Extensive studies on viral-mediated oncogenic transformation by human adenoviruses have revealed much of our current understanding on the molecular mechanisms that are involved in the process. To date, these studies have shown that cell transformation is a multistep process regulated by the cooperation of several adenoviral gene products encoded in the early regions 1 (E1) and 4 (E4). Early region 1A immortalizes primary rodent cells, whereas co-expression of early region protein 1B induces full manifestation of the transformed phenotype. Beside E1 proteins, also some E4 proteins have partial transforming activities through regulating many cellular pathways. Here, we summarize recent data of how adenoviral oncoproteins may contribute to viral transformation and discuss the challenge of pinpointing the underlying mechanisms.

**Keywords:** CBP; E1A; E1B-55K; E4; human adenovirus; oncogene; p300; p53; pRb; transformation

It is estimated that ~12% of human cancers worldwide have a viral etiology. Tumorigenesis induced by a viral infection has been shown to be slow and inefficient, usually with tumors developing in only a minority of infected individuals years or decades after primary infection. Therefore, most viruses do not cause cancer in their native host, but many can cause cancer in hosts where they persist or are replication-defective. Hence, after the first report from Trentin and coworkers showing that human adenovirus type 12 (HAdV-A12) can induce malignant tumors following inoculation into newborn hamsters, adenoviruses have not been shown to induce cancer in its natural host [1]. Nevertheless, it became apparent that adenoviruses provide an excellent experimental model to investigate molecular events involved in cell transformation. Transformation by viral proteins results from altering normal cell growth and differentiation pathways. Much of our current knowledge about the molecular mechanisms of viral-mediated oncogenic transformation derives from the study of the adenoviral gene products of the E1 and 4 (E4). In this review, we present the current state of knowledge of the adenoviral oncogenicity and the molecular mechanisms of the adenoviral gene products involved in the initiation and maintenance of morphologically transformed cells.

**Transformation in cell culture**

Despite HAdVs differ in their oncogenic activity, all types of the subgroups tested so far stably transform a broad range of rodent cells (e.g., from rat, mouse, or...
hamster) with comparable efficiencies [1–6], which could be extended to lagomorph cells, a closely related monophyletic group, such as primary rabbit lens epithelial cells [5]. However, HAdVs do not transform human cells. HAdV-A12 or HAdV-C5 DNA fragments have been shown to induce transformation of only a few types of cultured human primary cells, including human embryo kidney cells [6], human embryonic lung cells [7], human embryo retinoblasts [8–11], and amniocytes [12]. Additionally, Speiseder et al. [13] could only recently successfully transform multipotent human mesenchymal stem cells as efficiently as primary baby rat kidney (BRK) cells.

**Adenoviral oncogenes**

The E1 has been found to be integrated in the host-cell chromosomes, and expression of viral genes was found in most adenovirus-induced tumors, and tumor-derived and tumor-transformed cell lines [2]. Therefore, the classical concept of viral oncogenesis, in which viral genes persist within transformed cells, is given. Since only the E1 region is consistently found in virus-transformed cells and transfection of cultured cells with plasmids encoding E1 genes induces oncogenic transformation, it was believed that E1 genes are the only adenoviral oncogenes involved in cell transformation. Later on, reports on the frequent head-to-tail integration of the E1 and E4 region, which are encoded in the left and the right end of the viral DNA, respectively, suggested a possible contribution of the E4 region to transformation [14]. In line with this, the presence of E4-specific transcripts results in proteins with a molecular weight of 25 kDa, 24 kDa, and 20 kDa in adenovirus-transformed cells [15–18] and antibodies directed against E4 products were detected in tumor serum from hamsters [19–21].

Further evidence for the E4 region being involved in transformation has been deduced from a study of the subgroup D HAdV-D9, which has shown that the primary oncogenic determinant is encoded in the E4 [22]. Moreover, investigations revealed that the E4 region supports transformation of BRK cells in cooperation with E1A, and early region 1A (E1A) plus early region protein 1B (E1B) [23,24]. Recent publications have reported that the oncogenic properties of E1B and E4 open reading frame 3 (E4orf3) proteins could be related to nuclear tumor-suppressive promyelocytic leukemia nuclear bodies (PML-NB) [25–28]. Formation of PML-NBs is regulated by stress and leads to enhanced sequestration of target proteins allowing their regulation and/or posttranslational modification (PTM) by small ubiquitin modifier (SUMO) [24,27]. PML-NBs regulate many pathways associated with senescence, inflammatory responses, DNA damage, apoptosis, antiviral defense, and elevated ROS levels [29,30]. These regulations are dependent on intact PML-NBs and are a prerequisite for the tumor-suppressive role of PML [31]. The role of each viral oncogene on PML-NB is described in more detail in the next sections.

