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Viral manipulation of the host epigenome for oncogenic transformation

Roberto Ferrari

Department of Biological Chemistry, David Geffen School of Medicine, University of California, Los Angeles, California 90095, USA.

Arnold J. Berk

Department of Microbiology, Immunology, and Molecular Genetics, David Geffen School of Medicine, University of California, Los Angeles, California 90095, USA.

Siavash K. Kurdistani

Department of Biological Chemistry, David Geffen School of Medicine, University of California, Los Angeles, California 90095, USA.

Department of Pathology and Laboratory Medicine and the Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research, David Geffen School of Medicine, University of California, Los Angeles, California 90095, USA.

Abstract

The cancerous cellular state is associated with multiple epigenetic alterations, but elucidating the precise order of such alterations during tumorigenic progression and their contributions to the transformed phenotype remains a significant challenge in cancer biology. Here we discuss recent findings on how viral oncoproteins exploit specific epigenetic processes to coerce normal cells to replicate when they should remain quiescent — a hallmark of cancer. These findings may highlight roles of epigenetic processes in normal biology and shed light on epigenetic events occurring along the path of non-viral neoplastic transformation.

Widespread alterations of DNA methylation and histone modifications have been identified in cancer cells, rendering ‘cancer epigenetics’ a vibrant and growing field of study. In comparison with normal cells, cancer cells contain globally hypomethylated DNA, principally in intergenic regions and in the body of genes, the significance of which remains unclear. Cancer cells also display hypermethylation of CpG islands in promoters of specific sets of genes, including tumour suppressors, which leads to their repression, thereby conferring a growth advantage to the cancerous cells.

The contribution of alterations in histone modifications to the cancer phenotype has been much less clear, but numerous aberrations have been reported. These aberrations can occur locally at promoters by improper targeting of histone-modifying activities — leading to inappropriate expression or repression of individual genes, with important consequences for the tumour cells. Aberrations of histone modifications also occur at repetitive DNA elements¹ as well as globally at the level of whole nuclei². The extent of such global alterations vary in different cancer cells in the same tumour, generating a ‘cellular epigenetic heterogeneity’ that, remarkably, relates to the clinical outcome of cancer patients². Although these studies have established a strong

correlative link between histone modifications and cancer, the early patterns of epigenetic changes that may contribute to cellular transformation during tumour progression are unknown.

Viral oncoproteins have provided useful tools for investigating several aspects of cancer cell biology. DNA viruses often initiate infection of host animals by infecting cells that are fully differentiated and have left the cell cycle. Such non-cycling cells are poor hosts for viral replication. Consequently, many of these viruses have evolved proteins expressed immediately after infection that force the host cell back into the cell cycle, inducing expression of the cellular biosynthetic machinery that is required for producing progeny virions. In doing so, viruses have become invaluable for uncovering central molecular processes that regulate cell proliferation and the cell cycle — such as the functions of the tumour suppressor retinoblastoma (RB) and its family members *p130* and *p107* — as well as the importance of inactivation of the tumour suppressor *p53* in tumorigenesis³.

Several viral oncoproteins interact with cellular DNA methyltransferases (DNMTs) and histone-modifying enzymes, including lysine acetyltransferases (KATs), lysine deacetylases (KDACs) and lysine methyltransferases (KMTs) (TABLE 1). Mujtaba *et al.* were the first to show that, interestingly, *Paramecium bursaria* Chlorella virus 1 encodes its own viral KMT, named vSET, which methylates histone H3 on lysine 27 (H3K27) and represses certain host genes⁴. The widespread use of epigenetic modifiers by viral proteins indicates important roles for these DNA- and histone-modifying enzymes in manipulation of the host genome. Here we discuss recent findings on how one viral oncoprotein exploits cellular epigenetic machinery to induce oncogenic cell cycling.

