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- Review -

Circadian Clock Genes, PER1 and PER2, as Tumor Suppressors

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Disruptive expression patterns of the circadian clock genes are highly associated with many human diseases, including cancer. Cell cycle and proliferation is linked to a circadian rhythm; therefore, abnormal clock gene expression could result in tumorigenesis and malignant development. The molecular network of the circadian clock is based on transcriptional and translational feedback loops orchestrated by a variety of clock activators and clock repressors. The expression of 10~15% of the genome is controlled by the overall balance of circadian oscillation. Among the many clock genes, *Period 1* (*Per1*) and *Period 2* (*Per2*) are clock repressor genes that play an important role in the regulation of normal physiological rhythms. It has been reported that PER1 and PER2 are involved in the expression of cell cycle regulators including cyclins, cyclin-dependent kinases (CDKs), and CDK inhibitors. In addition, correlation of the down-regulation of PER1 and PER2 with development of many cancer types has been revealed. In this review, we focused on the molecular function of PER1 and PER2 in the circadian clock network and the transcriptional and translational targets of PER1 and PER2 involved in cell cycle and tumorigenesis. Moreover, we provide information suggesting that PER1 and PER2 could be promising therapeutic targets for cancer therapies and serve as potential prognostic markers for certain types of human cancers.

Key words : Circadian rhythm, clock gene, cell cycle, PER1, PER2, tumor suppressor

Introduction

A variety of cellular and physiological activities including cell cycle, proliferation, energy metabolism, and hormone fluctuation, rely on a master clock consisting of a 24 hr circadian rhythmic system [8]. The circadian system is controlled by a central oscillator located in the hypothalamic suprachiasmatic nuclei and peripheral oscillators in all cells and tissues of the body. The oscillations of circadian clocks are based on an intracellular molecular network that includes a set of autoregulatory feedback loops in which transcription of specific genes are negatively regulated by their own proteins. Several circadian clock genes including *brain and muscle aryl hydrocarbon receptor nuclear translocator-like 1* (*Bmal1*), *circadian locomotor output cycles kaput* (*Clock*), *Period* genes (*Per1* and *Per2*), *Cryptochrome* genes (*Cry1* and *Cry2*), and others have been identified [33]. These gene products take charge of many cellular activities by regulating transcription/translation levels of downstream clock-controlled genes (CCGs) that belong to various cellular signaling pathways. The causes of many diseases, such as cancer, neurological disorders, and metabolic disorders, are highly associated with alteration of clock gene expressions [4, 16, 36]. Among clock genes, *Per1* and *Per2* show crucial activities for regulation and maintenance of the circadian rhythms [22, 35]. Several studies have recently reported that PER proteins are involved in cell cycle regulation leading to imbalance between apoptosis and proliferation and consequent cancer progression [12, 22].

In this review, we focus on the functions of PER proteins, PER1 and PER2, in malignant transformation and tumor development and describe the potential anti-cancer strategies for PER-targeted cancer therapy as circadian rhythm-based approaches.

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PER proteins: negative-feedback repressors of circadian rhythm

Period 1 (*Per1*) and *Period 2* (*Per2*) are core clock genes playing important roles in the regulation of normal circadian rhythms in mammals. PER proteins belong to clock repressors with other proteins such as CRYs and ERV-ERBs, which are controlled by clock activators including CLOCK and BMAL1. The appropriate expression levels of these clock genes (repressors and activators) are necessary to keep constant circadian rhythms under normal conditions.

In Fig. 1, Schematic diagram illustrated the overview of the molecular mechanisms for the feedback loop of circadian clock genes. CLOCK/BMAL1 heterodimers as transcription factors bind and activate expression of their target CCG genes including *Per1*, *Per2*, *Cry1*, and *Cry2* (Fig. 1). PERs and CRYs form heterodimer and act as negative-feedback repressor complexes. PER and CRY dimers repress the activity of CLOCK/BMAL1 complexes in the nucleus. Following accumulation of PER and CRY proteins in the cytoplasm, they interact with casein kinase I d/e and AMP kinase and are phosphorylated. Once phosphorylated, PER and CRY proteins undergo polyubiquitination and degradation by Skp1-Cullin-F-box protein E3 ubiquitin ligase complexes including b-TrCP and FBXL3. These are the core CLOCK-BMAL1/PER-CRY feedback loops, which involve a feedback cycle that takes approximately 24 hr [23, 39]. In addition, there are additional feedback loops including REV-ERBa, PAR-bZip and others, which are transcriptional targets of CLOCK-BMAL1 as well [11, 23, 39]. At the molecular level, a variety of transcription factors are directly involved in the regulation of the central clock through autoregulatory transcription-translation feedback loops. The negative feedback loops operate approximately 24 hr oscillations, while the positive loops contribute on the stabilization and fine-tuning of the negative loops [7, 30].