**Early region 1**

The E1 region consisting of the transcriptional units E1A and E1B is required for complete morphological transformation of infected cells. Expression of the E1A gene alone immortalizes primary cells by altering the cell growth cycle [32]. Transformation of BRK cells is only successful if E1A is expressed at least together with E1B-55K [33] and becomes effective if the E1A, E1B-55K, and E1B-19K proteins are co-expressed. Intriguingly, in vivo latency experiments with promoter-driven lung-specific expression of HAdV-C5 E1A and E1B have shown that E1A alone is not sufficient to induce lung carcinomas and confirmed the results obtained in BRK cells. However, co-expression of E1A and E1B caused lung carcinogenesis and impaired p53 response [34]. The role of adenovirus E1 oncogenes in malignant transformation has been summarized in many excellent reviews, which supplement this one [30,35–40].

The early region 1A proteins in cell transformation

Early region 1A is an extensively studied protein since it mediates one of the first steps of the transformation process, which is important for transformation and/or tumorigenicity by inducing unscheduled DNA synthesis and cell proliferation, which lead primary rodent cells to become immortalized [41]. To this end, E1A interacts with several growth-regulatory proteins participating in transcription control, cell-cycle progression, and apoptosis [42,43] (Table 1). The E1A gene produces an RNA precursor, the alternative splicing of which gives rise to two major mRNAs (13S and 12S, according to their sedimentation coefficients). The 13S mRNA encodes a polypeptide of 289 amino acids (aa) in the case of Ad2/5, while the 12S mRNA encodes a polypeptide of 243 aa [38]. Comparison of E1A sequences from different adenovirus serotypes revealed four highly conserved regions (CR1–CR4) [44,45]. The first 40 residues of HAdV-5 E1A harbor the nonconserved N-terminal region (NTR) of E1A [46–48] followed by the CR1 (aa: 41–80), which interacts with at least 15 different cellular targets that directly regulate...
gene expression [49]. Among them are specific transcriptional regulators such as AP-2 [50], myogenin [51], and thyroid hormone receptor (TR) [52,53] and general transcriptional coactivators, such as p300/CREB-binding protein (CBP) [54,55], p400 [56], TRRAP [57,58], p300/CBP-associated factor (pCAF) [59], and TBP [60,61]. The ability of E1A to bind a broad range of cellular regulatory proteins is mediated by its integrated short linear amino acid motifs, called molecular recognition features [62]. Moreover, the NTR together with the CR1 and CR2 domains drive cell-cycle progression from the quiescent phase (G1 phase) to the synthesis phase (S phase). Therefore, at least two independent but possibly synergistic pathways controlled by retinoblastoma protein (pRb) and p300 [63,64] are activated.

First, E1A-mediated induction of cell-cycle progression is regulated by the release of E2F transcription factors (E2Fs) that are associated with the cellular transcriptional repressor pRb and the related members p107 and p130. This association inhibits the expression of cellular cell-cycle progression genes [65,66]. Depending on the isoform, E2Fs activate (E2F-1, E2F-2, and E2F-3) or repress (E2F-4, E2F-5, and E2F-6) gene expression. E1A counteracts the tight control of E2F by pRb through binding to the pocket domains of pRb via its LXCXE motif located in CR2. Thus, E1A interaction with pRb family members dissociates it from E2F [65,67,68], which in turn activates viral and cellular gene expression resulting in the S-phase promotion of the cell cycle [69,70].

Second, E1A binding to the histone-directed acetyltransferases p300/CBP controls DNA synthesis and S-phase progression to immortalize cells [55,71]. This interaction is important as p300/CBP has versatile roles in gene regulation. On the one hand, at least 411 proteins are implicated in binding p300/CBP through their various protein interaction domains [72]. On the other hand, p300/CBP regulates transcription by inducing acetylation of proteins, thereby altering protein–protein interactions of transcription complexes. To date, about 100 proteins are supposed to be acetylated by p300/CBP [72]. The p300/CBP E1A interaction illustrates how E1A embeds itself deeply within the cellular protein interaction network. Moreover, E1A binds to 32 primary cellular hub proteins leading to secondary interactions with over 2000 other cellular targets [73]. As a consequence, E1A-mediated retargeting of many different transcription factors to specific loci of host gene promoters results in regulated widespread changes in H3K18 acetylation [67,74]. Thus, many cellular genes involved in differentiation are transcriptionally inactivated, while those regulating cell cycle are upregulated inducing immortalization of primary cells.

