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Role of the H3.3 histone variant in establishment of mammalian circadian rhythms.

Circadian clocks are an important feature that allow organisms to adapt and to anticipate daily changes in their environment. Almost every cell has its own circadian clock and such timekeeping system is orchestrated by transcriptional-translational feedback loops. In mammals, robust circadian oscillators coordinate gene-expression programs in a tissue-specific manner, being critical for organismal physiology and behavior. The core- molecular clock comprises two activators, transcription factors (TFs) BMAL1 and CLOCK, which at the beginning of the day bind to circadian E-box sequences on DNA to turn on transcription of thousands of genes. Among BMAL1:CLOCK targets are Period (PER) and Cryptochrome (CRY), their own repressors. Upon sufficient accumulation of PER and CRY proteins in the cytoplasm at the beginning of the night, PER:CRY heterodimer translocates to the nucleus to repress BMAL1:CLOCK activity, and the next clock cycle begins upon PER:CRY degradation, at the beginning of the next day.

In order to allow BMAL1:CLOCK rhythmic binding at 'specific time and place'on the genome, chromatin has to be accessible and such dynamic changes in chromatin states epigenetically encoded. Over the past decades, it has been shown that circadian clock machinery is tightly linked with dynamics in chromatin landscapes. Deposition of epigenetic marks, such as acetylation or methylation of histone proteins, nucleosome remodeling and circadian gene expression are closely coordinated. Core-clock factors are directly involved in the recruitment of chromatin modifiers and deposition of epigenetic signatures, including histone variants, e.g. H2A variant, H2A.Z.

We focused on understanding the role of H3.3 variant in circadian clock function. Purification of specific H3.3 liver protein complexes over circadian time allowed us to identify dynamic assembly of PBAF/cBAF chromatin remodelers with the core-clock TF BMAL1. H3.3 deposition cycles over circadian time, and PBAF/cBAF-BMAL1 assemble on dynamic H3.3 nucleosomes marked with specific epigenetic marks linked to labile nucleosomes. Moreover, circadian-clock disruption (Per knock-out) results in an increased deposition of H3.3 on chromatin, accompanied by disruption of the PBAF complex and reorganization of remodelers regulating BMAL1 function. Our data highlights mechanisms how circadian disruption and associated epigenome changes could promote development and progression of cancers where SWI/SNF family remodelers are implicated.

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