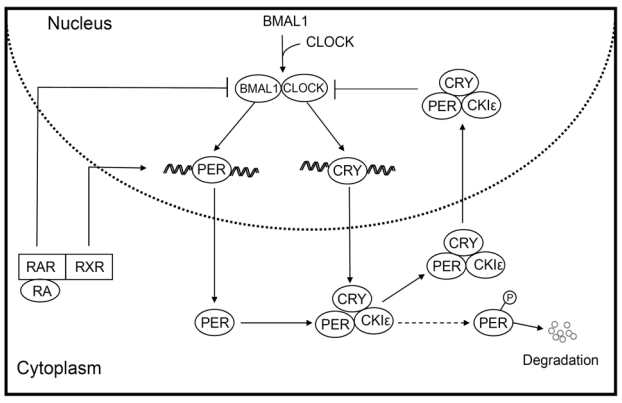

Fig. 1. The feedback loop of circadian clock genes.

Previously reported studies demonstrated that PER1 as a short period-associated protein and PER2 as a long period-associated protein work together to maintain the circadian period at 24 hr [40], although PER2 acts as a positive rather than a negative factor in the CLOCK/BMAL1 pathway [34]. PER1 and PER2 each play distinct, but important roles in circadian oscillation, as indicated by a study that showed *Per1/Per2* double-mutant mice immediately showed arrhythmic phenotypes [1]. There are emerging clues that the PER1 and PER2 are involved in circadian rhythm-regulated cell cycle arrest in normal and cancerous tissues, supporting their tumor suppressive activities [9, 12].

PER1 and PER2 as tumor suppressors, and their application to cancer therapy

In the view of pathology, abnormal regulation of the cell cycle results in unlimited cell division and, consequently, malignant cell transformation. Accumulated evidence indicates that the expression of several key players in cell cycle progression are dependent on oscillation of circadian genes, while disrupted circadian rhythms are highly associated with tumorigenesis and cancer development.

The clock genes may play a role in growth control in normal and cancer cells. Cell death and proliferation are controlled by circadian synchronization. Deregulation of circadian rhythms by clock gene mutation or external damage is responsible for aberrant cell cycle progression, a major hallmark of the cancer cells. The transcriptional levels of WEE1 kinase, a CDK inhibitor (CKI) of G2/M transition, are directly regulated by the CLOCK/BMAL1 loop. *Cry1/2*$^{-/-}$ mice showed increased levels of WEE1 in response to prolonged activation of CLOCK/BMAL1, leading to delayed M phase entry [24]. Another circadian loop (REV-ERB/ROR) is responsible for rhythmical expression of $p21^{Cip1}$ [15]. A recent study indicated that CRY2 plays a critical role in c-MYC degradation through the interplay with F-box and leucine rich repeat protein 3, leading to suppression of cancer cell proliferation [19]. In the case of PER1, it interacts with ATM and leads to CHK2 phosphorylation, consequently inducing cell cycle arrest and apoptosis upon genotoxic stress [12]. PER2 leads to increased p53 stability by interfering with Mdm2-induced ubiquitination in response

to DNA damage [13, 14]. In addition, the levels of b-catenin were increased by loss of *Per1* and *Per2*, resulting in b-catenin-mediated signaling associated with cell proliferation and tumorigenesis in colon and non-colon cancer cells [41]. In clinical studies subject to head and neck squamous cell carcinoma (HNSCC) patients and healthy individuals, several CCGs including *Per1*, *Per2*, *Per3*, *Cry1*, *Cry2*, *Clock*, *CKIε*, *Bmal1*, and *TIM* were down-regulated in HNSCC patients [17]. Moreover, lower expression levels of *Per1*, *Per2*, *Per3*, *Cry2*, and *Bmal1* were shown in the tumor tissues of colorectal cancer patients compared with their corresponding normal tissues [25]. Such clock genes exhibited tumor suppressor activities and their variants were discovered in human cancers [12, 31, 43]. These results provides an opportunity to develop novel therapeutic targets to enhance the sensitivity to anti-cancer therapy.