Besides direct interactions, E1A is also associated indirectly with histone acetyltransferases (HATs) by binding to TRRAP and p400 that are scaffolding proteins important for bridging interactions of HATs with transcriptional regulators [58]. The interaction of E1A with these proteins is important to transcriptionally activate cellular genes involved in cell proliferation in order to activate DNA synthesis and in stimulating cellular growth [75,76]. Therefore, CR1 and CR2 of E1A are involved in suppression of differentiation, induction of DNA synthesis and cell-cycle progression, and modulation of gene expression functions upon transformation [40,67,68,77,78].

The CR3 is crucial for transactivation of adenovirus early genes upon infection but is dispensable for immortalization and complete transformation by E1A in cooperation with E1B [79,80]. Furthermore, the CR3 is the most conserved domain among different adenovirus E1A proteins and is unique to 289R E1A [81], while the 243R E1A and 289R E1A proteins have in common the CRs 1 and 2 at their N terminus and the CR4 at their C terminus [82].

The CR4 is assumed to modulate the transforming activity of E1A and is required to maintain the cells in a proliferative state [48]. The mechanism behind this modulation is not completely solved as CR4 suppresses transformation by E1A in cooperation with ras by its binding to the C-terminal-binding protein [83,84]. Deletions of CR4 cause a ‘hyper-transformed’ phenotype [85]. In summary, E1A proteins are essential to mediate the most critical step in oncogenic transformation by invading and modifying protein interaction networks with far-reaching consequences.

**The early region protein 1B in cell transformation**

The E1B gene is located adjacent to E1A and produces two major mRNA species, 22S and 13S, with identical 5’ and 3’ termini derived from alternative splicing of a common mRNA precursor. The 22S mRNA encodes two major E1B proteins with overlapping reading frames. The first initiation site produces a 19K polypeptide of 176 residues (176R), whereas an internal initiation site with an alternative reading frame produces a 55K (495R) product. The second major E1B 13S mRNA encodes both 176R protein and an 84R protein, the N terminus of which is identical to that of 495R. Further minor mRNAs derived from the 22S precursor through alternative splicing are 14S and 14S [86]. 14S and 14S encode 55 kDa-related proteins namely 156R, 93R, and 84R [87] that have
the N-terminal 79 residues of E1B-55K in common, but differ at their C terminus. E1B-156R shares the 77 C-terminal residues of E1B-55K that harbors a transcription repression domain and contains homologous phosphorylation sites. However, 93R and 84R have unique C termini [87]. Generally, E1B proteins complete cell transformation of E1A-immortalized cells by counteracting E1A-induced programmed cell death (apoptosis) and growth arrest [88,89] (Table 1). It has been shown that the two major gene products E1B-19K and E1B 55K of the E1B region are involved in transformation [9]. It was suggested that both E1B proteins act in additive fashion as both proteins are individually capable of cooperating with E1A to transform BRK cells, but if both proteins are co-expressed with E1A the transformation efficacy is enhanced [90–93]. Furthermore, it has been shown that E1B-156R induces focal formation of BRK cells in cooperation with E1A.

