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- Review -

Biological Clock and Ultradian Metabolic Oscillation in *Saccharomyces cerevisiae*

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Biological clocks are the basis of temporal control of metabolism and behavior. These clocks are characterized by autonomous free-running oscillation and temperature compensation and are found in animals, plants, and microorganisms. To date, various biological clocks have been reported. These include clocks governing hibernation, sleep/wake, heartbeat, and courtship song. These clocks can be differentiated by the period of rhythms, for example, infradian rhythms (> 24-hr period), circadian rhythms (24-hr period), and ultradian rhythms (< 24-hr period). In yeast (*Saccharomyces cerevisiae)*, at least five different autonomous oscillations have been reported; (1) glycolytic oscillations (T = 1~30 min), (2) cell cycle-dependent oscillations (T = 2~16 hr), (3) ultradian metabolic oscillations (T = 15~50 min), (4) yeast colony oscillations (T = a few hours), and (5) circadian oscillations (T = 24 hr). In this review, we discuss studies on oscillators, pacemakers, and synchronizers, in addition to the application of biological clocks, to demonstrate the nature of autonomous oscillations, especially ultradian metabolic oscillations of *S. cerevisiae.*

Key words : Autonomous oscillation, biological clock, *Saccharomyces cerevisiae,* ultradian metabolic oscillation

Introduction

Living organisms from animals and plant to microorganisms exhibit numerous biological rhythms that are generated by numerous biological clocks [34]. Biological clocks are the basis of temporal control of metabolism and behavior [22], therefore the study of underlying mechanism of biological clock and periodic rhythms are highly concerned during the last decades. Biological clocks, which are characterized by autonomous free-running oscillation and temperature compensation (Q_{10}: ~1.0) [22, 34], could be differentiated by the period of rhythms, i.e., autonomous oscillation period. Here, an oscillation is considered sustained if phase, period and amplitude are stable over a long time range, and autonomous oscillation is considered if no external trigger is present to induce the oscillation.

To date, different periods of autonomous clocks from year (hibernation clock in reptiles) to millisecond (courtship song clock in *Drosophila* sp.) were reported [33, 49]. Humans also have multiple time-length of autonomous clocks, for example infradian rhythm (> 24 hr of period) for menstruation cycle, circadian rhythm (= 24 hr of period) for wake/sleep cycle, and ultradian rhythm (< 24 hr of period) for digestive enzyme secretion [33, 34]. Recently, it was reported that long period clock such as circadian oscillation comprise coupled short period of clock, such as ultradian oscillation [3, 9] (Fig. 1). Therefore, the study of ultradian oscillation could provide useful information to understand the biological clock as well as long period oscillations [29].

Saccharomyces cerevisiae, eukaryotic unicellular yeast, has been intensively studied in genetically, metabolically and physiologically. In this baking and wine yeast, at least five different autonomous oscillations are reported; (1) glycolytic oscillation (*T*= 1~30 min) [10], (2) cell cycle-dependent oscillation (*T*= 2~16 hr) [6], (3) ultradian metabolic oscillation (*T*= 15~50 min) [18], (4) yeast colony oscillation (*T*= a few hours) [32], and (5) circadian oscillation (*T*= 24 hr) [11]. Among them, at least, the ultradian metabolic oscillation was proved to be under the clock control based on its free running rhythm and temperature compensations [23, 24, 28]. Although, different autonomous oscillations are well characterized, the details of regulatory mechanism are still not clear. To understand the mechanisms, identification of regulatory circuits,

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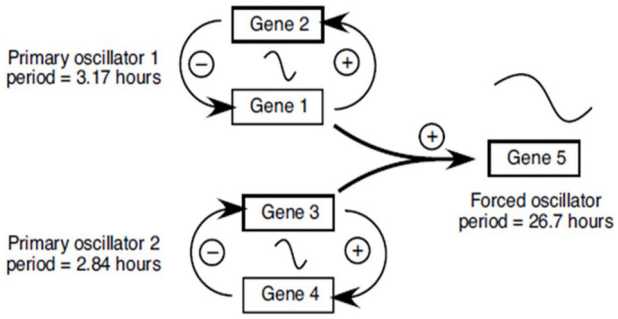

Fig. 1. A model for generating long-period oscillator by coupling of ultradian oscillator From [29].

