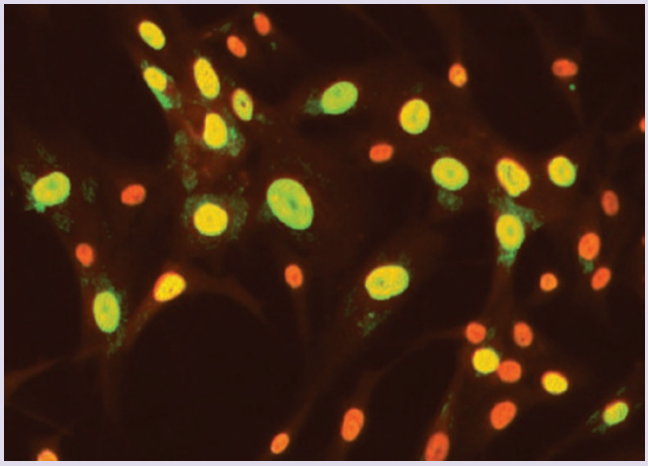
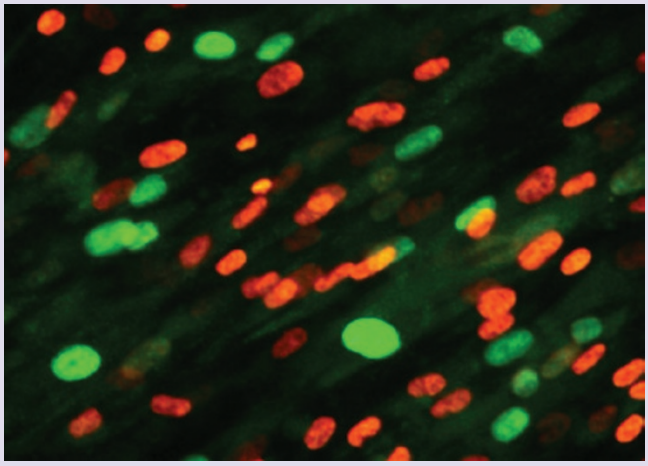
Sinister symphony in e1a





Adenovirus e1a is an early expressed viral protein whose past study has led to important insights into the basic processes of cell-cycle control and transcription. e1a has a key role in the transformation of infected mammalian cells as it has the dubious distinction of being able to kick-start the cell cycle in contact-inhibited stationary cells. Although e1a has been found to associate with multiple players in transcription, including the Mediator subunit 23, the retinoblastoma (RB) proteins, and acetyltransferase p300 and its close relative CREB-binding protein (CBP), the mechanism by which these associations lead to S phase promotion and transformation have remained unclear. Two papers from the Kurdistani and Berk laboratories working in collaboration now tie the mechanism of e1a action to regulation of acetylation at histone H3 lysine 18 (H3K18ac) (*Science* **321**, 1084–1085 (2008) and *Science* **321**, 1086–1088 (2008)). Recent studies had correlated tumor recurrence with global H3K18 hypoacetylation, and Berk and colleagues now test whether this hypoacetylation might result from e1a interaction with p300/CBP. The nuclei of e1a-infected primary embryonic lung fibroblasts show decreased immunostaining of H3K18ac (below), whereas acetylation at H3K9 is unaffected (above; green shows e1a, red shows specifically acetylated histone H3 and yellow shows overlapping expression). e1a mutants lacking the p300/CBP-interaction domain did not have this effect, implicating this interaction in H3K18 hypoacetylation. Indeed, small interfering RNAs (siRNAs) targeting p300 and CBP lead to hypoacetylation at the same residue. In addition, expression of the SV40 large T antigen also results in H3K18 hypoacetylation, leading the authors to speculate that regulation of this histone modification may well turn out to be a common feature of the mechanism by which the DNA tumor viruses transform infected cells, an interesting idea that awaits further analysis.

In the above paper, global histone modifications were examined, but how such changes would kick-start the cell cycle in infected cells remained unclear. Kurdistani and colleagues use genome-wide chromatin immunoprecipitation (ChIP) and microarray analysis to follow factors including e1a, RB-family proteins, p300/CBP and H3K18ac at promoters in the time following adenoviral infection of contact-inhibited primary human fibroblasts. Following e1a binding in such a manner, genes can be classified into three clusters according to distinct e1a binding patterns over time. Gene clusters 1 and 2 tend to bind e1a early; cluster 1 includes pathogen-response genes, whereas cluster 2 includes cell-cycle and replication-associated genes. Cluster 3 binds e1a at later time points after infection and is enriched for genes linked to development and differentiation. By the time the infected cells are in S phase, H3K18ac was found to be depleted at cluster 1 and 3 genes which were repressed, but was enriched at cluster 2 genes, which were activated. Thus, although H3K18 is globally hypoacetylated, reflected in its depletion at many genes, a subset of genes (cell-cycle related) continue to be acetylated at this histone residue and were strongly induced. This acetylation pattern was echoed by the presence of the p300/CBP acetyltransferase, which tends to be found at cluster 2 genes after adenoviral infection. Surprisingly, p300/CBP also became enriched at the repressed antiviral cluster 1 genes, and experiments with e1a mutants showed that, although the e1a-p300/CBP interaction is required for activation of cell-cycle and growth genes in cluster 2, it is also required for repression of cluster 1 genes. This is consistent with recent work on *Drosophila* CBP showing that it functions in both transcriptional activation and repression. To elucidate how the transcriptional repressor RB plays into this scenario, the authors performed ChIP analyses targeting RB and the related p107 and p130, and found these proteins to be depleted from cluster 2 genes but enriched at cluster 1 and 3 promoters. The authors confirmed the dependence of the above events on e1a interaction using mutants that respectively diminish either p300/CBP or RB interaction. Altogether the authors suggest that the previously observed interactions of e1a with the RB proteins and p300/CBP actually reflect a complex, well-defined relocalization of these chromatin-modifying complexes at virtually all active promoters in the infected cell. The redistribution of RB and p130 to cluster 1 and p107 eventually to cluster 3 genes, as well as movement of p300/CBP away from the latter, would tend to quell the host's anti-pathogenic response, as well as differentiation programs. Meanwhile, by conducting the RB family repressors away from and p300/CBP toward cell cycle and S phase–associated promoters, e1a rewrites the score and kick starts the cell cycle. Further analyses can now elucidate the mechanism underpinning the temporal order of recruitment of these factors as well as the migrations of e1a itself. ***Sabbi Lall***