**Table 1. Functional characteristics of HAdV oncoproteins.**

| HAdV proteins | Cellular targets | Mode of action | Effect on host | References |
|---------------|-----------------|----------------|----------------|------------|
| E1A | pRb, p300/CPB | Activation of E2F transcription factors | S-phase induction | [64,66–69] |
| | | Modulation of H3K18 acetylation | S-phase induction | [55,63,67,71–74] |
| | TRRAP, p400 | Indirect association with HATs | Activates cell proliferation | [57,58,75,76] |
| E1B | E1B-19K | E1B-19K (Bcl-2 homolog) heterodimerization inhibits Bax | Suppresses apoptosis | [38] |
| | P53 | Inhibition of mitochondrial dysfunction | Suppresses apoptosis | [107] |
| | | Transcriptional repression of p53-dependent genes: | Suppresses apoptosis | [99,108–114] |
| | | • Relocalization to perinuclear bodies | | |
| | | • Inhibition of p53 acetylation | | |
| | | E3 SUMO ligase of p53 | | |
| | PML-IV, PML-NB components (Daxx, Sp100, PML, RNF4) | Repression of p53 | Suppresses apoptosis | [125,127,128] |
| | | Daxx: | Suppresses apoptosis | [94,122,126] |
| | | • Intranuclear relocalization RNF4/E1B-55K interaction induces proteasomal degradation of Daxx | (indirect repression of p53 transcriptional activity) | |
| | | Sp100: | | |
| | | • Relocalization to nuclear matrix and into cytoplasmic inclusion bodies | | |
| | SUMO | Increased E1B-55K SUMOylation is linked to its nuclear localization | High transformation efficacy | [136,137] |
| | | Disruption of E1B-55K SUMOylation is linked to its cytoplasmic localization | Low transformation efficacy | |
| E4 | E4orf1 | PDZ proteins (MUPP1, DLG1, MAGI-1, and ZO-2) | Activation of the PI3K pathway | Promotes cell proliferation | [149–155] |
| | E4orf3 | P53 | Induction of H3K9 methylation at p53-dependent promoters | Suppresses apoptosis | [158,159] |
| | | PML-II | Reorganization of PML-NBs into track-like structures | Uncontrolled cell proliferation | [27,28,160,161] |
| | | MRN complex (Mre11, Rad50, NBS1) | Relocalization of MRN complex components into PML tracks | Inhibition of DSBR | [165] |
| | DNA PK | Inactivation of DNA PK | Inhibition of DSBR | [163] |
| | E4orf6 | P53 | Transcriptional repression of p53-dependent genes | Suppresses apoptosis | [159] |
| | DNA PK | Inhibition of DSBR | Inhibition of DSBR | [163] |
adhesive apoptotic pathways such as the TNF-
assuming that in contrast to E1B-55K, the p53-inde-
mechanism by which E1B-19K inhibits apoptosis dur-
ting the transformation process is unknown, but it is
assumed that in contrast to E1B-55KDa, the p53-inde-
apoptotic pathways such as the TNF-α and Fas ligand cell death pathways are inhibited [91,98,99].
E1B-19K is a Bcl-2 family analogue that shares their
BH domains, which are important to regulate apopto-
[100,101]. E1B-19 kDa functions independently
from E1B-55K protein to inhibit apoptosis. Pro-
apoptotic proteins, such as Bax, activate caspases to
induce cell death. Their function is inhibited upon
heterodimerization of the BH domain of Bcl-2 with Bax. The viral Bcl-2 functional homologue E1B-19K
inhibits pro-apoptotic activities of Bax and Bak compar-
ably to Bcl-2 [38]. Moreover, E1B-19K blocks fur-
ther mitochondrial signaling events which are regulating apoptosis [98,102–106]. Furthermore, it has
been shown that E1B-19K rescues cells from p53-medi-
apoptosis that may be induced by alleviated p53-
methylated transcriptional repression rather than by
transcriptional activation [107]. The p53-dependent
and p53-independent anti-apoptotic functions of
E1B-19K confer full transformation potential.

Role of E1B-19K in cell transformation

There are conflicting results regarding the role of E1B-
19K during transformation as another analysis from
HAdV-A12 and HAdV-C5 E1B-19K showed that it is
dispensable for efficient transformation of BRK and
baby mouse kidney cells [95–97]. The entire molecular
mechanism by which E1B-19K inhibits apoptosis dur-
ting the transformation process is unknown, but it is
assumed that in contrast to E1B-55KDa, the p53-inde-
apoptotic functions independent of inhibiting
p53-stimulated transcription [94].

Role of E1B-55K in transformation

Extensive studies on E1B-55K have revealed new
mechanisms whereby E1B-55K mediates transforma-
tion. Hence, we review its main regulatory function
in cell transformation and summarize recent discoveries
on the additional roles of E1B-55K in this process.

