

## **CELL CYCLE CONTROL OF EPIGENETIC SIGNALS REGULATING AGING AND CANCER**

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This position effect variegation in *Drosophila* and *S. Pombe*, and higher order chromatin structure regulation in yeast, is orchestrated by modifier genes of the Su(var) group, (e.g. histone deacetylases (HDACs), protein phosphatases) and enhancer E(Var group) (e.g. ATP-dependent nucleosome remodeling proteins). Higher order chromatin structure is regulated in part by covalent modification of the N-terminal histone tails of chromatin and histone tails in turn serve as platforms for recruitment of signaling modules that include non-histone proteins such as HP1 and NuRD. As the enzymes governing chromatin structure through covalent modifications of histones (acetylation, methylation, phosphorylation, ubiquitination) can also target non-histone substrates, a mechanism is in place by which epigenetic regulatory processes can affect the function of these alternate substrates. Histone acetylases (HATs) and deacetylases (HDACs) modify histones, coactivators, nuclear transport proteins, structural proteins, cell cycle components and transcription factors including p53 and nuclear receptors. Distinguishable sensitivity to TSA vs NAD separate histone deacetylases into distinct subgroups. The SIR2 family of nicotinamide adenosine dinucleotide (NAD)-dependent deacetylases modulates diverse biological functions in different species, including longevity, apoptosis, cell-cycle exit and cellular differentiation.

The incidence of prostate cancer, the second leading cause of cancer deaths in American males, increases substantially with age. Aberrant androgen receptor (AR) function plays an important role in prostate cancer growth. The AR, like several other nuclear receptors (NRs) is acetylated by p300. Acetylation of NRs occurs in cultured cells and point mutations at this acetylation site have been identified in breast and prostate cancer. The AR acetylation site governs ligand sensitivity, corepressor (NcoR/HDAC) and coactivator (p300) recruitment and growth properties of the receptors in cultured cells and *in vivo*. p300 induces AR signaling, binds the AR- and binding is regulated by the AR acetylation site. SIRT1 physically interacted with and represses p300 transactivation, requiring the NAD-dependent deacetylase activity of SIRT1. p300 is also repressed by the cell-cycle control protein, cyclin D1 through HDAC recruitment. Cyclin D1<sup>-/-</sup> cells evidence a role for cyclin D1 in recruitment of histone deacetylases HDAC1 and HDAC3, HP1 and SUV39, which thereby alters local histone acetylation and chromatin structure at select promoter sites. Cell-cycle control proteins, including cyclin D1, associate with and coordinate recruitment of chromatin modifying proteins to thereby alter the access of nuclear receptors to the promoters of target genes.