune activation were deacetylated and were associated with reduced gene expression in the virus-infected fibroblast cells compared to the mock infection. However, genes related to replication and cell cycling were hyperacetylated in the IRs of virus-infected cells and positively correlated with increased gene expression.[18]

E1A has also been observed to induce c-Myc expression by the selective regulation of host gene expression.[19] In this study, the authors show that soon after infection, E1A binds to p300 and disrupts the p300-HDAC3-YY1 complex (HDAC3 [histone deacetylase 3] and YY1 [Yin Yang 1], the transcription factor for Myc). This complex is bound at the YY1 binding site upstream of the Myc promoter (Figure 1B). In an uninfected, quiescent cell, the HDAC3 in the complex deacetylates the promoter, repressing Myc transcription. However, upon adenovirus infection, E1A binds to p300 and dissociates this complex, resulting in the upregulation of Myc expression. E1A-driven c-Myc expression is implicated in the cellular transition

to the S phase, a crucial step for viral replication. These studies suggest that while the activity of p300 acetyltransferase is altered upon the E1A-p300 interaction, some gene regions that bolster viral replication are selectively upregulated due to altered acetylation.

In addition to p300/CBP, E1A binds to other acetyltransferase enzymes, like GCN5 (general control non-depressible 5) and pCAF (p300/CBP-associated factor). E1A expression in BALB/c 3T3 cells increased H3K9 acetylation.[20] Furthermore, the ability of E1A to bind to TRRAP (transformation/transcription domain-associated protein; a multisubunit complex that recruits both GCN5 and pCAF to the catalytic unit) has been implied in acetylating H3K9/14 at cyclin A and cdc6 promoter regions, thereby promoting their expression[21] (Figure 1C). The upregulation of these genes was observed to aid in transitioning from a G_0 to an S phase in BALB/c 3T3 cells.[18] In the early stages of infection, the N-terminal and CR3 (conserved region 3) regions of E1A have been shown to bind to the GCN5 HAT complex and other cellular complexes for chromatin decondensation and remodeling.[20,22] Upon adenovirus infection, H3K9ac, the predominant target of GCN5, was seen to increase by 28.2% when compared to mock-infected fibroblast cells, observed by ChIP-seq.[18] Overall, these studies indicate that the effect of adenoviral infection on the activity of GCN5 and pCAF has an enzyme-upregulatory effect in that there is an increase in the acetylation of the respective histone residues. Although the interaction between viral proteins and the host cell proteins in the murine background can be informative, careful interpretation of its translatability in the human system is required, as the human adenovirus does not effectively replicate in the murine setting. While there have been substantial contributions toward understanding the impact of GCN5 and pCAF on the host genome in the process of adenoviral infection,[20–22] there has been a greater focus on studying the effects of the E1A-GCN5/pCAF interaction on the viral genome—as discussed in the following section.

Influence of acetylation on viral genome

Intriguingly, the viral genome is intrinsically organized into nucleosome-like chromatin structures around the viral core proteins. During infection, there is a transition phase where the viral genome is bound to both the viral core protein pVII and the host histone proteins.[23] Along the process of viral transcription, the "viral nucleosomes" acquire several host-like attributes, including post-translational modifications of histones.[23] A key player in this process is p300. Previous works demonstrate that p300 binding to the adenoviral CR3 region of 13S E1A (isoform 13 of E1A) is required for transcriptional activation.[24] Furthermore, 12S E1A (isoform 12 of E1A), which lacks the CR3 region, was shown to "squelch" or inhibit transcriptional activation by sequestering p300 through N-terminal/CR1 region binding.[24]

Mechanistically, it has been observed that E1A directs p300 acetyltransferase activity toward viral promoters, acetylating H3K18/27 at E2early, E3, and E4 viral promoters.[9] In addition, the authors of this study demonstrate through extensive sequence-specific mutations in E1A and ChIP-seq of H3K27ac, TBP (TATA binding protein), and RNA Pol II (RNA polymerase II) that the E1A-p300 interaction is required for recruiting TBP and RNA Pol II at these promoter regions. The authors of this study also showed that p300 influences the formation of the pre-initiation complex (PIC) at the E2early viral promoter—the loss of the E1A-p300 interaction results in reduced PIC formation, along with a reduction in the viral mRNA transcript. In addition, H3K18/27ac at the promoter region of E4 had little to no change in the PIC assembly but resulted in a near 10-fold reduction in the E4 transcript.

