Chromatin silencing as an antiviral innate immune response

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Chromatin has long been known to package the DNA and condense it to fit into the nucleus. The roles of chromatin in the regulation of gene expression have been identified more recently, and a new role for chromatin has started to be defined as an antiviral defense system in the last 5 years. Under this model, infected cells recognize viral DNA as foreign and chromatinize it to a silenced state in an attempt to prevent viral gene expression and replication. This model therefore predicts that nuclear replicating DNA viruses should have evolved mechanisms to counteract this cellular silencing defense. We analyze chromatin dynamics in cells infected with herpes simplex virus 1 (HSV-1), a nuclear replicating DNA virus. The main protein component of chromatin, the histones, are mobilized in infected cells. An early mobilization requires viral DNA but not viral proteins. This mobilization suggests that the infected cells mobilize histones away from the cellular genome to chromatinize and silence the infecting viral genomes. An enhanced later mobilization requires expression of a subset of viral proteins, but not viral DNA replication. This later enhancement of chromatin dynamics is at least in part a result of the fast dynamics of the viral chromatin, reflected in a highly dynamic and unstable HSV-1 chromatin. Using viral mutants, we identified that the major HSV-1 transcription activator, ICP4, is required for the enhanced later mobilization. Expression of ICP4, in the presence of foreign DNA, is sufficient to induce histone mobilization. The domains of ICP4 that are required to activate viral gene expression are also required to induce histone mobilization. We therefore propose that ICP4 activates HSV-1 gene expression, and therefore viral replication, by inducing a mobilization of the histones in the viral genome, destabilizing the viral nucleosomes and thus disrupting the silencing of the viral genome.