

“Histone Phosphorylation: An Epigenetic “Signature” Impacting on Human DNA Damage Response, Genomic Integrity and Oncogenesis”

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Abstract: During tumor progression, multiple genetic and epigenetic abnormalities will be selected by tumor cells to gain additional growth advantages. Recent studies demonstrate that phosphorylation events on histone H2A.X, a minor histone H2A variant, dedicated to the DNA damage response in human cells, constitutes an important hallmark of early stage human tumorigenesis. Indeed, phosphorylation of H2A.X is now widely regarded as a DNA damage “sensor” and a “caregiver” of our genome.

We have recently identified a novel mechanism regulating the DNA damage response that is mediated by an unique phosphorylation mark on H2A.X, tyrosine142 phosphorylation, in close vicinity to the well-known serine 139 phosphorylation (γ -H2A.X) mark. In addition, we have discovered that WSTF (William-Beuren Syndrome Transcription Factor, a gene implicated in the development of William Syndrome) has kinase activities towards tyrosine 142 of H2A.X, via an unconventional kinase domain at its N-terminus. Further, we have demonstrated that WSTF is essential for the maintenance of the γ -H2A.X foci and chromatin reorganization during the DNA damage response. These results suggest that the novel tyrosine kinase activity of WSTF is critical for regulation of the H2A.X-mediated DNA damage response pathway. We propose to use a combination of structural and biochemical approaches to investigate and fully characterize this novel kinase domain.

We have also discovered another potential link between histone phosphorylation and cancer. A novel phosphorylation mark on histone H2B at Ser6 recruits 14-3-3 σ , an important member of a family of signaling proteins that are critical for cell growth, death and human tumorigenesis. In this proposal, we propose to investigate the molecular mechanisms regulating this interaction using both structural and functional approaches.