Editorial

The role of circadian clock genes in leukemia

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Circadian rhythm is present in human and all eukaryotes whose 24-hour cycle of behavior and physiology changes are driven by an autonomous circadian clock within the organisms. The mammalian circadian clock is organized in a hierarchical manner. The master pacemaker, located at suprachiasmatic nucleus (SCN), and the core circadian clock genes constitute the circadian oscillator and circadian rhythms (1). The SCN clock is entrained to the 24-hour day by the daily light-dark cycle through the retina-to-SCN neural pathway (2) and the peripheral rhythms in the peripheral oscillators of body cells are possibly driven or synchronized by the SCN (3). Maintaining a proper circadian clock function is crucial for an organism to respond to light and dark cycle properly. Circadian oscillators use transcriptional-translational feedback loops that rely on positive and negative elements in oscillators, therefore the strong daily cycling of clock gene and clock controlled genes is characteristic of circadian systems. Epigenetic regulations (e.g., post-transcriptional regulation, posttranslational modifications, chromatin remodeling), availability of clock proteins, and regulation of intracellular localization are intricately regulated to ensure the precise periodicity of the clock to close to 24 hours (4).

It is believed the cell proliferation, DNA repair, angiogenesis and immune functions are controlled by the molecular clock (5). Indeed, many epidemiological studies have linked altered circadian rhythms in shift workers to cancer susceptibility, including breast (6), ovarian (7), and prostate (8) cancer. Therefore, it is not surprising to know the altered expression of circadian clock genes in almost all types of cancers including our previous reports of chronic myeloid leukemia (CML) (9,10), acute leukemia (11), head and neck squamous cell carcinoma (HNSCC) (12,13), and gastric cancer (14). Studies of animal models (15) and human cancers have established that disrupted circadian rhythm is an essential endogenous factor contributing to cancer development (16). Although the underlying mechanism has not been fully understood, they are generally considered as tumor suppressors. Mice deficient in the *Per2* gene were cancer prone and showed a markedly increased rate in tumor development and reduced apoptosis after irradiation (15). In addition, epigenetic silencing of many core circadian clock genes has been described in various cancers, such as CML (9), breast cancer (17), hepatocellular carcinoma (18).

In hematopoietic cancers, the regulatory role of circadian clock genes has not yet been entirely clarified. In a recent study, the circadian rhythm transcription factors *BMAL1* and *CLOCK* was shown to be required for the growth of leukemia stem cell of acute myeloid leukemia (AML) and disruption of circadian pathway components could produce anti-leukemic effects (19). The authors used shRNA silencing of *BMAL1* and *CLOCK* or pharmacological inhibition of *BMAL1* transcription to disrupt the integrity of circadian rhythms in both murine and human AML cells and demonstrated the induction of myeloid differentiation and impair cell-cycle progression (19). This study established a novel pro-tumorigenic role for circadian

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clock genes in AML. However, our previous reports have shown that core circadian clock genes are more likely to act as tumor-suppressors in leukemias, where down-regulated expression of most of the genes were observed (9-11). We have observed a decreased expression of *BMAL1* in AML (11) and CML (9,10) but when patients achieved remission the expression of *BMAL1* did not recover. Also, the daily pattern expression of *BMAL1* was disrupted in patients with CML but the recovery of expression pattern was not observed in patients after imatinib mesylate treatment and achieved remission (10). Therefore, it is speculated that *BMAL1* is essential for leukemia but may not be essential for normal hematopoiesis. Moreover, the expression of *CLOCK* in CML, AML and acute lymphoid leukemia (ALL) was not different from healthy individuals (9-11) and the expression of *CLOCK* did not display time-dependent variations in peripheral blood leukocytes of either healthy individuals or patients with CML (10). In consistent with our findings, *CLOCK* was found to be arrhythmic in peripheral blood mononuclear cells (20) and bone marrow $CD34^+$ cells (21). Although *BMAL1* and *CLOCK* were identified as essential transcription factors mediating leukemia stem cell growth and self-renewal, it seems to be conflict with the fact that expression of *BMAL1* was down-regulated in patients with AML. It is possible that the degrees of dependence on core circadian clock genes are different for normal and leukemic stem cells.

According to our experience in leukemias, *PER3* might be more decisive than *BMAL1* and *CLOCK* in maintaining circadian rhythm than we have expected. *PER3* was the most down-regulated circadian clock genes in AML, ALL and CML and recovery of *PER3* was correlated with better clinical outcome (11). In patients with CML, we found the daily pattern expression of *PER3* was disrupted in patients with newly-diagnosed pre-imatinib mesylate-treated and crisis-phase patients and when patients achieved complete cytogenetic response or major molecular response, a partial recovery of *PER3* expression was observed (10). *PER3* has been demonstrated to be required for *CHEK2* activation and *PER3* overexpression led to increased apoptosis and inhibition of cell proliferation (22). Since circadian clock has been shown to control the expression of cell cycle-related genes (23), it is reasonable to hypothesize that *PER3* may have regulatory functions in cell-cycle progression and coupled to circadian rhythms. Since asynchrony of cell proliferation between normal and malignant tissues was commonly observed (24) and loss of circadian rhythmicity was commonly seen in patients with advanced cancers, disrupted rhythms of circadian clock gene expression may disturb the balance of the restrains of cell division resulting in prosurvival and proliferation of tumor cells. Tumor cells may accelerate their own growth by disrupting circadian rhythms of normal cells and establish their own rhythms, so restoring circadian rhythms in cancer patients should improve their prognoses. It will be interesting to investigate if once *PER3* is restored it will further adjust the disrupted circadian clock back to its normal restrains.

As circadian clock has been shown to be controlled by sumoylation of *BMAL1* (25) and deregulated methylation status of circadian clock genes has also been demonstrated in various types of cancers, the mechanisms of transcriptional and epigenetic regulation are considered critical for better understanding of the circadian clock regulation and its deregulation during leukemogenesis. Therefore, the future goal for solving the leukemic mechanism will be to uncover the interactions between circadian clock and epigenome of leukemia. Hopefully, it will provide a better understanding for leukemogenesis as well as for better references for therapeutic designs.

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Footnote

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