Cell cycle stimulation by small e1a

The adenovirus 5 gene *e1a* can encode two regulatory proteins through alternative splicing — small e1a and large E1A. Small *e1a* consists of 243 amino acids and has the ability to force cell cycle-arrested primary human fibroblasts into S phase. This activity requires two regions of e1a (CR1 and CR2) that are highly conserved among primate adenoviruses, as well as the conserved N terminus³ (FIG. 1). e1a binds the RB family proteins through a high-affinity interaction with CR2 and a low-affinity interaction with an approximately ten amino acid region at the N terminus of CR1. These interactions allow e1a to displace RB pocket domains from the activation domains of the E2F transcription factor *in vitro*⁵. Displacement of RB by e1a relieves the RB-mediated repression of E2F target genes that, when expressed, induce cell cycling. The N-terminal region, together with most of CR1, also directly or indirectly binds to a plethora of KATs, including *p300* and its closely related paralogue *CBP* (hereafter referred to as *p300/CBP*), *PCAF* and *GCN5* (REF. 3). It is clear that the interactions of e1a with both *p300/CBP* and the RB proteins are crucial for the transformation process because mutations in e1a that abrogate either one of these interactions prevent the protein from stimulating entry into S phase in human cells⁶. However, despite evidence that binding of e1a to *p300/CBP* suppresses the transcriptional transactivation of reporter genes by *p300/CBP*, the relevance of e1a-*p300/CBP* interactions to the transformation process remained obscure⁷.

Epigenetic reprogramming by e1a

e1a expression alters global patterns of specific histone modifications

On the basis of cancer-associated global alterations, Horwitz *et al.*⁸ speculated that e1a, through its interactions with histone-modifying enzymes, might also cause global epigenetic changes that contribute to cellular transformation. Indeed, when they expressed small e1a in primary human cells, there was significant global reduction (~70%) of histone H3 lysine 18 acetylation (H3K18ac) compared with uninfected cells. The global reduction in H3K18ac was dependent specifically on the interaction of e1a with *p300/CBP*⁸, and a similar reduction was achieved

by RNAi knockdown of both p300 and CBP, but not by either one alone. Immunoprecipitated p300/CBP from e1a-infected cells still retained *in vitro* enzymatic KAT activities⁸. However, in extracts from the 293 cell line (kidney cells transformed by adenovirus 5 DNA) and from infected cells during the late stage of infection, p300 and CBP are quantitatively bound by e1a⁸, suggesting that this direct interaction somehow leads to global H3K18 hypoacetylation. As high levels of p300 do not reverse e1a-mediated repression of promoters bound by p300 in a transfection reporter assay⁹, there may be additional mechanisms by which e1a leads to H3K18 hypoacetylation⁶.

Small e1a mutants that failed to cause global H3K18 hypoacetylation are also defective for oncogenic transformation of cells in collaboration with the adenovirus E1B protein, which is required in the transformation process to inhibit the apoptosis that would otherwise be caused by the e1a-induced abnormal cell cycling³. Global loss of H3K18ac may therefore be one necessary step in the oncogenic transformation process. As oncogenesis is associated with a dedifferentiated phenotype, global loss of H3K18ac may also be related to the reversal of differentiation induced by e1a.

Defined epigenetic reprogramming during cellular transformation

A genome-wide time course analysis of e1a at human gene promoters by chromatin immunoprecipitation combined with microarrays (ChIP-chip) revealed a dynamic, transitory and temporally ordered binding of small e1a to the promoter regions of ~70% of genes in human fibroblasts during S phase induction⁶. At early post-infection (p.i.) time points, e1a bound to the promoter regions of two distinct sets of genes. One set comprises a large class of genes that are required for successful viral replication, including many genes that are targets of the E2F transcription factors and that function in host cell cycle regulation¹⁰. These genes were strongly induced by 24 hours p.i.. The genes in the second set were bound by e1a early after expression, and are involved in defence against pathogens. This set was initially induced at 6 hours p.i., but became strongly repressed by 24 hours p.i.. At later time points (12 and 24 hours p.i.), e1a became depleted from promoters of both gene groups and bound to the promoters of a third group of genes, which are involved in development, differentiation and cell–cell signalling. These genes were strongly repressed. Such a defined programme of target gene selection by e1a suggest that e1a restarts host cell cycling and establishes a successful infection by first activating cell cycle genes and repressing antiviral responses, and then inhibiting other molecular processes, such as differentiation, that would be inhibitory to cell replication (FIG. 2).