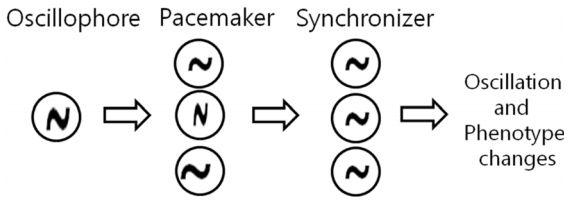

Fig. 2. Basic components of autonomous oscillation as a biological clock in cell population.

such as oscillator (oscillophore), pacemaker, synchronizer, and organization of the regulatory circuits by time basis are necessary (Fig. 2). In this review, we highlight a selection of studies about oscillator, pacemaker, and synchronizer in order to demonstrate the nature of autonomous oscillations, especially the ultradian metabolic oscillation, of *Saccharomyces cerevisiae*.

Autonomous glycolytic oscillation in *S. cerevisiae*

Glycolytic oscillation is characterized by autonomous oscillation of the metabolites of the glycolytic pathways. This oscillation is conserved in microorganism and human pancreatic β cell [40], and the period of oscillation is several minutes. Glycolytic oscillation is identified in intact yeast cells as well as in cell-free extract. It is commonly monitoring by NADH fluorescence and the key regulator was identified *PFK1* (phosphofructokinase) as oscillophore [13]. The consecutive feedback inhibition and precursor activation of phosphofructokinase by glycolytic metabolites, and AMP as the allosteric regulator of phosphofructokinase result in glycolytic oscillation [5, 36]. The glycolytic oscillation is occurred in continuous cell culture as well as single cell. In dense cell population, an active synchronization among the individual cells is necessary to sustained oscillation [15]. Through the intensive continuous culture and perturbation (desynchronization) experiments, acetaldehyde is identified as population synchronizer [13]. It was postulated that the autonomous glycolytic oscillation has advantages in efficiency and speed of metabolisms over steady-state glycolysis [36].

Autonomous cell cycle-dependent oscillation in *S. cerevisiae*

In a while, cell cycle-dependent oscillation was found in aerobic continuous culture. During the culture, robust oscillation of pH, dissolved oxygen (DO), glucose uptake was monitored with oscillatory budding index (G1 phase) [6, 7]. The oscillation was connected to the cellular stress, cellular trehalose concentration and *GTS1* [38, 46, 48]. The gene *GTS1* was originally isolated from a yeast cDNA library with oligonucleotides encoding three Gly-Thr repeats which had been found in the clock-related gene in mammalians [2]. The expression of *GTS1* was oscillated out of phase with DO and disruption mutant of *GTS1* did not show oscillation [21]. Furthermore, the *GTS1* gene product was identified to interact with glycerladehyde-3-phophate dehydrogenase [21]. As *TDH1* coding glycerladehyde-3phophate dehydrogenase was deleted, the oscillation was disappeared [21]. Although the details of cell cycle-dependent oscillation are still obscure, *GTS1* and *TDH1* may play important roles in *S. cerevisiae*.

Autonomous yeast colony oscillation in *S. cerevisiae*

In cell population, individual cells in liquid state and on solid substrate have to communicate each other in accordance with changes of environment and stimulus. In pioneer researches of Palkova et al., the colony oscillation, i.e,, yeast colonies in agar substrate (solid culture) exhibit a periodic behavior, was revealed [30-32]. This oscillation is characterized by periodic changes of pH of colony surroundings from acidic to alkali and vice versa [30], and the communicating signal between neighboring colonies was identified to ammonia [32]. The periodic production of ammonia was regulated by Ato1p, Ato2p, and Ato3p. This oscillation includes activation of amino acid catabolism, uptake of carboxylic acids into cytoplasm, uptake of oxalacetate into mitochondria, progressive repression of oxidative phosphorylation, peroxisomal fatty-acid β-oxidation leading to acetyl Co-A production, citrate and isocitrate synthesis in mitochondria and repression of other enzymes of the citrate cycle. The ammonia released from colonies act as a synchronizer and an alarm signal for limited nutrient [31].

