HBO1:JADE1 at the cell cycle chromatin crossroads


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The histone acetyltransferase (HAT) HBO1 participates in diverse molecular processes including transcription, DNA replication, and DNA repair. HBO1 is essential for the development of a number of organisms, its activity is modulated in response to different stresses, and it has been linked to oncogenesis. HBO1 is a member of a protein complex that includes the plant homeodomain (PHD) finger protein JADE1, which is required for recruitment of HBO1 to some chromatin targets. An important question is how HBO1-JADE1 is regulated to coordinate such diverse cellular functions.

In a previous issue of Cell Cycle, Panchenko and colleagues report dynamic regulation of HBO1-JADE1 during the cell cycle. They show in HeLa cells that most HBO1-JADE1 complexes are located in the nucleus and chromatin bound during interphase, whereas, during mitosis, HBO1-JADE1 departs chromatin and the majority of it is cytoplasmic. HBO1-JADE1 returned to chromatin at the end of mitosis at approximately the time of chromosome decondensation and nuclear envelope reformation. Interestingly, this timing of HBO1-JADE1 rebinding to chromatin correlates with reacquisition of bulk histone H4 acetylation, suggesting that regulation of the HBO1-JADE1 HAT complex may in part explain the global changes to the epigenome during the M to G1 transition. Late mitosis-early G1 is also the cell cycle phase during which pre-Replicative Complexes (pre-RCs) begin to be assembled onto origins, which licenses these origins for DNA replication in the ensuing S phase. HBO1 is a co-activator of the pre-RC protein Cdt1, which is required to clamp the MCM helicase onto origin DNA, the last step of pre-RC assembly. Thus, regulation of HBO1-JADE1 cellular location during the cell cycle may also contribute to the timing of pre-RC assembly at the end of mitosis.

Panchenko and colleagues go on to investigate the mechanism that regulates HBO1-JADE1 cellular location during the cell cycle. Periodic JADE1 phosphorylation correlated with its departure from chromatin and relocation to the cytoplasm during mitosis, with a rapid return to a non-phosphorylated form that was temporally coincident with the rebinding of HBO-JADE1 to chromatin at M-G1. Aurora A kinase inhibitors reduced phosphorylation of JADE1, suggesting that phosphorylation by this kinase could regulate the cell cycle timing of HBO1-JADE1 departure from chromatin. Using Mass spectrometry, they identified six serine and threonine residues of JADE1 that are more highly phosphorylated during mitosis than interphase, with phosphorylation on two of these residues (S121, S392) being specific to mitotic cells. None of these sites, however, are good matches to the Aurora A kinase target consensus sequence, and some more closely matched the consensus for CDK target sites. Thus, although phosphorylation of JADE1 is prevented by Aurora A kinase inhibitors, it remains an open question whether regulation by this kinase is direct, and whether other cell cycle kinases contribute to the phosphorylation of JADE1 in mitosis. Another important question is what effect mutation of the phospho-sites in JADE1 will have on HBO1-JADE1 cellular location and function.

Last, Panchenko and colleagues show that the dynamic relocalization of HBO1-JADE1 during the cell cycle also occurs in vivo in a mouse model for regeneration after renal tubule injury. This demonstration of relevance to proliferative cells in vivo is important. Although analysis of transformed cell lines in vitro has contributed significantly to our understanding of cell cycle, a current challenge for the field is to define the relevance of these cell cycle mechanisms, and their developmental variations, to different settings in vivo. In fact, the importance of analysis in vivo is underlined by previous research on HBO1. HBO1 was essential for MCM loading onto origins and cellular proliferation in transformed cultured cells, whereas HBO1 null mutant Drosophila and primary mouse embryonic fibroblasts (MEFs) had at most mild defects in DNA replication and cellular proliferation. Future experiments should evaluate the regulation and function of HBO1-JADE1 during the cell cycles of other tissues and its redundancy with other HAT complexes. The data from the Panchenko lab has opened a new vista for understanding the cell cycle regulation of HBO1-JADE1, an epigenetic integrator at the crossroads of DNA replication, DNA repair, transcription, cell cycles, and development.

References