Although not involved in regulating PIC assembly, p300/CBP recruitment to the E4 promoter is critical to acetylate H3K18/27 and release the RNA Pol II into productive elongation during its transcription[25] (Figure 1D). Furthermore, using a p300-specific HAT inhibitor, A-485, it was observed that the acetyltransferase activity of p300 drives the RNA Pol II release into elongation at the E4 promoter. Using mutant E1A that is defective for p300 binding, the authors also demonstrate that the E1A-p300 interaction is vital for the super-enhancer complex (SEC) recruitment at the E4 promoter. While investigation into the epigenetic influence of adenoviruses has been primarily focused on the two most common serotypes, Ad5/2, studies using Ad12 demonstrate that E1A 12S forms a ternary complex with CREB-1/ATF-1 and p300/CBP. This complex is essential to bind to the E2-CRE (cAMP responsive element) and induce expression. The binding of p300/CBP was also found to drive H4 acetylation at the E2 promoter, thereby inducing gene expression.[26] Observations from these studies indicate the vital role of p300 in viral promoter acetylation, thereby upregulating their expression. Furthermore, these observations point to a multifaceted role of p300 in enabling viral replication.

GCN5 has been observed to act as a regulatory factor, negatively impacting virus replication (Figure 1E). Pharmacological inhibition of GCN5 increased E1A CR3 transactivation.[20] In addition, another study pointing to a regulatory role of GCN5 demonstrates that in mouse embryonic fibroblasts with homozygous expression of acetyltransferase-defective GCN5, activation of the E4 promoter increased.[20] Binding of GCN5 was required at both the N-terminal and CR3 regions of E1A to acetylate the viral genome at the E4 promoter at H3K9/K14—this epigenetic modification was found to repress E4 activation by reducing phosphorylated RNA Pol II occupancy. The authors of this study also observed that KAT inhibition through cyclopentylidene-[4-(4′-chlorophenyl)thiazol-2-yl]hydrazone (CPTH2) reduced virus yield. However, this effect could be the consequence of CPTH2 inhibiting p300 and GCN5.[27]

In a recently published study, the acetyltransferase enzyme HBO1 (histone acetyletransferase binding to ORC1), belonging to the MYST (MOZ, Ybf2/Sas3, Sas2, Tip60) family of acetyltransferases, was observed to complex with E1A during adenovirus replication[28] (Figure 1F). In this study, the authors observe that HBO1-mediated acetylation of H3K14 at the viral promoters is essential for virus replication. HBO1 was found to co-localize in the virus replication centers along with the viral DNA-binding protein (DBP). Short hairpin RNA