As e1a does not bind DNA directly, it must utilize cellular transcription factors or co-factors to bind to its target genes. Indeed, the binding of e1a to different target genes, and even to different regions of the same promoter, depends on its interactions with p300/CBP and the RB proteins. Binding of e1a to cell cycle genes requires both e1a–RB and e1a–p300/CBP interactions, but only the latter interaction is required for binding to antiviral gene promoters. The mechanism of e1a binding to developmental genes is less clear but may also involve binding to the RB proteins. The temporal order of e1a binding also requires its interactions with p300/CBP and the RB proteins but, interestingly, e1a has a very short half-life of ~80 min¹¹. Consequently, different e1a molecules associate with the promoter regions at early and late post-infection time points. Thus, the ‘movement’ of e1a to different promoter regions may also be influenced by known post-translational modifications of e1a, including acetylation by p300 (REFS 12,13). It is also possible that progression through the cell cycle, with its attendant alterations in cyclin–CDK and ubiquitin ligase activities, influences the temporal binding pattern of e1a.

The e1a binding pattern may provide an explanation for the puzzling finding that expression of e1a in cancer cells can suppress some of their tumorigenic properties, such as anchorage-

independent growth¹⁴. This may be due to the inability of e1a to complete its transcriptional programme in cancer cells that are missing cellular factors — such as inactive RB in HeLa cells — that are needed for e1a ‘movement’. Incomplete transcriptional reprogramming by e1a could result in a cancer cell that has lost some of its phenotypes but has not fully established an e1a-induced gene expression programme.

Cell cycle control: removal of co-repressors and delivery of co-activators

Induction of S phase by e1a has been postulated to require the displacement of RB proteins and their associated repressive complexes from E2F transcription factors^{3,5}. This expectation was indeed borne out by the genome-wide promoter binding analyses of RB, p130 and p107, which showed depletion of all three proteins from cell cycle gene promoters. However, the induction of cell cycle genes was also associated with binding of p300, CBP and PCAF to their promoter regions, leading to H3K18 acetylation. These data partially explain the dependence of e1a transforming activity on the e1a–p300/CBP interaction, which is necessary for full activation of cell cycle genes.

Repression of antiviral responses: using co-activators to deliver co-repressors

The e1a–p300/CBP interaction is also required for binding of e1a to, and repression of, antiviral genes. The dual function of p300/CBP in both activation and repression mechanisms has also been noted for the single *Drosophila melanogaster* CBP¹⁵. Small e1a also induces the association of RB and p130 with these promoter regions, as well as deacetylation of H3K18 and other chromatin changes (FIG. 2). Thus, the repression of antiviral genes may involve two potentially linked mechanisms. One may be through p300/CBP, the transcriptional co-activators that cells use to mount an antiviral response but that e1a uses to target the antiviral genes and repress their expression. A second mechanism involves recruitment of RB and p130 and their co-repressor complexes to these promoters, perhaps by e1a itself. Thus, the interactions of e1a with RB and p130 may not simply displace them from E2F transcription factors — it may also ‘deliver’ them to the antiviral genes.

Active repression of differentiation

Small e1a inhibits the differentiation of precursor cells, such as myoblasts, when they are induced to differentiate¹⁶. The repression of differentiation by e1a was thought to be a consequence of its presumed inhibition of p300/CBP activity and the resulting inhibition of many transcriptional enhancers that require these KATs for full activity. This may be the case as p300, CBP and PCAF, along with the histone modification H3K18ac, are all depleted from developmental and differentiation genes by e1a (FIG. 2). However, e1a also binds directly to the promoters of developmental genes, which is concomitant with binding of the p107 co-repressor and transcriptional repression⁶, suggesting that repression of differentiation by e1a is not a passive process. Repression of cellular differentiation may contribute to viral replication by preventing the cell cycle exit that is often associated with differentiation and by possibly suppressing the antiviral functions of differentiated fibroblasts, such as antigen presentation to immune cells and expression of cell surface ligands that attract invading macrophages and granulocytes.