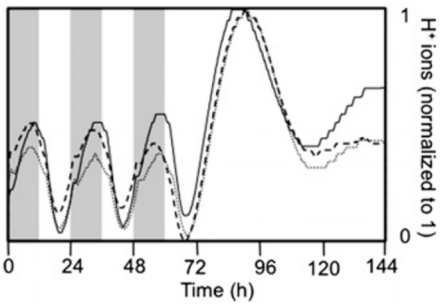

Fig. 3. Circadian oscillation of *Saccharomyces cerevisiae* in pH-uncontrolled, a rich medium continuous culture. Gray panels represent cool temperature (21℃), Open panels represent warm temperature (28℃). Consecutive oscillation of pH during temperature cycle (21~28℃) was damped by set to constant temperature (28℃). From [11].

Autonomous circadian oscillation in *S. cerevisiae*

Recently, the circadian oscillation was observed in pH-uncontrolled, a rich and complex nutrient continuous culture of *S. cerevisiae* [11]. When the cultures were subjected to temperature cycles with a period of 24 hr (11 hr at 21℃, 11 hr at 28℃ with 1 hr transitions between temperatures), DO and pH of the culture were oscillated with period of 24 hr. By changes of intensity or period of temperature cycles, the oscillation was entrained or damped Fig. 3), and the expression of MEP2 (ammonium permease) and GAP1 (amino acid permease) showed high intensity oscillations in phase of pH oscillation under constant condition. Recently, the alteration of metabolic oscillation in *S. cerevisiae* by visible light was reported [37], which may provide additional clue for circadian oscillation in yeast. These results suggested that unicellular yeast also has circadian clock, and the short period of rhythms could be used as building blocks for longer circadian rhythms [11, 29].

Ultradian metabolic oscillation in *S. cerevisiae*

Characteristics of ultradian metabolic oscillation

Ultradian metabolic oscillation in yeast was firstly reported in 1992 [39]. This oscillation is easily monitored by consecutive changes of DO and NADH fluorescence during continuous culture when glucose or ethanol was used as carbon source (Fig. 4). Also, the restricted ultradian metabolic oscillation was observed during batch cultures on trehalose [17]. During the oscillation, the cell numbers and budding index were constant [39], therefore it is discriminated to the cell cycle-dependent respiratory oscillation [36, 38]. The rhythmicity of this process appears to be independent of the glycolysis, environmental triggering or dark-light transitions, and appears to be dependent on nutrients, air flow rate, dilution rate, and pH levels [18, 27]. During the aerobic continuous culture, cyclic changes of various metabolites, e.g. concentration of ethanol [18], reduced form of glutathione (GSH) [26], cysteine [43], and cellular amino acids [41, 43] were observed. Therefore, this ultradian metabolic oscillation also provides an excellent system to investigate dynamic metabolic regulation.

Population synchronizer of ultradian metabolic oscillation

Ultradian metabolic oscillation arises from the metabolic sum of individual cells in the population [4]. When the individual cells oscillate with a slightly different frequency or different period, the population oscillation will be dis-

