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Review

Redox regulation and pro-oxidant reactions in the physiology of circadian systems

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ABSTRACT

Rhythms of approximately 24 h are pervasive in most organisms and are known as circadian. There is a molecular circadian clock in each cell sustained by a feedback system of interconnected "clock" genes and transcription factors. In mammals, the timing system is formed by a central pacemaker, the suprachiasmatic nucleus, in coordination with a collection of peripheral oscillators. Recently, an extensive interconnection has been recognized between the molecular circadian clock and the set of biochemical pathways that underlie the bioenergetics of the cell. A principle regulator of metabolic networks is the flow of electrons between electron donors and acceptors. The concomitant reduction and oxidation (redox) reactions directly influence the balance between anabolic and catabolic processes. This review summarizes and discusses recent findings concerning the mutual and dynamic interactions between the molecular circadian clock, redox reactions, and redox signaling. The scope includes the regulatory role played by redox coenzymes (NAD(P)+/NAD(P)H, GSH/GSSG), reactive oxygen species (superoxide anion, hydrogen peroxide), antioxidants (melatonin), and physiological events that modulate the redox state (feeding condition, circadian rhythms) in determining the timing capacity of the molecular circadian clock. In addition, we discuss a purely metabolic circadian clock, which is based on the redox enzymes known as peroxiredoxins and is present in mammalian red blood cells and in other biological systems. Both the timing system and the metabolic network are key to a better understanding of widespread pathological conditions such as the metabolic syndrome, obesity, and diabetes.

1. Preface

Since early in the history of our planet and as a consequence of the formation of the moon, the Earth has rotated around its own axis once in about 24 h [1]. This characteristic has had defining significance for the ecological adaptations of most organisms. The temporal organization of cycles such as wakefulness–sleep, feeding–fasting, and arousal–resting are among these adaptations. Underlying these periodic activities was the emergence of an endogenous timing system that confers on most organisms the capacity to display ~24-h fluctuations in physiological parameters. These daily variations are known as circadian rhythms (from *circa*, approximately, and *dies*, day) [2].

There are 3 components constituting the circadian rhythms: 1) a molecular clock that has the capacity to measure time and is formed by an interconnected set of genes/proteins regulated by feedback loops; 2) synchronizing elements that allow the molecular clock to be entrained by environmental cues; and 3) output signals that communicate the oscillatory activity of the molecular clock from metabolic to behavioral activities within any organism [3].

In mammals, the circadian timing system involves a master clock localized in the hypothalamic suprachiasmatic nucleus (SCN) and a set of peripheral oscillators that are coordinated by the SCN [4]. Most of the time, the circadian timing system is synchronized by a light stimulus [5]; however, in some circumstances the

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Acronyms

ΔEh	redox potential
ΔG	Gibbs free energy
ADP-ribose	adenosine diphosphate ribose
AMPK	adenosine monophosphate-activated kinase
BMAL1	brain and muscle ARNT-like protein 1
CLOCK	circadian locomotor output cycle kaput
CRY1	cryptochrome circadian clock 1
CuZnSOD	cupper/zinc superoxide dismutase
EGF	epidermal growth factor
FAA	food anticipatory activity
$FADH_2$	flavin adenine dinucleotide (reduced form)
FEO	food entrained oscillator
GSH	reduced glutathione
GSSG	oxidized glutathione
H_2O_2	hydrogen peroxide
$HO^•$	hydroxyl radical
IDH-$NADP^+$	$NADP^+$-dependent isocitrate dehydrogenase
LD	light-dark cycle
LL	constant light conditions
MCC	molecular circadian clock
MnSOD	manganese superoxide dismutase
$NAD(P)^+$	nicotinamide adenine dinucleotide (phosphate) oxidized
NAD(P)H	nicotinamide adenine dinucleotide (phosphate) reduced
NO	nitric oxide
NO_3–NO_2	nitrates–nitrites
Nox-1	NADPH oxidized isoform 1
Nox-4	NADPH oxidized isoform 4
NPAS2	neuronal PAS domain protein 2
Nrf2	nuclear factor erythroid 2–related factor 2
O_2^-	superoxide anion
$ONOO^-$	peroxynitrite anion
PER2	period circadian protein homolog 2
PGC1α	peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PPARα	peroxisome proliferator-activated receptor α
PPARγ	peroxisome proliferator-activated receptor γ
RNS	reactive nitrogen species
ROS	reactive oxygen species
$RO^•$	alkoxyl radical
$ROO^•$	peroxyl radical
RORα	retinoic acid-related orphan receptor alpha
ROS	reactive oxygen species
RZR	melatonin receptor ligand
SCN	suprachiasmatic nucleus
SIRT1	NAD^+-dependent deacetylase sirtuin-1
VEGF	vascular endothelial growth factor
XPA	xeroderma pigmentosum, complementation group A

