INTRODUCTION

Living organisms experiencing periodic changes in the environment in the course of evolution developed an adaptation to these changes. Even in unicellular prokaryotes, the diurnal cycle resulted in the development of a molecular oscillator system synchronizing biological processes and environmental rhythms. Endogenous fluctuations in gene expression responsible for physiological indices and change of behavioral programs with 24 h periodicity are maintained in the absence of external regulatory stimuli. These are called circadian or circadian rhythms from *circa diem*—around a day in Latin [1]. According to some studies, about 20% of genes in every human cell depend on circadian regulators [2]. Others noted that up to 43% of protein-coding genes exhibit circadian transcriptional activity in at least one tissue [3]. Along with other studies, the list of genes controlled by elements of an oscillator includes age-related genes such as those encoding elements of kinase cascade TOR/S6K [4], members of transcription factors FoxO [5, 6], NF-κB signaling cascade members [7], and also factors responsible for epigenetic DNA modification and histones [8]. The aging process is associated with changes in expression of the circadian genes themselves [9].

The aim of this study is to determine the role of circadian rhythm genes in the course of aging from the analysis of published sources. The review describes the functioning of oscillators at different levels. An association was revealed between circadian genes with aging genetic determinants and pathogenesis of age-related diseases. Using published sets of complete transcriptome data, we conducted a comparative analysis of changes in the expression of circadian genes with aging in animal tissues, which differ in the rate of aging.

CENTRAL OSCILLATOR GENES

Genes which are expressed rhythmically and are capable of synchronizing their cyclic activity with environmental challenges were observed even in Archaea and Cyanobacteria (gene groups *cir* and *kai*), but their mode of intragenic interactions differ significantly from that in eukaryotic cells [10–12]. DNA-binding domains were not found in proteins encoded by circadian rhythm genes in prokaryotes. Therefore, the observed feedback loops can be called post-translational [13]. For example, 60% of the *Synechococcus elongatus* genome is controlled by an oscillator composed of three proteins KaiA, KaiB, and KaiC, which do not bind DNA [14, 15].

KaiA, KaiB, and KaiC interact with each other [16, 17]. KaiC is expressed as an autokinase together with an autophosphatase, which is a very rare property of a protein [18, 19]. KaiC phosphorylation is increased by interaction with KaiA [19–21], while KaiB is an antagonist of KaiA [19, 21]. Two hypothesis were proposed: either KaiA, KaiB, and KaiC control transcription factor activity [22, 23], or oscillator proteins rhythmically change nucleotide topology and provide torsion-dependent transcription [24–26]. A circular DNA molecule capable of such type of interactions was called “oscilloid” [25, 27, 28].
It is difficult to indicate an association of KaiA, KaiB, and KaiC with the aging process as for prokaryotes the term itself is a subject of a discussion and not all of the scientific community accepts it [29].

Ascomycetes Neurospora crassa can serve as an example of a eukaryotic single cell oscillator. This fungus forms a transcriptional-translational loop of negative feedback association of circadian oscillator [30]. Its basic element is formed by proteins WC-1 (which are responsible for photoreception) and WC-2, which produce a transactivation complex WCC, which induces expression of frequency genes and many other genes under their control which do not belong to the central oscillator [31]. FPQ, which determines the period of oscillations, is linked to FRH, forming a dimer capable of repressing wc-1 and wc-2 and closing the loop [32].

Among multicellular eukaryotes, circadian genes of nematodes should be mentioned. At present, the oscillator activity of lin-42 (PER homolog of mammals) and aha-1 (CLOCK homolog) has been proved. These are the key genes in the process of rhythmic determination [33–35]. However, homologs and paralogs of other circadian genes from highly developed organisms (tim-1, ces-2, aff-2, kin-20/kin-19, gsk-3, kin-3, kin-10, gsp-1/gsp-2, and sur-6) with the exception of pdf-1,-2 are involved in developmental processes but likely are not involved in generation of circadian rhythms. A recent study of C. elegans transcriptome has shown that oscillations in gene expression in response to classical factors determining the oscillation period, namely, light and temperature regimens, were observed in homologous groups having little in common with circadian rhythms in other organisms [36] (Table 1).

