



Opinion

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Circadian Rhythm-Related Molecular Mechanisms and Chemotherapy

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To Cite This Article: Hasibe Vural Cingilli. Circadian Rhythm-Related Molecular Mechanisms and Chemotherapy. Am J Biomed Sci & Res. 2022 - 16(4). AJBSR.MS.ID.002252. DOI: [10.34297/AJBSR.2022.16.002252](https://doi.org/10.34297/AJBSR.2022.16.002252)

Received: 📅 June 13, 2022; Published: 📅 June 17, 2022

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Cancer cells manipulate the biological clock that regulates the functioning of the body to regulate their own rhythms. It is known that the biological clocks of individuals with cancer activate tumor cells and feed them. The genes and gene products of the circadian clock that make up our biological rhythm have a critical role in the physiological pathways that are important for cell metabolism. The cell cycle and the circadian rhythm are in constant interaction, and circadian clock genes and gene products are involved in the control of the cell cycle. Although circadian control and the cell cycle are composed of different molecular mechanisms, these two cycles are interrelated in mammals. Because circadian clock gene mutations can alter the expression of important cell cycle regulators. Therefore, it is a fact that the circadian clock is associated with the regulation of cell division. In short, the cell cycle and the circadian clock are generally the regulatory systems of all organisms.

Most of the anticancer drugs prevent the growth and proliferation of malignant cells with their cytotoxic effects and cause their death. A radical treatment is destroying all cells without leaving a single malignant cell in the body. However, such a situation cannot be achieved with existing drugs, with few exceptions. An important factor limiting the therapeutic efficacy of an antineoplastic drug is the decreased sensitivity of tumor cells to the drug, in other words, the development of drug resistance. This may occur spontaneously in some types of cancer (natural or primary resistance) or may develop after chemotherapy. Necessity

of investigating molecular mechanisms; It is aimed at using specialized gene panels and gene products such as biological clock / circadian rhythm in biotechnological applications and cancer treatment.

Biological rhythms are our rhythms controlled by the suprachiasmatic nucleus located in the anterior hypothalamus of our brain. It is also called the circadian rhythm. It is responsible for the synchronization of our twenty-four-hour biological, physiological and social behaviors. Almost all organs, including the brain, have their own biological rhythms and are synchronized by an endogenous stimulus. The circadian rhythm expresses the changes in the physiological and biological processes of the organism for approximately one day. The human sleep-wake cycle is the most fundamental and decisive circadian rhythm. The main events that regulate the circadian rhythm in humans and other mammals are melatonin secreted from the pituitary and body temperature. In addition, proteins called "cryptochromes", which have been well preserved throughout evolution in many living things, including humans, also play an important role in regulating the circadian rhythm. When the circadian clock is inside the cell; that is, "cellautonomous".

Different forms of communication create a specific response by technical signaling. This ensures periodic release of hormones from the endocrine glands in the brain. As a result of the interaction of these hormones with their receptors, peripheral clocks



start to work synchronously in many organs. The discipline of "chronobiology" deals with the classification of biological rhythms as daily, weekly, seasonal or annual. The molecular mechanisms of circadian effects are related to the biological clock and synchronize drug distribution in the body. The circadian rhythm is of great importance in terms of taking the drugs at the right time. Correct intake of drugs is important for drug pharmac/toxicodynamics and pharmac/toxicokinetics. Because of the circadian rhythm, taking the drugs at the right time is important in terms of ensuring the maximum effectiveness of the drug and creating minimum toxicity. Chronopharmacology examines the effects that may occur with both acute and chronic use of the drug and is important in determining the changes that can be seen during the day with different administration routes and dosage forms.

When should the drug be taken for its effectiveness to be high? in the morning or in the evening? And Is it hungry or full? These are the most frequently asked questions by patients, especially when starting a new drug. When timing the drug, it is desired that the therapeutic effect is maximum and adverse reactions are minimal. The interaction of drugs with food and other drugs should be considered. Because taking drugs at the wrong time can reduce their effectiveness or change their tolerance to the drug. For this reason, in order to achieve the desired goal in the treatment and to increase the patient's treatment compliance, the drug intake time should be adjusted in accordance with the daily routine of the patient. It is important to plan for a particular chronic illness such as cancer. Findings from chronotherapy studies can guide the determination of this timing. Encouraging patients to take their medication in the most appropriate way to their daily routine will optimize treatment adherence. To further improve therapeutic outcomes, it is necessary to explain to patients the importance of taking nutrients and medications at the appropriate time. To assist patient-centered treatment, healthcare professionals should regularly update their knowledge of treatment planning and timing of medication.