Period 1 (Per1)

PER1 showed tumor suppressor activities (Fig. 2). Previous studies have reported that various cancer types including prostate cancer, brain cancer, breast cancer and non-small cell lung cancer (NSCLC) show low expression levels of PER1 [3, 4, 22, 42]. Moreover, PER1 can modulate cell cycle progression and cell proliferation through regulation of several cyclins. The increased expression of cyclin D1, cyclin E, cyclin B1, CDK1, and WEE1 and the decreased expression of p53, cyclin A2, p16, p21, and CDC25 were accompanied by low levels of PER1, resulting in increased G2/M phase transition and cell proliferation [10, 12]. A recent study

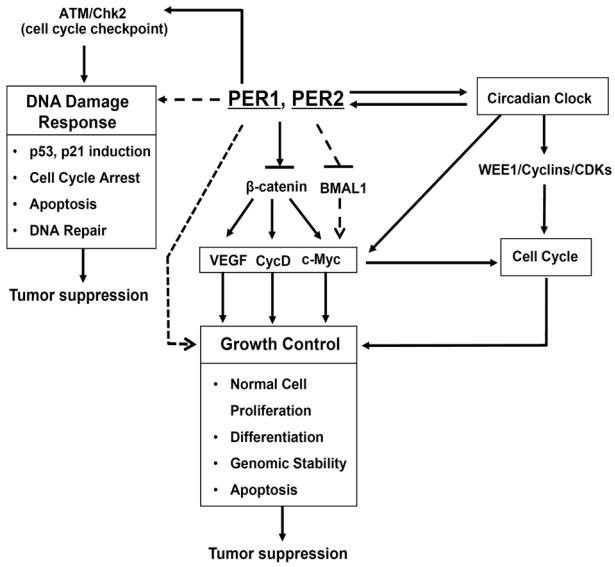

Fig. 2. PER1 and PER2 act as tumor suppressor.

demonstrated that PER1 can be regulated by c-MYC at the post-transcriptional level [29]. C-MYC overexpressed in many types of cancer can be recruited to *Per1* promoter with BMAL1, resulting in repression of *Per1* expression followed by alteration of the CLOCK/BMAL1-PER/CRY feedback loop and promotion of cancer development. In a HNSCC study, recovery of PER1 expression was associated with positive prognosis in postoperative patients [17]. In addition, *Per1*-low expressing NSCLC patients showed a shorter survival period compared with *Per1*-high expressing ones [22]. A few studies supported that PER1 might be a potential target for cancer therapy. High expression of PER1 contributes increased radiosensitivity to glioma tissues [44]. Another study showed that haloperidol, an antipsychotic drug, can increase mRNA levels of *Per1* expression in U87MG glioblastoma cells although further studies to investigate the molecular mechanisms are required [26].

To support the information about tumor suppressive activities of PER1, we analyzed several cancer-associated databases. Upon examination of the Oncomine database (http://www.oncomine.org/), we found several datasets demonstrating that *Per1* expression is significantly down-regulated in lung adenocarcinomas [2] and ductal breast carcinomas [32] compared to corresponding normal tissues (Fig. 3A). Moreover, the dataset obtained from The Human Protein Atlas (http://www.proteinatlas.org/) indicated that PER1-negative (low expression) patients showed poor prognosis compared to PER1-positive (high expression) patients (Fig. 3B). These data indicated the importance of PER1 as a tumor suppressor and a prognostic marker for (at least) certain types of human cancers.

Period 2 (Per2)

Like PER1, PER2 also acts as a tumor suppressor (Fig. 2). Accumulated evidence confirms that deregulation of PER2 is correlated with cancer development and PER2 was down-regulated in various cancer types, including breast cancer, colorectal cancer, non-small lung cancer, skin cancer and myeloid leukemia [6, 20-22, 28, 45]. Overexpression of PER2 in cancer cells resulted in reduced cell proliferation capacity and induction of apoptotic rate accompanied with decreased levels of cyclin B1, Bcl-2 and c-MYC and increased levels of p53 [18, 38]. A recent study showed that down-regulation of PER2 is associated with induction of drug resistance in NSCLC cells [5]. $Per2^{m/m}$ mutant mice showed c-Myc up-regulation and p53 down-regulation and they became