The binding of e1a to p300/CBP inhibits activation by enhancers in transient transfection assays⁷. The new findings suggest that the inhibition of p300/CBP transactivation function may be due to the ability of e1a to sequester catalytically active p300/CBP away from most promoters and to restrict p300/CBP distribution to a limited number of promoter regions. Restricted binding of p300/CBP may also account for the reduction in total cellular H3K18ac to approximately one-third the level in uninfected cells⁸. Because the promoter regions analysed in these studies constitute only ~4% of the genome, further experiments will be

required to determine if this is the explanation for the global H3K18 hypoacetylation induced by e1a.

Perspectives: beyond e1a

Small e1a is not just a ‘trigger switch’ that induces a cascade of events leading to cell transformation. Rather, e1a binds and regulates almost every cellular promoter region to regulate host cell gene expression in a way that benefits the virus. Such a defined and coordinated mechanism of regulation of thousands of host cell genes in a time-dependent manner provides a model for epigenetic contributions to oncogenic cell cycling. Other DNA tumour viruses, such as simian virus 40 (SV40) and papillomavirus E7, might share similar mechanisms of epigenetic reprogramming for transformation. Features of this model may also apply to non-viral mechanisms of oncogenesis. For instance, the Polycomb protein *EZH2*, a KMT, is overexpressed in many cancers¹⁷ and is also upregulated in e1a-infected cells⁶. As the roles of *EZH2* in tumorigenesis are not fully understood, the time and order of *EZH2* upregulation by e1a may now provide a model for understanding how *EZH2* contributes to cancer initiation and/or progression.

Similar to e1a, another DNA tumour virus oncoprotein — SV40 large T antigen — also causes global H3K18 hypoacetylation when expressed in human cells⁸. Considering that many viral proteins also bind to p300/CBP (TABLE 1), it will be interesting to determine whether global H3K18 hypoacetylation is a general feature of any viral protein that interacts with the p300/CBP KATs. The global reduction and redistribution of H3K18ac by e1a raises the possibility that a similar process may occur in cancers with low levels of H3K18ac and poor outcome². Perhaps in these cancer cells H3K18 acetylation is limited to genes that are induced and confer a more aggressive phenotype.

Although the precise function of H3K18ac remains to be determined, e1a has underscored H3K18 as a distinct site of histone modification in regulation of transcription. Such insight would have been hidden in assays such as genome-wide mapping experiments owing to similar distributions of other histone acetylation sites, such as H3K9ac. Most histone acetylation sites are modified by several KATs and KDACs — H3K18 is unique as the closely related p300 and CBP KATs account for most H3K18 acetylation. The relative lack of redundancy for the H3K18ac mark may explain why only a small fraction of histones are acetylated on H3K18 — ~9% in fibroblasts⁸, ~4% in HeLa cells⁸ and ~3.5% in yeast¹⁸.

The mechanism by which e1a inhibits differentiation processes may harbour important lessons for processes other than cancer that cause dedifferentiation, such as induced reprogramming of differentiated cells into pluripotent stem cells¹⁹. For instance, e1a induces transient expression of *Nanog*, a key regulator of pluripotency, at 12 hours p.i., which is 8–10 hours before repression of other differentiation genes⁶. This provides a model to understand how expression of *Nanog* during a defined window of time may contribute to acquisition of a dedifferentiated cellular state. Additionally, a thorough analysis of e1a binding throughout the entire human genome should reveal the organization of the chromatin that is being exploited by e1a but that may also be altered during other cell fate transitions: why does e1a target certain chromatin regions at a particular time? To which chromatin elements does e1a bind? How does chromatin differ after e1a binding? If history repeats itself, we should expect viral oncoproteins to teach us a great deal about the functions and mechanisms of fundamental epigenetic processes in normal biology and human disease, especially cancer.

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Figure 1. Schematic structure of small e1a and its interactions with cellular proteins required for induction of cell cycling

Small e1a possesses three conserved regions (CRs), CR1, CR2 and CR4, and lacks CR3, which is present in large E1A. The CR1 region and conserved residues in the N terminus are required for interaction with the lysine acetyltransferase p300 or its closely related paralogue CBP. CR2 and residues in CR1 bind to the tumour suppressor retinoblastoma (RB) protein family.