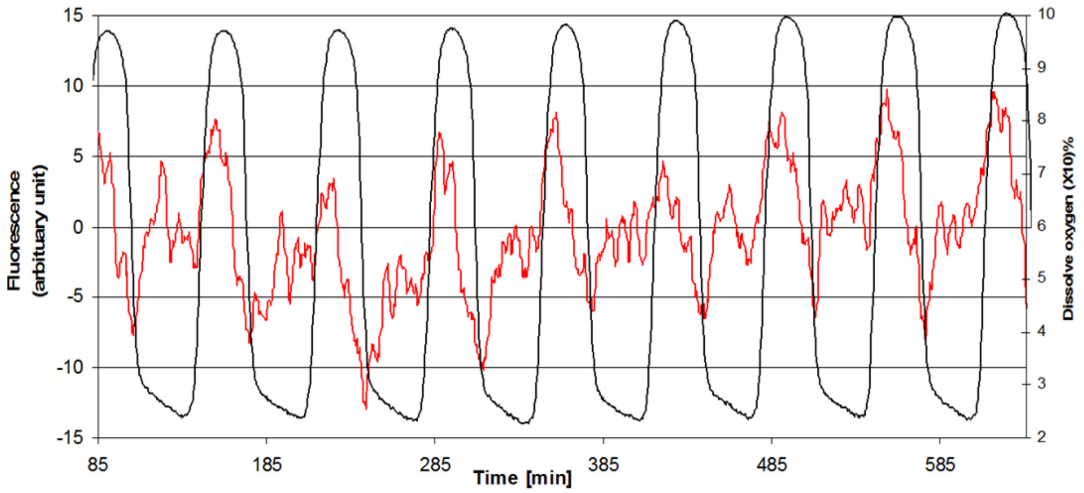

Fig. 4. Consecutive changes of dissolved oxygen and NADH fluorescence during continuous culture of *Saccharomyces cerevisiae*. High intensity and stable oscillation: dissolved oxygen, low intensity and intermediate oscillation: NADH fluorescence.

appeared [29, 36]. In population synchronization, H_2S and acetaldehyde was strongly suggested as synchronizer, which periodically emit from cell without any trigger. During the metabolic oscillation, the H_2S production was first detected at the onset of low respiration and reached a maximum (1.5 μM) prior to minimum respiratory activity [45]. Then H_2S concentration fell rapidly to below 0.2 μM before the onset of high respiration (Fig. 5). This cyclic production of H_2S resulted in ultradian metabolic oscillation *via* periodic inhibition of respiratory activity. Since H_2S is unstable and freely diffusible, it successfully acts in population as temporal, extracellular signal molecule. The consecutive cyclic production of H_2S was dependent on sulfite reductase in sulfate assimilation pathway. [42]. The concentrations of extracellular sulfate, intracellular glutathione and cysteine oscillated during metabolic oscillation but only the oscillation of sulfate concentration was out of phase with H_2S production [26, 42]. Disturbances in the sulfate assimilation and cysteine synthesis pathway perturbed the rhythm of H_2S production and metabolic oscillation [41, 42]. The disruption mutants of sulfate permease (*SUL1*), sulfite reductase (*MET10*), glutathione synthetase (*GSH1*) and glutathione reductase (*GLR1*) did not show consecutive H_2S production, and perturbed metabolic oscillation [44, unpublished data]. Above results was further confirmed by mathematical modeling based on end-products feedback inhibition on the sulfate assimilation pathway and periodic respiratory inhibition by H_2S (Fig. 6) [50]. Therefore, H_2S acts as a population synchronizer in ultradian metabolic oscillation.

Controller of synchronizer production

During the ultradian metabolic oscillation, the level of lipid peroxides oscillated out of phase with DO; its level was

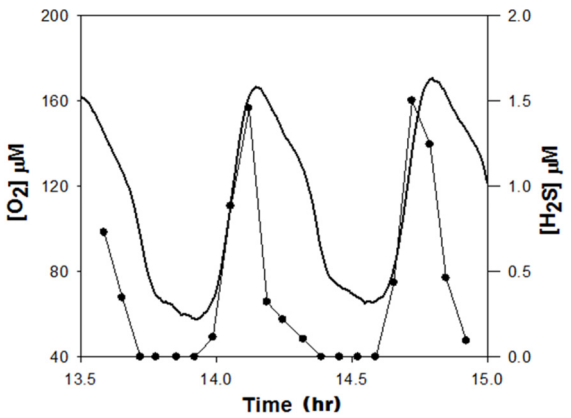

Fig. 5. Cyclic production of H_2S during ultradian metabolic oscillation of *S. cerevisiae.*