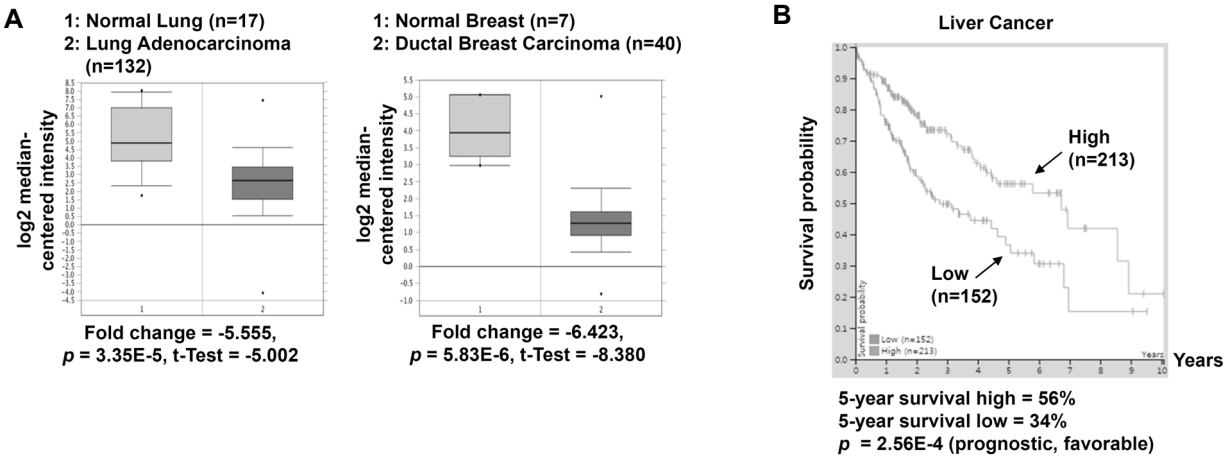

Fig. 3. Expression levels and prognostic value of PER1 in certain types of human cancers. (A) Datasets obtained from Oncomine (http://www.oncomine.org/) demonstrated that lung adenocarcinomas and ductal breast carcinomas expressed low levels of *Per1* to normal counterparts ([Left] Ref#2, p = 3.35´10^{-5}, fold change = -5.555; [Right] Ref#32, p = 5.83´10^{-6}, fold change = -6.423). (B) Datasets available from The Human Protein Atlas (http://www.proteinatlas.org/) demonstrated the prognostic value of PER1 in liver cancer patients. The results indicated that PER1-negative (low levels) patients showed poor prognosis when compared to PER1-positive (high levels) patients (p-value = 2.56´10^{-4}).

cancer-prone after DNA damage [9]. Abnormal levels of PER2 expression were associated with an imbalance between apoptosis and cell proliferation in response to genotoxic stress. Knockdown of PER2 led to increased expression of MDM2, c-MYC, Bcl-2, MMP2, and VEGF, and decreased expression of p53, Bax, and TIMP-2, indicating that PER2 knockdown promotes tumorigenicity of cancer cells [37]. In a study using rodent hepatocellular carcinoma models, PER2 as a liver tumor suppressor played a critical role in tumor initiation as well as malignant progression [27]. Loss of *Per2* in NSCLC patients showed high correlation with negative values of clinicopathological factors, including differentiation level, tumor status, and lymph node metastasis, indicating that *Per2* might be a potential prognostic marker in NSCLC [22]. PER2 expression is positively associated with increase of sensitivity to radiotherapy in glioma although the molecular mechanisms remain elusive [44].

