Annals of Pharmacology and Pharmaceutics

Short Communication
Published: 14 Feb, 2017

Therapeutic Implications of Cancer-Specific Clocks

Benedetto Grimaldi*

Department of Drug Discovery and Development, Fondazione Istituto Italiano di Tecnologia, Italy

Short Communication

The proper functionality of our cells requires a temporal orchestration of many physiological processes. The "art director" of this symphony is represented by the endogenous molecular clock, which is able to activate or repress the expression of more than 10% of human genes in a "crescendo" and "decrescendo" in time with the environment [1].

Being designated to modulate important physiological activities, such as brain functions, pathogen defense and metabolism, it is not surprising that disruption of the molecular clock is associated with a variety of human pathologies [1-5]. Less obvious, but highly fascinating, would be the possibility to modulate the molecular clock to cure a pathology.

Recently, we obtained the first prove that the pharmacological modulation of a clock-related protein is a suitable strategy for the identification of innovative anticancer approaches [6]. Although it is wide recognized that cancer cells and normal cells do not share a common clock, the molecular basis of this difference is still unclear. We discovered an unpredicted cancer-specific "paralog switch" of the clock regulatory nuclear receptor, REV-ERB [6]. This receptor exists in two variants, REV-ERBα and REV-ERBβ, transcribed from different genomic loci. Opposite to non-cancer human mammary epithelial, a number of human tumor tissue cells predominantly express the beta REV-ERB variant. Accordingly, REV-ERBβ functions as an unpredicted major regulator of cancer clock gene expression in cancer cells [6]. Notably, REV-ERBα and REV-ERBβ displayed a similar circadian oscillatory pattern in both synchronized non-cancer and cancer cells. Nonetheless, in cancer cells REV-ERBβ expression was higher than that of REV-ERBα at all timepoints. This result has an interesting and important implication. Because of the circadian oscillatory expression of clock genes, a comparison between healthy and tumor tissues would require a synchronized sample collection from patients at different time points over a 24h period. This kind of analysis is clearly unfeasible. Nevertheless, our discovery that cancer cells present a specific "clock paralog switch" offers the unique opportunity to evaluate alteration of the clock machinery directly in primary tumor tissues, independently of the time in which the sample has been collected from the patient. Following this idea, we were able to show that while REV-ERBα was more abundant than REV-ERBβ in various normal human tissues, the latter was more highly expressed in several primary tumor samples of different origin [6]. Further studies revealed that REV-ERBβ functions as an unpredicted major regulator of cancer clock gene expression and it plays an unexpected role in sustaining cancer cell survival when the autophagy flux is compromised [6]. Indeed, molecular genetic analyses revealed that REV-ERBβ is required to support cancer cell viability when the autophagy process is blocked. Accordingly, genetic inhibition of REV-ERBβ sensitizes cancer cells to cytotoxicity induced by chloroquine (CQ), a lysosomotropic autophagy inhibitor that is currently being evaluated in cancer clinical trials [6]. The importance of this result lies on the fact that many cancer cells require high micromolar concentrations of CQ to block autophagy in vitro, yet such levels are rarely achieved in patients [7]. Consequently, a dual inhibition of both REV-ERBβ and autophagy may be a successful alternative strategy for developing more efficient anticancer agents. Following this idea, we initiated a successful drug discovery project that resulted in the disclosure of the first dual inhibitor of REV-ERBβ and autophagy [6,8]. Remarkably, the most potent inhibitor of this class of dual inhibitors, ARN16090, decreases the viability of different tumor tissue cells at concentrations up to 50 times lower than single autophagy inhibitor, CQ [8,9]. Moreover, ARN16090 did not showed toxicity against non-cancer cells at the doses tested and preliminary pharmacokinetic analyses indicated the suitability of this compound for testing anticancer effects in pre-clinical models. It is now well accepted that the efficacy and the collateral toxicity of different many drugs, including antitumor agents, are greatly affected by circadian timing and recent studies have revealed that adopting an anticancer chronotherapeutic strategy leads to better therapeutic outcomes [10]. In this scenario, "clock modulators" are natural candidates for a chronotherapeutic approach. As a consequence, a chronotherapy-based administration of our compounds may effectively improve the efficacy against

OPEN ACCESS

Correspondence:
Benedetto Grimaldi, Department of Drug Discovery and Development, Fondazione Istituto Italiano di Tecnologia, Italy,
E-mail: benedetto.grimaldi@iit.it

Received Date: *16 Dec 2016*
Accepted Date: *13 Feb 2017*
Published Date: *14 Feb 2017*

Citation:
Grimaldi B. Therapeutic Implications of Cancer-Speci ic Clocks. Ann Pharmacol Pharm. 2017; 2(2): 1023.

tumor cells while decrease potential unwanted side-effects toward non-cancer cells. We are actually evaluating this hypothesis in pre-clinical tumor models. Overall, our studies reveal the existence of a cancer-specific molecular clock, which can be used for the discovery and the development of novel therapeutic approaches to treat cancer.

Acknowledgement

This work has been partly supported by the AIRC (Associazione Italiana per la Ricerca sul Cancro) grant No. 17005.

References

1. L Ercolani A, Ferrari C, De Mei C, Parodi M, Wade B. Grimaldi, Circadian clock: Time for novel anticancer strategies? Pharmacol Res. 2015; 100: 288-295.
2. B Grimaldi, MM Bellet, S Katada, G Astarita, J Hirayama, RH Amin, et al. PER2 controls lipid metabolism by direct regulation of PPAR gamma. Cell Metab. 2010; 12: 509-520.
3. Bellet MM, Deriu E, Liu JZ, Grimaldi B, Blaschitz C, Zeller M, et al. Circadian clock regulates the host response to Salmonella. Proc Natl Acad Sci U S A. 2013; 110: 9897-9902.
4. Hastings MH, Reddy AB, Maywood ES. A clockwork web: circadian timing in brain and periphery, in health and disease. Nat Rev Neurosci. 2003; 4: 649-661.
5. Rossetti S, Esposito J, Corlazzoli F, Gregorski A, Sacchi N. Entrainment of breast (cancer) epithelial cells detects distinct circadian oscillation patterns for clock and hormone receptor genes. Cell Cycle. 2012; 11: 350-360.
6. C De Mei, L Ercolani, C Parodi, M Veronesi, C Lo Vecchio, G Bottegoni, et al. Dual inhibition of REV-ERBbeta and autophagy as a novel pharmacological approach to induce cytotoxicity in cancer cells, Oncogene. 2015; 34: 2597-2608.
7. JS Carew, KR Kelly, ST Nawrocki. Autophagy as a target for cancer therapy: new developments. Cancer Manag Res. 2012; 4: 357-365.
8. Torrente E, Parodi C, Ercolani L, De Mei C, Ferrari A, Scarpelli R, et al. Synthesis and in Vitro Anticancer Activity of the First Class of Dual Inhibitors of REV-ERBbeta and Autophagy. J Med Chem. 2015; 58: 5900-5915.
9. C Wang, Q Hu, HM Shen. Pharmacological inhibitors of autophagy as novel cancer therapeutic agents, Pharmacol Res. 2016; 105: 164-175.
10. Fu L, Kettner NM, The circadian clock in cancer development and therapy, Prog Mol Biol Transl Sci. 2013; 119: 221-282.