Inhibition of p53 functions

The most extensively studied role of the E1B-55K pro-
tein regarding transformation is the inhibition of the
tumor suppressor p53 and specifically the inactivation of
p53 pro-apoptotic functions [99,108,109] and/or in-
duction of cell-cycle arrest [110,111]. E1B-55K is targeted to
p53-responsive promoters [112] by binding to p53 [113]
leading to efficient repression of p53-mediated tran-
scription [114]. Moreover, it is assumed that E1B-55K
sequesters p53 into perinuclear bodies to inhibit its tran-
scriptional activity [115]. It has been shown that a cellu-
lar corepressor that copurifies with RNA polymerase II
is required for the repressive activity of HAdV-C5 E1B-
55K together with p53 [114]. In line with this, binding
to cellular transcriptional repression factors such as his-
tone deacetylase 1 and mSin3A [116] is involved in the
E1B-55K-mediated transcriptional repression.

Besides modulating p53 itself, E1B-55K regulates
PTM of p53 in multiple ways to counteract its func-
tions. On the one hand, E1B-55K inhibits acetylation
by binding to both p53 and the transcriptional coacti-
vator PCAF [117]. On the other hand, E1B-55K serves
as a p53-SUMO1 E3 ligase that inhibits p53 functions
by relocating it into PML-NBs [118,119]. The above
summarizes multiple ways of E1B-55K-mediated p53
inhibition contribute to our understanding of p53 inhibi-
tion in transformation. Furthermore, targeting the
function of p53 in different ways ensures that although
the large E1B of HAdV-C5 and HAdV-A12 is sub-
stantially different from each other, some functions are
retained during evolution to inhibit p53, which is
important to counteract apoptosis.

Relocalization to PML-NB

Many of the so far identified interaction partners of
E1B-55K are transient or constitutive components of
the PML-NBs [120], such as p53 [121], Daxx [122],
ATRX [123], Sp100 [124], PML [125], and RNF4
[126]. Generally, it has been shown that the PML-NB
scaffold protein PML can reduce HAdV-C5-mediated
transformation of BRKs [24]. More detailed analysis
illustrated that HAdV-C5 E1B-55 kDa interacts with
the PML isoforms IV and V in a SUMO-dependent
and SUMO-independent manner, respectively [125].
Furthermore, PML-IV is the only known isoform,
which recruits and modulates p53 [127,128]. Therefore,
interaction of E1B-55K with p53 and PML-IV might
be important to repress p53 functions and contribute
to oncogenesis. Moreover, the PML-NB-associated
protein Sp100A has been identified as a tumor sup-
pressor protein, which, like p53, is being repressed in
cocartivation of p53-dependent promoters by being
recruited from the nucleoplasm to the nuclear matrix
and in cytoplasmic inclusion bodies [129]. Hence, the
relocalization of Sp100A by E1B-55K promotes E1A/
E1B-55K-mediated transformation. In summary, the
increasingly detected numbers of interaction between
E1B-55K and PML-NB components and their inhibi-
tory influence on the transformation capacity of
E1B-55K suggest how essential the interplay is in regulating transformation.

Posttranslational modifications in transformation

Protein SUMOylation has an important role in modulating cellular function, in which deregulation could induce cell transformation and has been linked to DNA repair, intracellular trafficking, cell signaling, and stress responses [130–133]. E1B-55K-mediated regulation of SUMOylation on target proteins increases their functional diversity. It has been shown that the capability of E1B-55K to regulate p53 is dependent on its SUMOylation at its conserved SUMO conjugation motif (SCM) as it ensures nuclear targeting of E1B-55K where it can inhibit p53 transcriptional activity [25]. Another PML-NB-associated protein that regulates E1B-55K SUMOylation dependently is Daxx, which is important for efficient transformation [134]. It has been shown that E1B-55K together with the cellular SUMO-targeted ubiquitin ligase RNF4 mediates ubiquitinylination of SUMOylated Daxx resulting in proteasomal degradation of Daxx [126]. Moreover, E1B-55K interacts with Daxx and relocates it within so far unknown nuclear structures [94,122]. The role of Daxx in transformation is not completely understood, but its inhibition inactivates its elevating function on p53-mediated transcription [122].

E1B-55K SUMOylation is crucial for its transforming activity, and cellular factors that regulate this PTM on E1B-55K could potentially modulate its transformation capacity.

A cellular protein, which has been shown to regulate E1B-55K SUMOylation, is the Kruppel-associated box (KRAB)-associated protein 1 (KAP1), which induces SUMO2 modification of E1B-55K, and in turn drives KAP1 deSUMOylation and phosphorylation during viral infection to activate transcription [135].