Consistent with the PER1 case, we also analyzed can-

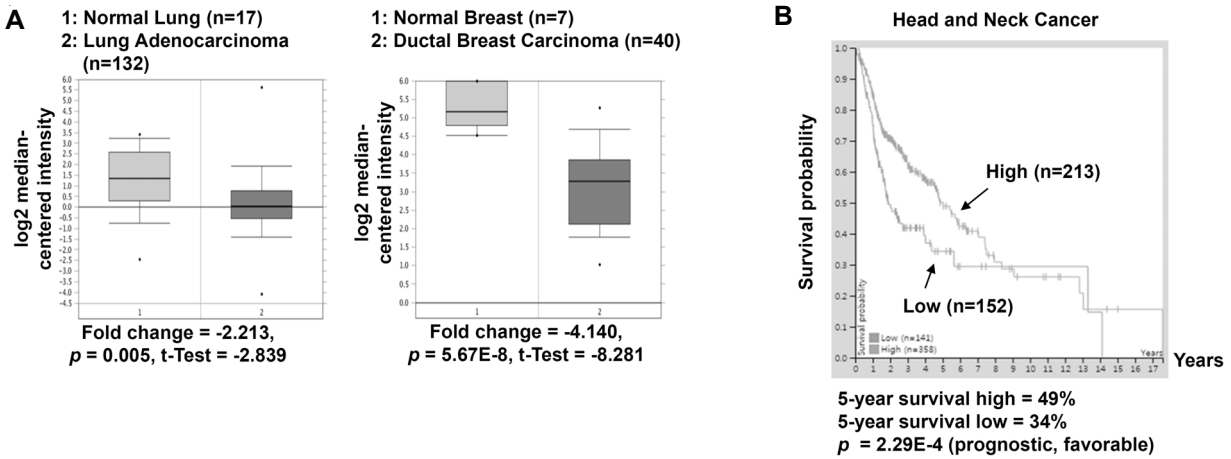

Fig. 4. Expression levels and prognostic value of PER2 in certain types of human cancers. (A) Datasets obtained from Oncomine demonstrated that lung adenocarcinomas and ductal breast carcinomas expressed low levels of *Per2* relative to normal counterparts ([Left] Ref#2, p = 0.005, fold change = -2.213; [Right] Ref#32, p = 5.67´10^{-8}, fold change = -4.140). (B) Datasets available from The Human Protein Atlas demonstrated the prognostic value of PER2 in head and neck cancer patients. The results indicated that PER2-negative (low levels) patients showed poor prognosis compared to PER2-positive (high levels) patients (p-value = 2.29´10^{-4}).

cer-associated databases to provide supporting information regarding the tumor suppressive activities of PER2. Several datasets from the Oncomine database demonstrated that *Per2* expression is significantly down-regulated in lung adenocarcinomas [2] and ductal breast carcinomas [32] when compared with corresponding normal tissues (Fig. 4A). Additionally, the dataset from The Human Protein Atlas indicated that PER2-negative (low expression) patients showed poor prognosis compared to PER2-positive (high expression) patients (Fig. 4B). This information indicated that PER2 can also play a tumor suppressive role and is a potential prognostic indicator for human cancers.

Conclusions

This review indicated that PER1 and PER2 are important tumor suppressors that function through interplay with cell cycle regulators. PER proteins are involved in regulation of various cell cycle genes and cancer-associated genes, indicating that they are closely correlated with tumorigenesis and malignant development. Recent studies provided accumulated evidence that pharmacological targeting of circadian-associated proteins might be potent anti-cancer strategies, although there is still debate regarding whether a single-targeting drug would be a proper approach because of compensation of other downstream effectors in the circadian feedback loops. Further studies will need to focus on the molecular mechanisms of PER1 and PER2 in the circadian gene network and cell cycle network, and the development of specific pharmacological agents for expression and activation of PER1 and PER2, providing potential molecular targets for anti-cancer therapeutic strategies.

