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Hypothesis Article

Interaction of iron ions with oxygen or nitrogen monoxide in chromosomes triggers synchronous expression/suppression oscillations of compact gene groups (“genomewide oscillation”): Hypothesis

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Abstract

It has been proposed that the “oxygen-endogenous reductants” system responsible for oscillatory changes in the redox potential of the cell fulfills the function of a “central oscillator” by inducing synchronous oscillations of an immense array of genes in the cell genome (so-called “genomewide oscillation”). The effect of the redox potential on the genome can be mediated by copper or iron ions. Copper ions can induce oscillating change of the DNA double helix stability through the change of guanine–cytosine pair stability depending from valence state of copper ions. Iron ions can have a redox potential effect on the genome mediated by iron + thiol groups localized in chromosomes. Cyclic changes in the thiol content concomitant with oxidation of thiols to disulfides trigger oscillatory changes in the activity of multiple redox-sensitive transcription factors eventually resulting in genomewide oscillation. In the presence of nitric oxide, oscillatory changes in thiol levels in chromosomes can be induced by *S*-nitrosylation of thiols. The latter is catalyzed by iron ions and results in incorporation of nitric oxide into dinitrosyl complexes with thiol-containing ligands. It is not excluded that by virtue of their ability to react with *S*-nitrosothiols, thiols and nitric oxide, these complexes contribute to the formation of a steady-state self-regulating oscillating chemical system and thus fulfill the function of “central regulators” of genomewide oscillation.

Keywords: Genomewide oscillations; Oxygen; Nitric oxide; Iron; Copper; Thiol compounds; Dinitrosyl iron complex; *S*-Nitrosylation

Recent studies with synchronous cultures of eukaryotic microorganisms, such as yeasts (*Saccharomyces cerevisiae* and *Schizosaccharomyces pombe*), established synchronous oscillatory activity (expression/suppression) of several hundreds of genes. This phenomenon was described as a “genomewide oscillation” [1–8]. It could be proposed that the regulation of genomewide oscillation “is not a result of a central oscillator, but, rather, it emerges from numerous subgraphs with the potential to oscillate” [8]. However, the existence of a close correlation between the main oscillatory characteristics of genome expression in yeast cells and oxygen-dependent oscillatory changes in the intracellular redox potential is accepted by many authors [1–7]. This correlation is manifested, in particular, in virtually complete coincidence of respiratory and genome activity of oscillation periods of *S. cerevisia*e and *S. pombe* cells (40 min and 5 h, respectively). It may thus be inferred that it is the intracellular redox potential that plays the role of a “central oscillator” triggering the genome function in the oscillatory regime and is responsible for the oscillatory dynamics of other intracellular systems.

There is every ground to believe that redox changes triggering intracellular genomewide oscillations are mediated

Abbreviations: DNIC, dinitrosyl iron complex; NO, nitric oxide; NOS, NO synthase; RS–NO, S-nitrosothiol

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by transition metals, e.g., copper and iron. Studies carried out in the 1960s established that copper ions strongly influence DNA stability [9,10]. Binding of monovalent copper ions to the N_7 atom in the guanine base of DNA is accompanied by a transfer of protons to the complementary cytosine base (Fig. 1). As a result, guanine and cytosine acquire different charges (− and +, respectively) concomitantly with a sharp increase of the binding energy of the G–C pair and stabilization of DNA. In the latter case, the stabilizing effect is manifested in a pronounced (by about 20 °C) shift of the melting curve of DNA towards higher temperatures (Fig. 1) [10]. In contrast, bivalent copper ions destabilize DNA (Fig. 1) [10] indicating that oscillatory changes in the redox potential in the DNA environment initiate copper-mediated periodic changes in DNA, in promoter DNA, and thus contribute to synchronous oscillatory expression/suppression of definite groups of genes. The role of redox agents initiating reversible changes in the electric charge of copper ions upon their binding to the G–C pair can be ascribed to, e.g., ascorbic acid, under the stipulation that its structure is sterically fully appropriate to the structure of the five-membered ring of guanine. The proton-donor center of ascorbate is localized just above the copper ion bound to the N_7 nitrogen atom in guanine [10].