Figure 2. A model for e1a-induced epigenetic reprogramming in primary human fibroblasts

Three classes of gene capture the main trends in global gene expression changes induced by small e1a. Small e1a associates transiently with the cellular antiviral response gene promoters through its interaction with the lysine acetyltransferase p300 (or its closely related paralogue CBP) early after infection (6 h); p300/CBP remains associated with these genes at 24 h post-infection at which time point it may have a repressive function. By 24 h, and maybe earlier, the tumour suppressor proteins retinoblastoma (RB) and p130 also associate with these genes, which show an increased density of histones and histone H4 lysine 16 acetylation (H4K16ac), low H3K18ac and H3K9ac levels, and are repressed. Small e1a also binds transiently to growth and cell cycle genes through interactions with p300/CBP and with the RB proteins that are bound to the DP1 and E2F transcription factors (TFs), causing the displacement of the repressive RB proteins. Small e1a-induced binding of p300/CBP and the lysine acetyltransferase PCAF at these genes causes hyperacetylation of H3K18 and probably other histone lysines, leading to transcription induction. Genes involved in differentiation, development and cell-cell signalling are bound by e1a and p107 mainly at 24 h post infection and are depleted of p300/CBP and H3K18ac, resulting in repression. The model describes average molecular events for each class; however, certain genes show expression changes and/or binding patterns that are different from the main trends illustrated here. TSS, transcriptional start site. Figure is modified, with permission, from REF. ⁹ © (2008) The American Association for the Advancement of Science.

Table 1
Interactions of viral proteins with cellular epigenetic modifiers

Virus	Viral protein	Epigenetic modifier	Description *	Refs
Adenovirus	e1a	p300/CBP	KAT: H3 (K14, K18), H4 (K5, K8), H2A (K5), H2B (K12, K15)	20
		PCAF	KAT: H3 (K9, K14, K18)	21
		DNMT1	DNA (cytosine-5-)-methyltransferase	22
		p400	Chromatin remodelling	23
		TRRAP (GCN5)	KAT: H3 (K9, K14, K18)	24
Epstein–Barr virus	BZLF1 (also known as Zta or Zebra)	CBP	KAT: H3 (K14, K18), H4 (K5, K8), H2A (K5), H2B (K12, K15)	25
		p300/CBP		26
		PCAF	KAT: H3 (K9, K14, K18)	27
		CBP	KAT: H3 (K14, K18), H4 (K5, K8), H2A (K5), H2B (K12, K15)	28
		DNMT1	DNA (cytosine-5-)-methyltransferase	29
Kaposi's sarcoma associated herpesvirus	vIRF	p300	KAT: H3 (K14, K18), H4 (K5, K8), H2A (K5), H2B (K12, K15)	30
		CBP		31
		DNMT3a	DNA (cytosine-5-)-methyltransferase	32
Hepatitis B virus	HBx	DNMT3a	DNA (cytosine-5-)-methyltransferase	29
		CPB, HDAC1	KAT, HDAC	33
Papillomavirus	E2	p300	KAT: H3 (K14, K18), H4 (K5, K8), H2A (K5), H2B (K12, K15)	34
		CBP		35
		p300		36
	E6	CBP		37
		PCAF	KAT: H3 (K9, K14, K18)	38
		Mi2	Chromatin remodelling	39
		p300	KAT: H3 (K14, K18), H4 (K5, K8), H2A (K5), H2B (K12, K15)	37
<i>Paramecium bursaria</i> Chlorella virus 1	vSET1	DNMT1	DNA (cytosine-5-)-methyltransferase	22
		self	KMT: H3 (K27me3)	4
	Simian virus 40 large T antigen	p300	KAT: H3 (K14, K18), H4 (K5, K8), H2A (K5), H2B (K12, K15)	40
		CBP		40

* The histone subtypes and residues within each histone that are modified are indicated. BZLF1 and BRLF1, Epstein–Barr virus immediate-early proteins; EBNA, Epstein–Barr virus nuclear antigen; HBx, hepatitis B virus X protein; HDAC, histone deacetylase; KAT, lysine acetyltransferase; KMT, lysine methyltransferase; LANA, latency-associated nuclear antigen; LMP1, latentmembrane protein 1; vIRF (viral interferon regulatory factor),