References

1. Bae, K., Jin, X., Maywood, E. S., Hastings, M. H., Reppert, S. M. and Weaver, D. R. 2001. Differential functions of mPer1, mPer2, and mPer3 in the SCN circadian clock. *Neuron* **30**, 525-536.
2. Bhattacharjee, A., Richards, W. G., Staunton, J., Li, C., Monti, S., Vasa, P., Ladd, C., Beheshti, J., Bueno, R., Gillette, M., Loda, M., Weber, G., Mark, E. J., Lander, E. S., Wong, W., Johnson, B. E., Golub, T. R., Sugarbaker, D. J. and Meyerson, M. 2001. Classification of human lung carcinomas by mRNA expression profiling reveals distinct adenocarcinoma subclasses. *Proc. Natl. Acad. Sci. USA* **98**, 13790-13795.
3. Cadenas, C., van de Sandt, L., Edlund, K., Lohr, M., Hellwig, B., Marchan, R., Schmidt, M., Rahnenfuhrer, J., Oster, H. and Hengstler, J. G. 2014. Loss of circadian clock gene expression is associated with tumor progression in breast cancer. *Cell Cycle* **13**, 3282-3291.
4. Cao, Q., Gery, S., Dashti, A., Yin, D., Zhou, Y., Gu, J. and Koeffler, H. P. 2009. A role for the clock gene per1 in prostate cancer. *Cancer Res.* **69**, 7619-7625.
5. Chen, B., Tan, Y., Liang, Y., Li, Y., Chen, L., Wu, S., Xu, W., Wang, Y., Zhao, W. and Wu, J. 2017. Per2 participates in AKT-mediated drug resistance in A549/DDP lung adenocarcinoma cells. *Oncol. Lett.* **13**, 423-428.
6. Chen, S. T., Choo, K. B., Hou, M. F., Yeh, K. T., Kuo, S. J. and Chang, J. G. 2005. Deregulated expression of the PER1, PER2 and PER3 genes in breast cancers. *Carcinogenesis* **26**, 1241-1246.
7. Dardente, H. and Cermakian, N. 2007. Molecular circadian rhythms in central and peripheral clocks in mammals. *Chronobiol. Int.* **24**, 195-213.
8. Dibner, C., Schibler, U. and Albrecht, U. 2010. The mammalian circadian timing system: organization and coordination of central and peripheral clocks. *Annu. Rev. Physiol.* **72**, 517-549.
9. Fu, L., Pelicano, H., Liu, J., Huang, P. and Lee, C. 2002. The circadian gene Period2 plays an important role in tumor suppression and DNA damage response *in vivo*. *Cell* **111**, 41-50.
10. Fu, X. J., Li, H. X., Yang, K., Chen, D. and Tang, H. 2016. The important tumor suppressor role of PER1 in regulating the cyclin-CDK-CKI network in SCC15 human oral squamous cell carcinoma cells. *Onco Targets Ther.* **9**, 2237-2245.
11. Gachon, F. 2007. Physiological function of PARbZip circadian clock-controlled transcription factors. *Ann. Med.* **39**, 562-571.
12. Gery, S., Komatsu, N., Baldjyan, L., Yu, A., Koo, D. and Koeffler, H. P. 2006. The circadian gene per1 plays an important role in cell growth and DNA damage control in human cancer cells. *Mol. Cell* **22**, 375-382.
13. Gotoh, T., Vila-Caballer, M., Santos, C. S., Liu, J., Yang, J. and Finkielstein, C. V. 2014. The circadian factor Period 2 modulates p53 stability and transcriptional activity in unstressed cells. *Mol. Biol. Cell* **25**, 3081-3093.
14. Gotoh, T., Kim, J. K., Liu, J., Vila-Caballer, M., Stauffer, P. E., Tyson, J. J. and Finkielstein, C. V. 2016. Model-driven experimental approach reveals the complex regulatory distribution of p53 by the circadian factor Period 2. *Proc. Natl. Acad. Sci. USA* **113**, 13516-13521.
15. Grechez-Cassiau, A., Rayet, B., Guillaumond, F., Teboul, M. and Delaunay, F. 2008. The circadian clock component BMAL1 is a critical regulator of p21WAF1/CIP1 expression and hepatocyte proliferation. *J. Biol. Chem.* **283**, 4535-4542.
16. Green, C. B., Takahashi, J. S. and Bass, J. 2008. The meter of metabolism. *Cell* **134**, 728-742.
17. Hsu, C. M., Lin, P. M., Lai, C. C., Lin, H. C., Lin, S. F. and Yang, M. Y. 2014. PER1 and CLOCK: potential circulating biomarkers for head and neck squamous cell carcinoma. *Head Neck* **36**, 1018-1026.
18. Hua, H., Wang, Y., Wan, C., Liu, Y., Zhu, B., Yang, C., Wang, X., Wang, Z., Cornelissen-Guillaume, G. and Halberg, F.