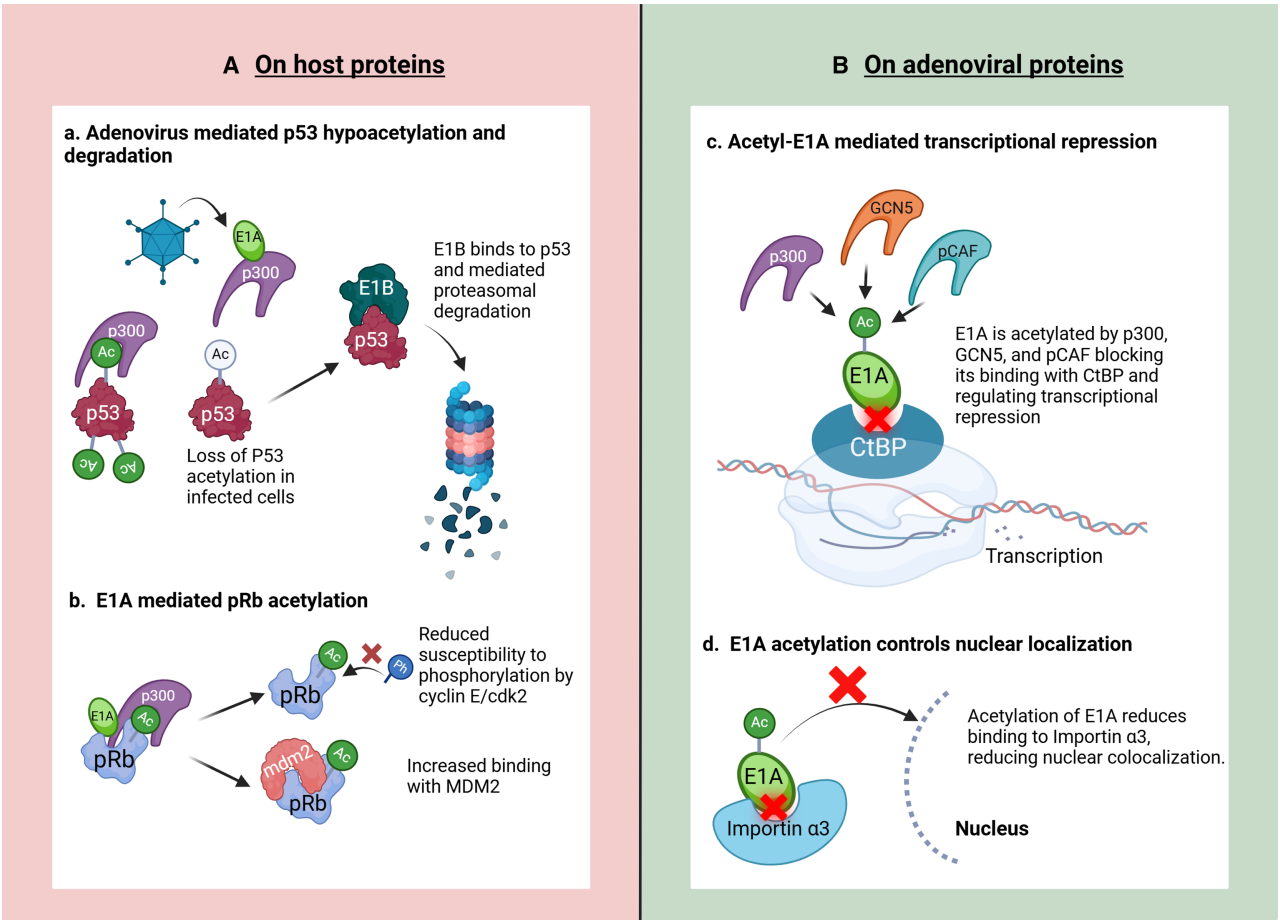

Figure 2. Adenovirus-induced alterations in acetylation and their effects on the proteome

(A) E1A-p300 interaction inhibits p53 acetylation, reducing its stability and promoting E1B-55K-mediated proteasomal degradation. (B) E1A forms a complex with p300 and pRb, leading to pRb acetylation, decreased pRb phosphorylation, and enhanced pRb-mdm2 binding. (C) Acetylation of E1A by various acetyltransferases modulates its CtBP binding and transcriptional repression activities. (D) Acetylated E1A cannot bind to importin α3, preventing its nuclear translocation and subsequent influence on gene expression. This figure was created with BioRender.com.

(shRNA)-mediated knockdown of HBO1 reduced H3K14ac at the viral promoters along with the mRNA expression of viral transcripts (E2, VA, E3, E4Orf6/7, and hexon) following infection with adenovirus serotype 5 in HEK293 cells. Knocking down HBO1 reduced the viral titer, indicating that HBO1 positively regulates viral replication.

From the perspective of host defense, the acetyltransferase enzyme TIP-60 is observed to bind to the promoter region of E1A to repress E1A gene expression. However, as a counteraction, the viral proteins E1B55k and E4orf6 bind to TIP60 to promote its proteasomal degradation.[29] These observations demonstrate the ability of the virus to hijack specific host acetyltransferase enzyme activity to boost viral protein expression for the establishment of successful viral replication.

