Role for *Clockwork Orange* Gene in Drosophila Circadian Clock

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Previous study has suggested a two-loop model for the Drosophila circadian clock gene network which contains a negative feedback loop consists of PER-TIM dimer and CLK-CYC dimer and a regulation loop consists of VRI, PDP1 and CLK-CYC dimer. CLK-CYC dimer which contains a DNA-binding domain can recognize the E-box within the promoter region of *per, tim, vri* and *pdp1* gene. Once binding to the E-box, CLK-CYC will activate transcription of the genes. However, a novel core clock gene – *Clockwork Orange* (*CWO*) was identified in 2007 whose detailed function has not been clearly investigated. Here, I studied the *CWO* function using a mathematical model.

***Keywords* — Circadian clock, Drosophila, Clockwork Orange**

I. INTRODUCTION

CIRCADIAN clock is an internal oscillatory mechanism whose period is around 24 hours and can be regulated by zeitgeber. Circadian clock is widely conserved in fungi, plants and animals and is helpful for organism to sense and adapt the rhythm signal like light and temperature surrounded. Drosophila melanogaster is an ideal model organism to study circadian clock. Previous study has suggested a two-loop model for the Drosophila circadian clock gene network which contains a negative feedback loop consists of PER-TIM dimer and CLK-CYC dimer and a regulation loop consists of VRI, PDP1 and CLK-CYC dimer. Particularly, VRI repress the transcription of *clk* while PDP1 promote the expression of *clk* [1].CLK-CYC dimer which contains a DNA-binding domain can recognize the E-box within the promoter region of *per, tim, vri* and *pdp1* gene. Once binding to the E-box, CLK-CYC will activate transcription of the genes. PER and TIM will be phosphorylated by kinase DBT, CK2 and SGG in cytoplasm. Only by forming a dimer, can PER and TIM be stable or they will be degraded by further phosphorylation. When PER-TIM dimer accumulated to a degree in cytoplasm, they will translocate into nucleus and interact with CLK-CYC dimer to form a tetramer so that CLK-CYC dissociate with the E-box and repress transcription [2].

There were three labs that identified a novel core clock gene – *Clockwork Orange* (*CWO*) nearly in the same time in 2007 [3-5]. Applying microarray and Chip-Seq, they found that CWO will bind to the E-box competing with CLK-CYC dimer so that repress transcription. However, the mRNA level of *per*, *tim* and *vri* is lower in CWO deficient mutant than in wild type which seems inconsistent to common sense. It may be caused by the system effect. Here, I studied the *CWO* function using a mathematical model.

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II. RESULTS

The mathematical model consisted of 14 ordinary differential equations and was mainly based on assumptions listed below:

i. All biochemical reactions take place in the whole cellular environment so that the translocation time of protein and nucleic acid can be ignored.

ii. CLK-CYC binding to E-box activate transcription while CWO repress it.

iii. The concentration of CYC is high enough to form dimer with CLK for it is constituted expression in cells. So CLK-CYC is regarded as unity in this model whose concentration is represented by CLK.

iv. As there are kinases catalyzed the degradation of PER and TIM, the model ignored their spontaneous degradation.

Compared with experimental data before, the model can finely simulate the fluctuation of per, tim, clk mRNA level under light/dark condition [6].

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