2006. Circadian gene mPer2 overexpression induces cancer cell apoptosis. *Cancer Sci.* **97**, 589-596.
19. Huber, A. L., Papp, S. J., Chan, A. B., Henriksson, E., Jordan, S. D., Kriebs, A., Nguyen, M., Wallace, M., Li, Z., Metallo, C. M. and Lamia, K. A. 2016. CRY2 and FBXL3 Cooperatively Degrade c-MYC. *Mol. Cell* **64**, 774-789.
20. Jung-Hynes, B., Huang, W., Reiter, R. J. and Ahmad, N. 2010. Melatonin resynchronizes dysregulated circadian rhythm circuitry in human prostate cancer cells. *J. Pineal Res.* **49**, 60-68.
21. Lengyel, Z., Lovig, C., Kommedal, S., Keszthelyi, R., Szekeres, G., Battyani, Z., Csernus, V. and Nagy, A. D. 2013. Altered expression patterns of clock gene mRNAs and clock proteins in human skin tumors. *Tumour Biol.* **34**, 811-819.
22. Liu, B., Xu, K., Jiang, Y. and Li, X. 2014. Aberrant expression of Per1, Per2 and Per3 and their prognostic relevance in non-small cell lung cancer. *Int. J. Clin. Exp. Pathol.* **7**, 7863-7871.
23. Lowrey, P. L. and Takahashi, J. S. 2004. Mammalian circadian biology: elucidating genome-wide levels of temporal organization. *Annu. Rev. Genomics Hum. Genet.* **5**, 407-441.
24. Matsuo, T., Yamaguchi, S., Mitsui, S., Emi, A., Shimoda, F. and Okamura, H. 2003. Control mechanism of the circadian clock for timing of cell division *in vivo*. *Science* **302**, 255-259.
25. Mazzoccoli, G., Panza, A., Valvano, M. R., Palumbo, O., Carella, M., Pazienza, V., Biscaglia, G., Tavano, F., Di Sebastiano, P., Andriulli, A. and Piepoli, A. 2011. Clock gene expression levels and relationship with clinical and pathological features in colorectal cancer patients. *Chronobiol. Int.* **28**, 841-851.
26. Mokros, L., Karbownik, M. S., Nowakowska-Domagala, K., Szemraj, J., Wieteska, L., Wozniak, K., Witusik, A., Antczak, A. and Pietras, T. 2016. Haloperidol, but not olanzapine, may affect expression of PER1 and CRY1 genes in human glioblastoma cell line. *Biol. Rhythm Res.* **47**, 865-871.
27. Mteyrek, A., Filipski, E., Guettier, C., Okyar, A. and Levi, F. 2016. Clock gene Per2 as a controller of liver carcinogenesis. *Oncotarget* **7**, 85832-85847.
28. Okabe, T., Kumagai, M., Nakajima, Y., Shirotake, S., Kodaira, K., Oyama, M., Ueno, M. and Ikeda, M. 2014. The impact of HIF1alpha on the Per2 circadian rhythm in renal cancer cell lines. *PLoS One* **9**, e109693.
29. Repouskou, A. and Prombona, A. 2016. c-MYC targets the central oscillator gene Per1 and is regulated by the circadian clock at the post-transcriptional level. *Biochim. Biophys. Acta.* **1859**, 541-552.
30. Reppert, S. M. and Weaver, D. R. 2002. Coordination of circadian timing in mammals. *Nature* **418**, 935-941.
31. Reszka, E., Przybek, M., Muurlink, O. and Peplonska, B. 2017. Circadian gene variants and breast cancer. *Cancer Lett.* **390**, 137-145.
32. Richardson, A. L., Wang, Z. C., De Nicolo, A., Lu, X., Brown, M., Miron, A., Liao, X., Iglehart, J. D., Livingston, D. M. and Ganesan, S. 2006. X chromosomal abnormalities in basal-like human breast cancer. *Cancer Cell* **9**, 121-132.
33. Scheiermann, C., Kunisaki, Y. and Frenette, P. S. 2013. Circadian control of the immune system. *Nat. Rev. Immunol.* **13**, 190-198.
34. Shearman, L. P., Sriram, S., Weaver, D. R., Maywood, E. S., Chaves, I., Zheng, B., Kume, K., Lee, C. C., van der Horst, G. T., Hastings, M. H. and Reppert, S. M. 2000. Interacting molecular loops in the mammalian circadian clock. *Science* **288**, 1013-1019.
35. Siepka, S. M., Yoo, S. H., Park, J., Song, W., Kumar, V., Hu, Y., Lee, C. and Takahashi, J. S. 2007. Circadian mutant Overtime reveals F-box protein FBXL3 regulation of cryptochrome and period gene expression. *Cell* **129**, 1011-1023.
36. Storch, K. F., Lipan, O., Leykin, I., Viswanathan, N., Davis, F. C., Wong, W. H. and Weitz, C. J. 2002. Extensive and divergent circadian gene expression in liver and heart. *Nature* **417**, 78-83.
37. Su, X., Chen, D., Yang, K., Zhao, Q., Zhao, D., Lv, X. and Ao, Y. 2017. The circadian clock gene PER2 plays an important role in tumor suppression through regulating tumor-associated genes in human oral squamous cell carcinoma. *Oncol. Rep.* **38**, 472-480.
38. Sun, C. M., Huang, S. F., Zeng, J. M., Liu, D. B., Xiao, Q., Tian, W. J., Zhu, X. D., Huang, Z. G. and Feng, W. L. 2010. Per2 inhibits k562 leukemia cell growth *in vitro* and *in vivo* through cell cycle arrest and apoptosis induction. *Pathol. Oncol. Res.* **16**, 403-411.
39. Takahashi, J. S., Hong, H. K., Ko, C. H. and McDearmon, E. L. 2008. The genetics of mammalian circadian order and disorder: implications for physiology and disease. *Nat. Rev. Genet.* **9**, 764-775.
40. Tamiya, H., Ogawa, S., Ouchi, Y. and Akishita, M. 2016. Rigid Cooperation of Per1 and Per2 proteins. *Sci. Rep.* **6**, 32769.
41. Wood, P. A., Yang, X. and Hrushesky, W. J. 2009. Clock genes and cancer. *Integr. Cancer Ther.* **8**, 303-308.
42. Xia, H. C., Niu, Z. F., Ma, H., Cao, S. Z., Hao, S. C., Liu, Z. T. and Wang, F. 2010. Deregulated expression of the Per1 and Per2 in human gliomas. *Can. J. Neurol. Sci.* **37**, 365-370.
43. Zeng, Z. L., Wu, M. W., Sun, J., Sun, Y. L., Cai, Y. C., Huang, Y. J. and Xian, L. J. 2010. Effects of the biological clock gene Bmal1 on tumour growth and anti-cancer drug activity. *J. Biochem.* **148**, 319-326.
44. Zhanfeng, N., Yanhui, L., Zhou, F., Shaocai, H., Guangxing, L. and Hechun, X. 2015. Circadian genes Per1 and Per2 increase radiosensitivity of glioma *in vivo*. *Oncotarget* **6**, 9951-9958.
45. Zhao, H., Zeng, Z. L., Yang, J., Jin, Y., Qiu, M. Z., Hu, X. Y., Han, J., Liu, K. Y., Liao, J. W., Xu, R. H. and Zou, Q. F. 2014. Prognostic relevance of Period1 (Per1) and Period2 (Per2) expression in human gastric cancer. *Int. J. Clin. Exp. Pathol.* **7**, 619-630.