Virus-mediated acetylation of cellular proteins

Adenovirus hinders p53 function on multiple stages—first, E1B binding to p53, which mediates proteasomal degradation, and second, E1A binding to p300, thereby reducing its availability to acetylate p53, ultimately affecting its stability and activity.[11] In this study, it was found that although E1B mutant adenoviruses increased the accumulation of p53 in cells, the expression of the downstream targets of p53, namely P21 and MDM2, was not increased[11] (Figure 2A). The authors then demonstrate that E1A, which is still expressed by the mutant adenovirus, blocks the acetylation of p53 by binding to p300 and reducing its availability to acetylate p53. This reduction in p53 acetylation was shown to hamper its activity. Blocking both E1B expression and the ability of E1A to bind to p300 led to the increased accumulation and activity of p53.

As we commented earlier, E1A is also known to bind to the tumor-suppressor protein pRb. E1A binds to pRb and frees it from E2F, stimulating gene expression and pushing the cell to a pseudo-S phase. The multimeric E1A-P300-pRb complex that leads to pRb acetylation also influences changes in protein-protein interactions

with pRb[30] (Figure 2B). The acetylated pRb was found to have reduced susceptibility to phosphorylation by cyclin E/cdk2 and increased binding with MDM2, the subsequent effect of which is implicated in E1A-dependent apoptosis. 12S E1A is also shown to inhibit cyclin D1 expression by binding to p300 and preventing the deposition of acetyl marks on the cyclin D1 promoter region. Cyclin D1 acts as a checkpoint at the G_1/S phase transition and blocks S-phase entry when DNA-damaging agents are present.[31] Cyclin D1 is also essential in negatively regulating apoptosis. Furthermore, c-Fos/c-Jun also positively regulates cyclin D1 induction, and E1A represses c-Jun activity by inhibiting acetylation via p300/CBP.[32]

In the context of increasing the infected cellular susceptibility to apoptosis, E1A was observed to block the expression of cytoprotective genes interleukin (IL)-6, MnSOD (manganese superoxide dismutase), and ferritin H in a nuclear factor κB (NF-κB)-dependent manner.[33] These genes are conventionally upregulated when tumor necrosis factor alpha (TNF-α) levels increase, which, in turn, enhances the activity of NF-κB. NF-κB activity is also attributed to its acetylation following dissociation from the inhibitor, IκB. However, in the presence of E1A, p300/CBP binds to E1A; thereby, its availability is limited, and NF-κB does not get acetylated. Thus, this block in NF-κB activity downregulates cytoprotective factors, making the cell more susceptible to apoptosis.

Influence of acetylation on viral proteins

In 1980, Fedor et al. showed that viral core proteins pV and pVII were acetylated and that viral protein acetylation occurred concurrently with their synthesis.[34] However, viral protein acetylation was stable and not dynamic like histone acetylation, which is influenced by the interplay between HATs and HDACs. The acetyltransferase enzymes p300, GCN5, and pCAF also acetylate the 12S E1A protein and histones.[35] pCAF and p300 acetylate the Lys-239 residue on 12S E1A and negatively regulate E1A-CtBP (C-terminal binding protein) binding, which, in turn, influences E1A-directed transcriptional repression (Figure 2C). Additionally, pCAF is observed to bind to the CR3 region in 13S E1A—a region not present in the 12S E1A.[36] The CR3 region is involved in E1A-mediated transcriptional activation. The authors of this study found that the inhibition of pCAF-CR3 binding reduced E1A-mediated transcriptional activation. In contrast, another study demonstrates that only a small amount of E1A is acetylated *in vivo* and that CtBP-mediated transcriptional control is not influenced by whether CtBP binds to E1A. Instead, acetylation of E1A by p300/CBP at Lys-239 confers localization specificity to E1A, wherein acetylation of Lys239 reduces E1A binding to importin-α3 and hence restricts E1A to the cytoplasm[37] (Figure 2D). However, reducing Lys-239 acetylation increases E1A-importin-α3 binding, which enables E1A shuttling to the nucleus. Depending on its location, E1A-mediated functions may be affected.