The question on the role of copper ions as mediators of genomewide oscillations still remains open because of the lack of explicit and reliable information about their content in chromosomes. From this standpoint, possible involvement of iron ions in this process is much more probable. Evidence for Fe^{3+} accumulation in chromosomes can be derived from fast incorporation of the radioactive label (^{55}Fe) into HeLa chromosomes [11] and virtually complete coincidence of ^{55}Fe uptake autoradiograms and distribution patterns of chromosomes in the mitotic phase of the cell cycle [11]. The hypothetical role of direct targets for redox activity of iron ions in chromosomes is ascribed to thiol groups; their redox state can determine the activity of transcription factors in a large group of genes. Correspondingly, any change in the thiol:disulfide ratio stimulates the functioning of this group of genes in the oscillatory regime.

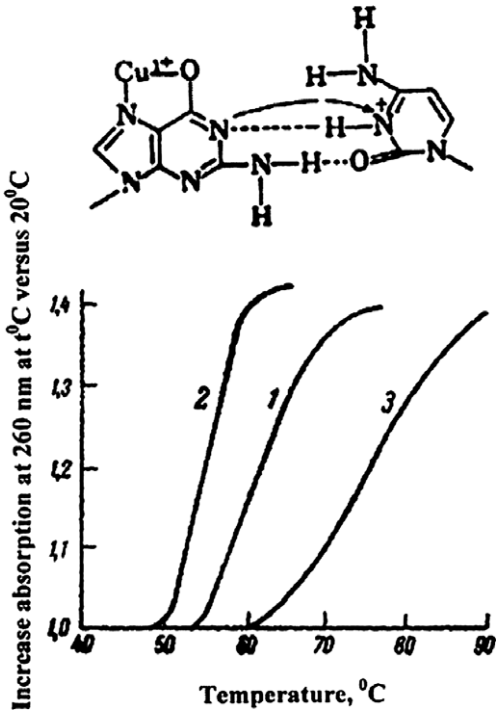

Fig. 1. Influence of copper ions on DNA molecules. (Top) Proton transfer from a guanine N_1 atom to a cytosine base induced by Cu^+ ion; (Bottom) Influence of Cu^{2+} or Cu^+ ions (6×10^{-5} M) on melting curves of DNA from calf thymus (8.3×10^{-5} M) (curves 2 and 3, respectively). (Curve 1) Control preparation of DNA (without addition of copper) [5,6]. Reduction of Cu^{2+} to Cu^+ ions was made by ascorbate addition.

Evidence for the crucial role of thiols in this mechanism can be derived from cyclic changes in thiol titers in the course of mitosis (so-called Rapkine cycle) [12]. It is not excluded that changes in the thiol–disulfides ratio modulate the activity of redox-sensitive chromosomal transcription factors. In this paradigm, the mechanism of genomewide oscillation can be presented as follows. Any increase in intracellular oxygen content is accompanied by oxidation of iron ions in chromosomes followed by oxidation of thiol groups by Fe^{3+} and reduction of Fe^{3+} as a result of which the thiol–disulfide ratio is shifted towards disulfides. Enhanced production of disulfides stimulates activation/deactivation of transcription factors and a resulting synchronous expression/suppression of a large group of genes controlled by redox-active transcription factors. Further decline of intracellular O_2 content and a concomitant increase in the concentrations of reducing agents reverse the process by shifting the thiol–disulfide equilibrium/ratio in chromosomes towards thiols and channeling the activity of the corresponding genes in the opposite direction. The oscillatory dynamics of the cyclic mechanism of gene function/expression resembles oscillatory changes in intracellular O_2 content (oscillatory changes in the redox potential of the cell). Besides, one should not rule out the possibility that the activity of genes triggering the synthesis of antioxidant enzymes and reducing agents is induced by changes in gene activity at peak concentrations of O_2 inside the cell. Under these conditions, enhanced production of antioxidants and endogenous reductants might be the reason for the depletion and cyclic changes in O_2 content in the cells.

Lloyd and coworkers reported on oscillatory dynamics of the redox potential induced by addition of nitrosonium ions (NO^+) [13]. In the authors' opinion, the change of the redox potential can be due to interaction of NO^+ ions with thiols or metal ions. Although the mechanism of this phenomenon is still poorly understood, it is not excluded that nitrogen monoxide (NO) being the main source of NO^+ ions influences genomewide oscillation directly; the role of a mediator is played by iron ions. As a matter of fact, in the presence of thiols the reaction of bivalent iron with neutral NO molecules yields dinitrosyl iron complexes (DNIC) with thiol-containing ligands, viz.,