The field of chronotherapy has emerged with the consideration of circadian rhythms in the prevention and treatment of diseases. Asthma, cardiovascular diseases, cancer, ulcers and many other diseases show circadian features, and the resolution of these features brings new treatment approaches to the agenda. The irregularity of sleep timing leads to sleep disorders and related clinical conditions ranging from obesity to metabolic syndrome, diabetes to Alzheimer's disease. The role of chronotherapy is most evident in the field of drug therapy, doctors prescribe medications not only for a disease or condition, but also for the time of day. Some formulations of drugs had a better time to release their active ingredients, and these were called chronotherapeutics. Some drugs

used to fight cancer through chemotherapy are more effective at certain times of the day and their toxicity is reduced. Chronotherapy can also affect the amount of medication a patient takes. Sometimes less dosage of certain types of drugs is desired if the body's clock is optimized. Some doctors like the advantage that chronotherapy provides because they found that patients adhered better to their medication schedule when the drugs worked better, and sometimes less irritating side effects also had an added benefit.

Disruption of the circadian clock is effective in the development of many different human cancers. Disruption of the circadian rhythm leads to epigenetic modifications that alter cell proliferation and result in oncogenesis and cancer. For example, the melatonin system is linked to carcinogenesis. The clockwork is in functional interaction with cell cycle regulators, thus changes in clock function result in uncontrollable cell cycle progression and cell proliferation. The relationship between the circadian clock and cell metabolism results in the disruption of the circadian clock in abnormal cell metabolism. All of these abnormalities play an important role in carcinogenesis processes and may result in multi-tumorigenesis. The connection between the cell cycle and the circadian clock is determined by the regulation of the circadian rhythm and is controlled by the cell cycle.

The purpose of this review is to understand the functioning of the circadian system and how internal and external factors that affect humans affect the circadian rhythm. In this study, it is stated that the results of modern life, when evaluated in terms of cell cycle, cell proliferation and development of necrosis, increase the risk of many diseases by affecting the circadian system. The circadian system, which is directly related to our health, should be a followable target in order to reduce the incidence of many diseases. The circadian clock is an extraordinary system. The central timer in the hypothalamus coordinates the peripheral clock network found in almost all organs and tissues, and It activates or inactivates groups of genes, including genes that encode the molecular targets of drugs and enzymes that break down drugs into their molecules. These clock genes are particularly important. Because it manages cell cycles, cell proliferation, cell death and DNA damage repair, in short, all processes that can become chaotic and out of tune in cancer.

Accurate and regular adjustment of the circadian rhythm and biological clock enables the identification of genetic changes, signaling pathways, oncogenes and tumor suppressor genes involved in the physiopathology of cancer, angiogenesis and apoptosis, while illuminating the basic mechanisms that predispose to disease. It also helps to understand how cellular mechanisms such as cell proliferation, differentiation and death are organized. In this case, molecular methods should be used in the diagnosis

of cancer and in the follow-up of patients, and awareness should be raised about the intake of chemotherapeutics that are suitable for cancer treatment, have low side effects and are non-toxic. The rational picture is particularly important in the use of targeted drugs against disease. In summary, this situation provides the opportunity to benefit from molecular methods in the diagnosis of cancer and in the follow-up of patients, raises awareness about the use of targeted drugs against the disease, and raises awareness

about the use of non-toxic drugs or chemotherapeutics with low side effects.

Thus, it will enable new treatment approaches such as circadian clock / biocompatibility / bioavailability / cell cycle and even personalized medicine to be brought to the agenda and researched. In order to organize our life comfort in the best way, we should plan what and when we will do by harmonizing our life rhythm with our biological rhythm together with nutrition.