circadian physiology can be entrained by non-photic parameters, such as the access to food [6].

It has been recognized that there is an intimate and reciprocal relation between the timing of the molecular clock and the networks of metabolic pathways [7,8]. This interaction confers unique characteristics to the expression of the circadian rhythmicity of each tissue and organ [9,10]. Regulation of cellular metabolism takes place on different levels and on different time scales, for example, control of enzyme synthesis, feedback modulation of enzymatic activities, and availability of substrates and processing of products. However, three, higher-order regulatory parameters discovered in the sixties have a more extensive scope to control the network of metabolic reactions: organelle compartmentalization, energy charge, and redox state [11]. In this wide context, this review summarizes recent advances in the redox regulation of circadian physiology.

2. The molecular circadian clock

The circadian rhythmicity is maintained by well-defined transcriptional-translational and biochemical machinery, the molecular circadian clock (MCC). The canonical MCC is at the core of the timing system, and it is formed by a set of auto-regulatory loops of transcriptional and translational where factors known as "clock genes/proteins" are involved to ensure an adequate oscillation of a variety of genes. The MCC is an example of evolutive convergence, since cyanobacteria, algae, fungi, plants, flies, birds, and mammals all possess their own circadian clock [12]. In several species, some clock proteins contain structural sequences that sense redox environment. In this regard, mammalian PER and CLOCK contain PAS-domains and the flavoprotein CRY contain one or more flavin nucleotides (FAD or FMN) as redox cofactors [13]. The stimulatory loop of the mammalian MCC is formed by the heterodimer CLOCK:-BMAL1 transcription factors, which activates the transcription by recognizing promoters containing specific sequences known as E boxes and consequently, the synthesis of PER1-3 and CRY1-2. Subsequently, the PER:CRY heterodimer enters the nucleus and inhibit CCG expression by inhibiting BMAL1:CLOCK activity on E boxes. The consequence is the reduction of CLOCK:BMAL1 activity which, in turn, decreases the transcription of the *Per* and *Cry* genes, thereby allowing the activation of CLOCK:BMAL1 again [[14] and references within]. Other factors such as RevErbs and RORs integrate additional loops that confer plasticity and adaptability to the core loop (Fig. 1). REV-ERBα and β represses *Bmal1* transcription by binding to Rev-Erb/ROR response elements in the Bmal1 promoter, whereas RORα acts as an activator [15]. Most of the clock proteins are regulated biochemically through covalent modifications such as phosphorylation, acetylation, or ubiquitination, which controls their transit to the nucleus as well as their stability and half-life [16]. In particular, BMAL1/CLOCK modification by O-linked β-D-N-acetylglucosamine makes more stable the dimer by inhibiting their ubiquitination [17].

A variety of genes contain E boxes, found in promoter regions of a variety of genes, that form the basis of a transcriptional response conferring a specific timing output in every cell and tissue [16]. Although cycling levels of mRNA provide valuable information

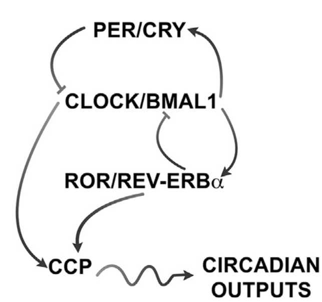

Fig. 1. Molecular circadian clock. Positive and negative loops controlling the timing system. All the transcriptional factors are "clock proteins" whose role was mentioned in the text. CCP, Clock Controlled Proteins. → Gene activation; ⊥ gene repression.