Small ubiquitin modifier modification and localization of E1B-55K are tightly linked to each other, as loss of SUMOylation by a conservative amino acid substitution from lysine to alanine at its SCM K104R results in cytoplasmic localization [25], whereas disruption of the nuclear export signal (NES) induces nuclear retention and increased SUMOylation of E1B-55K [26]. However, whether E1B-55K SUMOylation induces its nuclear retention or nuclear E1B-55K is increased SUMOylated, remains to be elucidated. As high transformation efficiency in the increased SUMOylated E1B-55K NES mutant has been determined, as opposed to low transformation efficiency in the non-SUMOylated E1B-55K K104R mutant, either E1B-55K localization to the nucleus or its level of SUMOylation is necessary for the transformation capacity [136,137].

Besides SUMOylation, E1B-55K is phosphorylated by casein kinase 2 within its C-terminal region at serine 490/491 and threonine 495 [109,138]. Interestingly, mutational inactivation of the SUMO and phosphorylation sites revealed remarkably similar regulatory roles on p53 comprising repression of p53-mediated transactivation and p53 nucleo-cytoplasmic relocation [139]. Furthermore, efficient E1B-55K-mediated Daxx degradation needs both PTMs [139]. These regulations by both E1B-55K PTMs seem to correlate with its oncogenic potential as mutational analysis of either PTM reduced focus-forming activity in contrast to E1B-55K-wt in combination with E1A.

**Early region 4 in transformation**

The E4 region with its various gene products produced by alternative splicing has an supportive effect in lytic infection and oncogenesis, which has been reviewed by Täuber et al. [36]. The E4 proteins cover diverse functions ranging from transcriptional regulation, inducing cell-cycle progression, counteracting antiviral defense mechanisms such as apoptosis and DNA repair, cell signaling, PTMs, and the integrity of PML-nuclear bodies (PML-NB) [140–142]. The E4 region is located at the right-hand end of the virus genome encoding for one precursor RNA [142,143]. The pre-RNA is alternatively spliced, encoding seven polypeptides named according to the arrangement of their open reading frames (orf) they are derived from, producing E4orf1, E4orf2, E4orf3, E4orf4, E4orf6, E4orf6/E4orf7, and the putative E4orf3/E4orf4 proteins [21,144–148]. Transformation potential is associated with three gene products of the E4 region namely E4orf1, E4orf3, and E4orf6 (Table 1). The role in oncogenicity has been revealed by investigating HAdV-D9, in which transformation capacity is unique among HAdVs as their E1 oncoproteins are dispensable for mammary tumorigenesis [22].

The oncogenic activity of HAdV-D9 E4orf1 is mediated by its C terminus harboring a functional PDZ (for ‘PSD-95/Discs Large/ZO-1’) domain-binding motif that is important for protein–protein interaction for proteins, which are involved in signal transduction [149]. The four E4orf1-associated PDZ proteins are multi-PDZ protein (MUPP1) [150], and the three membrane-associated guanylate kinase (MAGUK)-family proteins are DLG, MAGI-1, and ZO-2 [151–153]. E4orf1-associated PDZ proteins localize signaling complexes such as assembled receptors and cytosolic factors to the plasma membrane to selectively activate
Conclusion and perspectives

Adenoviruses encode oncogenes within their E1 and E4 regions that are functionally essential for viral replication but can also cause cell transformation as a side effect. E1 and E4 oncogenes serve as initiating or promoting factors, which appear to be not only sufficient but also necessary for transformation. These factors induce additional changes that modulate regulatory pathways and checkpoints in normal cells, in turn leading to complete transformation. Cancer develops upon accumulation of multiple noxious events, whereas the E1A proteins immortalize cells and, in cooperation with the multifunctional E1B proteins, induce a fully transformed cell phenotype. Additionally, some of the E4 region proteins either enhance E1A- and E1B-mediated transformation or contribute, together with E1A, to the transformation process by an unconventional ‘hit-and-run’ mechanism. However, although there appear to be general patterns of how adenoviral oncogenes function, which share with other viral oncogenes the interaction with cell tumor suppressor proteins p53 and pRB, a deeper insight into the fine-tuning of these processes through the identification of new binding partners and posttranscriptional modifications of the viral oncogenes is urgently needed. Importantly, adenoviruses provide an excellent model system for investigating basic molecular and cellular events that can unravel the steps and mechanisms underpinning oncogenesis.

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