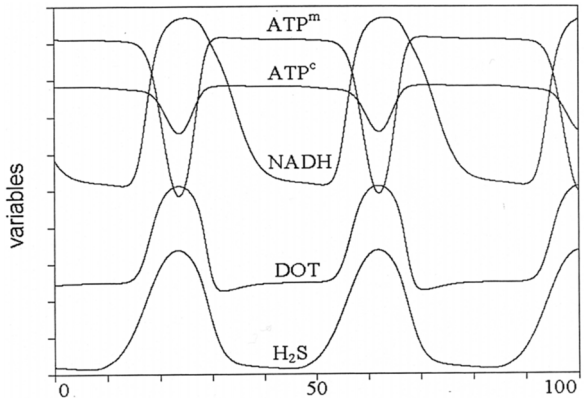

Fig. 6. Mathematical modeling of ultradian metabolic oscillation of *S. cerevisiae* based on end-product(s) feedback inhibition on the sulfate assimilation pathway and respiratory inhibition by H_2S.

minimal at near maximum DO, increased during respiration, and reached a maximal level toward the end of the maximum respiration phase [20]. Addition of antioxidant, such as *N*-acetylcysteine or ascorbic acid, decreased H_2S production in the subsequent cycles, activated respiration, and perturbed respiratory oscillation (Fig. 7). Increases of oxidative stress by pulse injection of inhibitors of catalase or superoxide dismutase, H_2S or superoxide all perturbed respiratory oscillation with increased H_2S production [20]. Therefore, it was suggested that oxidative stress results in periodic depletion of GSH and cysteine, which in turn causes stimulation of the sulfate assimilation pathway and H_2S production [20, 44]. These notions provide a new insight that H_2S acts as a detoxifier as well as a cellular redox controller

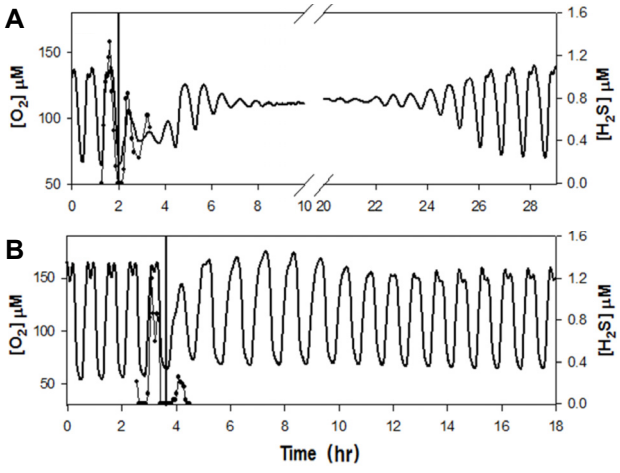

Fig. 7. Perturbation of dissolved O_2 oscillation and H_2S concentration by pulse injection of 100 μM of (A) *N*-acetylcysteine and (B) ascorbic acid. From [20].

and population synchronizer. Recently, the role of H_2S as a detoxifier was further identified in plant and mammals. Although H_2S is toxic to respiratory organisms by inhibition of cytochrome C oxidase [41], the production of H_2S in yeast, plant and animal was reported [1, 12, 16]. In cadmium-induced oxidative stress [8], O_2-induced lung injury [47], and drought-induced oxidative stress [51], H_2S showed successful protections of ROS related damages.

Dynamic oscillation of gene expressions

During the last decades, enormous progress in biological clock research has provided a new insight into the molecular architecture. Regulatory circuits involving feedback inhibition and stimulation of mRNA transcription and translation are thought to be critical for many autonomous biological rhythms and clock mechanism [25]. Genome-wide transcriptional monitoring using microarray analysis showed a dynamic nature of gene expression and periodic metabolic reprogramming [19, 35]. Cluster analysis of gene expressions revealed the majority of oscillating transcripts could be classified into three superclusters. In respiratory phase (oxidative phase), the transcription of the genes related to sulfur uptake and sulfate assimilation pathways, amino acid biosynthesis, synthesis of ribosomal proteins and translation-initiation factors is highly increased. When the DO level of culture reached an end of minimal, the reductive phase is started. In this early respiratory inhibition phase (early reductive phase), transcription of the majority of nuclear-encoded genes for mitochondrial proteins is increased, i.e., transient short period is for mitochondria rebuilding before late respiratory inhibition phase. In late reductive phase