While a significant portion of studies focus on the epigenetic modulation by the early protein E1A, it has been described that the viral protein pVII, an essential protein found in the core of the adenovirus, binds with the cellular histones and the host nucleosomes.[38] In part, the phenomenon of pVII co-localization depends on the acetylation of pVII itself. pVII binding to the cellular chromatin was found to limit access to DNA—which could be interpreted as selective control of the host gene expression to restrict antiviral defense mechanisms.

Viral proteins modulate the acetylation of host cell proteins to alter immune attack

In the process of viral proteins binding to host chromatin, pVII was also found to bind to HMGB1 (high-mobility group box 1), a known activator of the inflammatory immune response. Sequestering of HMGB1 by the viral protein pVII was observed to limit the ability of the host cell to mount an effective antiviral inflammatory immune response as measured by neutrophil accumulation.[38]

The early region viral protein E1A is also observed to repress inflammation by blocking COX-2 (cyclooxygenase-2) expression.[39] E1A binds to p300 and prevents acetylation of the COX-2 promoter region, thereby reducing gene expression.

In the context of antiviral defense, E1A has been previously shown to influence the expression of interferon (IFN)-regulated genes, including IRFs (IFN regulatory factors). One study demonstrates that E1A blocks IRF-2 activity by binding to p300/CBP, preventing p300-mediated acetylation of IRF-2.[40] In this study, the authors demonstrate that IRF-2 acetylation is required for the expression of H4, one of the downstream targets of IRF-2, and that in the presence of E1A-p300 binding, IRF-2 cannot upregulate H4 expression. E1A alone is also shown to block STAT2-mediated type I IFN gene stimulation by binding to GCN5 and blocking its ability to acetylate histones at these promoter regions.[41]

Ad-12 E1A, known to downregulate major histocompatibility complex (MHC) class I genes, is shown to complex with HDAC1, -3, and -8. Eliminating E1A-12, as well as treatment with TSA (trichostatin A), an HDAC inhibitor, resulted in an increase in acetylation and expression of class I MHC.[42]

Exploiting adenovirus-mediated change in acetylation to enhance oncolytic virotherapy

Several reports show that HDAC inhibitors increase the infection and activity of adenoviruses in various cell types.[43–46] The combination of oncolytic adenoviruses with acetylation modifiers like HDAC inhibitors to increase the oncolytic effect of the adenovirus has been studied in multiple cancer contexts. One study observed increased virus replication and therapeutic benefit when triple-negative breast cancers and PDACs (pancreatic ductal adenocarcinomas) were treated with HDAC inhibitors 24 h after viral infection.[46] Interestingly, another report showed the therapeutic benefit of treating glioblastoma simultaneously with oncolytic adenovirus and HDAC inhibitors.[45] Previous works also demonstrated increased adenoviral infectivity of melanoma cells previously treated with the HDAC inhibitor FK 228. This study showed an increase in CAR (coxsackie

adenovirus receptor) expression upon FK 228 treatment, which subsequently allows for increased binding and infection by adenoviruses and subsequent oncolysis.[44]

As for the viral protein E1A, studies demonstrate that combining HDAC inhibitors with E1A alone can induce apoptosis in ovarian cancer and breast cancer cells through the Egr1-Bim (early growth response 1/Bcl-2 interacting mediator of cell death) pathway.[47] While the HDAC inhibitor SAHA (suberoylanilide hydroxamic acid) hyperacetylated H3K9 at the promoter regions of both Bim and Egr1, E1A upregulated their expression by activating the DNA element, serum responsible element (SRE) in the promoter region. In yet another context of using HDAC inhibitors to improve the oncolytic efficacy of adenovirus, one study demonstrates the benefit of using HDAC6 inhibitors in improving viral prevalence within the cell.[48] In this study, the authors explore the role of acetylation on TRIM21 (tripartite motif-containing protein 21), an intracellular antibody receptor protein that recognizes virus-antibody complexes and facilitates proteasomal degradation. Removing the acetyl marks from K385 and K387 of TRIM21 by HDAC6 propagates dimerization and activation of TRIM21, which then mediates virus clearance via proteasomal degradation. However, treatment with the HDAC6 inhibitor tubacin increased acetylation at K385 and K387 and reduced dimerization and ubiquitination of TRIM21, thereby increasing viral persistence within the cell.

