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Series - 35

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Affiliation: Senior Scientists AIST



Epigenetic Regulation of the Circadian Clock Yoshiaki Onishi

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Circadian rhythms control all aspects of physiology and are associated with diseases including cancer through effects on the cardiovascular, renal, immune, endocrine, neuropsychiatric and metabolic systems. Although Bmai1 is a key component of the mammalian clock system, little is understood about the actual mechanism of circadian Bmal1 gene transcription, particularly at the chromatin level, we discovered a unique chromatin structure within the Bmail promoter. The RORE region, which is a critical cis element for the circadian regulation of the Bmal 1 gene, is comprised of GC-rich open chromatin. Investigating transcriptional regulation of the BMAL1 gene including epigenetic regulation, we found that CpG islands in the BMAL1 and the PER2 promoters were hyper- and hypomethylated, respectively and that 5-aza-2'deoxycytidine (aza-dC) not only enhanced PER2 gene expression but also PER2 oscillation within 24 h in leukemic cells. That is such hypermethylation of CpG islands in the BMAL1 promoter restricted PER2 expression which was recovered by aza-dC within 1 day in these cells. These results suggest that the circadian clock system can be recovered through BMAL1 expression induced by aza-dC within a day. The RPIB9 promoter of RPMI8402 cells, which is a methylation hotspot in lymphoblastic leukemia, was also hypermethylated and aza-dC gradually recovered RPIB9 expression in 3 days. In addition, methylation-specific PCR revealed a different degree of aza-dC-induced methylation release between BMAL1 and RPIB9. These results suggest that the aza-dC-induced recovery of gene expression from DNA methylation is dependent on a gene, for example the rapid response to demethylation by the circadian system, and thus, is of importance to clinical strategies for treating cancer.

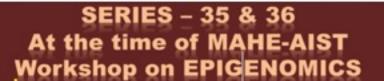
Epigenetic regulation of tumor suppressor miRs - CARF as a potential target

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microRNAs (miRs) have recently emerged as small non-coding regulators of gene expression. We recruited arbitrary manipulation of genome and escape from demethylation (5-Aza-2'-deoxycytidine) induced senescence as a cell-based loss-of-function screening system. Cells that escaped 5-Aza-dC-induced senescence were recovered and subjected to miR-microarray analysis with respect to the untreated We identified miR-335 and -451 as upregulated miRs implying that they are normally silenced by methylation. In order to characterize their functional significance, we undertook extensive molecular analysis in cells either overexpressing or compromised for these miRs. We report that miR-335 and -451 caused growth arrest in cells leading to their resistance to 5-Aza-dC-induced senescence. We demonstrate that CARF (Collaborator of ARF) is a new target of miR-335 and -451. It regulates DNA damage signaling and several key components (Cyclin D1, CDK4, p16INK4A, pRB, HDM2 and p21WAF1) of cell proliferation, stress and tumor suppressor signalings.



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