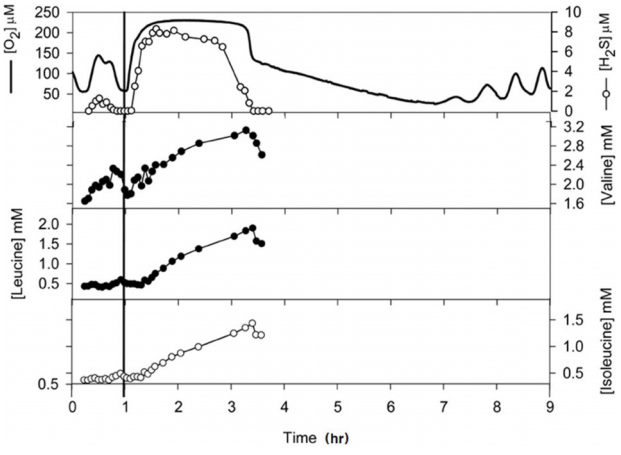

Fig. 8. Perturbation of ultradian metabolic oscillation by pulse injection of glutathione (100 μM) and dramatic increases of cellular content of branched amino acids.

when the DO level of culture reached a maximal, the transcription of the genes that are involved in non-respiratory modes of energy generation, such as glycolysis, acetyl Co A production and fatty-acid oxidation, are highly expressed. Therefore, cellular metabolism, cell division, and organelle synthesis are temporally oscillated.

Metabolic engineering for essential amino acid production by perturbation

During the continuous culture of yeast, oscillations of cellular amino acid pools, including cysteine and other essential amino acids, were reported [14, 43]. As the oscillations of cellular aspartate, phenylalanine, lysine, leucine, isoleucine, and valine showed in phase with DO oscillation, those amino acids were considered to be synthesized and stored during the reductive phase. Perturbation of the oscillation by injection of glutathione resulted burst H_2S production and extended reductive phase for 2~3 hr [26, 43]. As extension of reductive phase during perturbation, the content of branched-chain amino acids were increased to 2~4 folds [43](Fig. 8). Although commercial application of metabolic oscillation and its perturbation is limited, these results suggest a possibility of metabolic engineering by control of biological clock, for example, a production of valuable metabolites.

As described in this review, continuous or batch culture of *S. cerevisiae* provides a powerful and efficient model system for autonomous oscillation and biological clock. Further studies on the identification of oscillophore, synchronizer, and pacemaker for the respective oscillation are necessary. The expanded knowledge in oscillatory biological clock of yeast will provide clues for different clock-related diseases.

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초록 : *Saccharomyces cerevisiae*의 생물시계와 초단기 대사진동

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생물시계(Biological clock)는 생명체에서 나타나는 반복되는 자율적인 리듬을 말하며, 단일세포는 물론 다세포 생명체의 기본적인 대사와 이에 따른 표현형과 행동을 직접적으로 조절하고 있다. 이러한 생물시계는 동면 리듬, 수면 리듬, 심장박동 리듬 및 짝짓기 노래 리듬 등 매우 다양하며, 24시간 이상의 주기를 infradian rhythm, 24시간 주기를 circadian rhythm, 24시간 이내의 짧은 주기를 ultradian rhythm으로 구분한다. 효모 *Saccharomyces cerevisiae*는 최소 5종 이상의 반복되는 자율적인 리듬이 알려져 있으며, 이중 일부는 생체시계로 인식되고 있다. 본 리뷰에서는 *Saccharomyces cerevisiae*의 glycolytic oscillation (*T*= 1~30분), cell cycle-dependent oscillation (*T*= 2~16시간), ultradian metabolic oscillation (*T*= 15~50분), yeast colony oscillation (*T*= 수 시간) 및 circadian oscillation (*T*= 24시간)에 대한 연구 결과를 제시하고, 특히 ultradian metabolic oscillation의 특징, 집단 동조인자(population synchronizer), 동조인자의 조절 기작 및 효모 생물시계의 대사공학 분야의 이용성을 제시하여 효모를 이용한 동적 대사조절 및 생물시계 연구가 가능함을 제시하였다.