Adenoviral infections are also associated with an increase in microtubule acetylation in the context of increasing microtubule stability. As microtubule stability is vital for viral infection and transport to the nucleus, recent combinatorial approaches with oncolytic virotherapy demonstrate the combinatorial benefit of using chemotherapeutic drugs like paclitaxel, which increases microtubule stability via acetylation, with oncolytic adenoviruses in the context of cervical cancer[49] and ovarian cancer.[50]

The ability of E1A to bind to p300 has also been investigated in the context of conferring sensitivity to anti-cancer drugs. For instance, one study explores the effect of E1A in drug-resistant breast cancer. HSPA5 is a heat shock protein that promotes proliferation, migration, and drug resistance.[51,52] Acetylation of HSPA5 at K353 by p300 confers stability to the protein, potentiating its pro-cancer effects. The authors show that, upon E1A expression, HSPA5 acetylation decreases due to insufficient p300 availability. The hypoacetylated HSPA5 is then ubiquitinated and undergoes proteasomal degradation. The loss of HSPA5 upon adenovirus infection makes the cancer cells more susceptible to anti-cancer drugs.

CONCLUSIONS

This review summarizes the current knowledge on adenovirus-mediated modifications of the cancer acetylome during oncolytic viroimmunotherapy. The report is timely because oncolytic virotherapy is receiving regulatory approval as a treatment for solid tumors.[53,54] However, to enhance the efficacy of viroimmunotherapy for patients with cancer, a deeper understanding of the intricate mechanisms that govern the interactions between adenoviral proteins and the cancer cell epigenome is crucial. Over the years, researchers have partially documented the differential acetylation patterns in both host cells and viruses, which play a significant role in virus-influenced epigenetic changes. This review aims to provide a comprehensive overview of the oncolytic adenovirus's effect on acetylation, focusing on histone acetylation and its impact on gene expression, non-histone protein acetylation, and the role of these acetylation processes in facilitating successful viral infection, replication, and immune evasion.

Understanding the role of oncolytic viruses in modifying the acetylome is of critical importance in elucidating the mechanisms of oncolysis and the reshaping of the tumor microenvironment, particularly in light of the fact that hyperacetylation appears to be a significant driver of oncogenesis and tumor progression in certain malignancies. This is especially relevant in the context of pediatric malignant gliomas and other neoplasms, where epigenetic dysregulation plays a crucial role in tumor development and resistance to conventional therapies.

Oncolytic viruses, such as adenoviruses, have shown promise in targeting and lysing cancer cells while simultaneously stimulating antitumor immune responses. Their ability to modulate the host cell acetylome may contribute to their therapeutic efficacy in multiple ways. Firstly, by altering the acetylation patterns of key regulatory proteins and histones, these viruses can potentially reverse the hyperacetylation state that promotes tumor growth and survival. Secondly, changes in the acetylome can lead to the expression of viral antigens and cellular stress proteins, enhancing the immune recognition of the tumor cells. Moreover, the virus-induced modifications of the acetylome may extend beyond the infected cancer cells, influencing the broader tumor microenvironment. This could include alterations in immune cell function, stromal cell behavior, and the production of soluble factors that mediate intercellular communication within the tumor ecosystem. By comprehensively mapping these acetylome-mediated changes, researchers may uncover novel targets for combination therapies that synergize with oncolytic virotherapy, potentially leading to more effective treatments for aggressive cancers.

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AUTHOR CONTRIBUTIONS

Conceptualization, A.P., C.G.-M., and J.F.; literature analysis, A.P., C.G.-M., and J.F.; writing – original draft, A.P.; writing – review & editing, A.P., M.F., A.G.G., M.M.A., C.G.-M., and J.F. All authors have read and agreed to the published version of the manuscript.

DECLARATION OF INTERESTS

M.M.A., C.G.-M., and J.F. report intellectual property related to oncolytic adenoviruses.

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