In a fruit fly Drosophila melanogaster, homologs of mammalian genes Clock (Clk) and cycle encode proteins CLK/CYC of a dimer, which further stimulates expression of period (per) and timeless (tim). Later, per and tim form dimers which implement repression of CLK/CYC and their own, respectively [37]. In another negative feedback loop, complex CLK/CYC induces expression of transcription factor Par domain protein 1e (Pdp1e) and wrille (vri) genes, the first of which is an activator Clk, while the second is its repressor [38]. One should specifically mention the cwo gene. Its product represses its own repression, transcription of tim, Pdp1, per, and vri. Functionally, the CWO protein is an antipode of the CLK/CYC dimer [39] (Table 1, Fig. 1).

The modern model of molecular oscillator in mammals comprises two interrelated feedback loops. CLOCK, along with NPAS2 and BMAL1, which is also known as ARNTL, activates transcription of genes encoding proteins PER1 and PER2 as well as CRY1 and CRY2 [40]. Multicomponent co-repressor complexes based on PER and CRY, which include many other polypeptides, reach the highest concentration and bind with the CLOCK/BMAL1 complex, thus inhibiting its capacity of activating transcription of genes Per and Cry [41]. Gradually, the system reaches the state where the concentration of the aforementioned proteins becomes insufficient for maintenance of CLOCK/BMAL1 in a deactivated state [41]. The first loop launches again when the process of PER/CRY accumulation resumes [41] (Fig. 1).

A hypothesis was suggested on independence of repressor properties of PER and CRY. The main argument of its supporters is the capacity of mCRY2 to functionally replace mPER2 in knockout animals.

In another negative feedback loop, CLOCK/BMAL1 provides a positive transcription control of REV-ERBα and REV-ERBβ, which repress the Bmal1 gene [42]. REV-ERBα and REV-ERBβ regulate transcription of Per and Cry by modulation of their expression phase along with expression of many genes not related to the oscillator [43, 44]. The concentrations of REV-ERBα and REV-ERBβ vary with high amplitude. These proteins from time to time bind with RORE sequences in the DNA promoters of the Clock and Bmal1 genes, where they compete with RORα, RORβ, and RORγ, which serve as Clock and Bmal1 transactivators [42] (Table 1).

**THE ROLE OF CIRCADIAN RHYTHM GENES IN AGING MECHANISMS**

Some studies confirmed that 20–43% of genes in every human cell depend on circadian regulators [2]. For example, it is well established that basic heterodimer CLOCK/BMAL1 controls expression of various groups of genes (CCGs—clock controlled genes).

An example of a transcription factor affected by heterodimer CLOCK/BMAL1 is a product of the NRF2 gene expressed in the lungs and entailing an oscillator with local systems of free radical detoxification, including Gclm (glutamate-cysteine ligase modifier) and Gsta3 (glutathione S-transferase A3). Therefore, an increase in concentration of a heterodimer could enable delaying aging in respiratory system tissues by increasing resistance to oxidative stress [54–56].

Circadian rhythms control genes which regulate the cell cycle and inhibit cellular aging (an irreversible exit from the cell cycle). In particular, the CLOCK/BMAL1 gene directly controls expression of the Weel gene, which is further responsible for the G2/M transition in the cell cycle [57]. In addition, the dimer regulates expression of oncogene c-myc, which controls transition from the interphase to presynthetic phase, and the Cyclin D1 gene, regulating transition from the presynthetic phase to synthetic phase [58].

It is worth noting that some studies have shown an association between signaling pathways, which are responsible for the response to DNA damage (a key factor of cellular aging induction), and circadian proteins. PER1 and TIM interact with cell cycle checkpoint kinases, ATM and ATR [40]. They are in charge