초록 : 체내 시계 유전자 PER1과 PER2의 종양억제자 기능

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암을 포함한 다양한 인간의 질병 발생이 circadian clock 유전자의 변형된 발현 양상과 깊은 연관관계를 나타내고 있다. 세포 주기와 세포 성장은 circadian rhythm과 연결되어 있으며, 이를 조절하는 clock 유전자의 비정상적인 발현은 결국 종양 발생과 암의 발달을 유발하게 된다. Circadian clock에 관한 분자적 기전은 다수의 clock activator와 clock repressor의 통합적인 조절에 따른 전사 및 번역이 포함된 음성피드백 고리로 구성되어 있다. 이러한 circadian rhythm의 자동조절 기전에 의해 전체 유전체의 약 10~15%가 전사 수준에서 영향받는 것으로 나타났다. 많은 clock 유전자들 중, *Period 1* (*Per1*)과 *Period 2* (*Per2*)는 clock repressor 유전자로 정상적인 생리적 리듬을 조절하는 것에 기여한다. PER1과 PER2는 cyclin, CDK, CKI를 포함하는 세포 주기 조절자의 발현에 관여함이 밝혀졌으며, 다양한 암에서 PER1과 PER2의 발현 감소가 보고되었다. 따라서, 본 논문에서는 PER1과 PER2의 circadian rhythm에서의 분자적 기능과 종양 발생과 관련된 PER1과 PER2의 하위 표적인자에 대해 살펴보고, 암 치료를 위한 새로운 치료 표적과 암의 예후를 예측하기 위한 분자 지표로써의 PER1과 PER2의 가능성에 대해 서술하고자 한다.