Detecting Rhythmic Components transcript and the effect of 2,3,7,8-Tetrachlorodibenzo-ρ-dioxin in hepatic metabolic activity in mice

{ Daniel Kwabena Marri } Michigan State University

Introduction

- Circadian rhythyms are sustained oscillations which occur spontaneously with a period close to 24h in most living organisms. These rhythms are produced by a group of genes named as the clock genes.
- The core circadian clock gene network consist of the core clock activators,clock repressors and clock nuclear receptors.
- The cellular regulatory network of circadian clocks involves several genes and proteins, and relies on multiple interactions, transcriptional as well as post-translational.

Problem Statement

- Identification of rhythmic gene expression is crucial for understanding the gene regulatory networks and functions of these biological process for:
- Theoritical modeling and effect of its sensitivity analysis.
- The idea of this study is to evaluate an existing method on a published dataset using different normalization approach and compare the results to the published result.

Materials & Methods

JTK-CYCLE is used to efficiently identify and characterize cycling variables in large dataset. The algorithm is also used to distinguished between rhythmic and non-rhythmic transcript more reliable and efficiently.

The JTK-CYCLE algorithm is a combination of two statistical methods:

- The Jonckheere-Terpstra (JT) test in a non-parametric test that is most powerful for detecting monotonic orderings of data across ordered independent groups.
- Kendall's tau is a measure of rank correlation that is used to measure the association between two measured quantities.

This algorithm estimates the amplitude, lag, period, p-values and BH.q-values to signify rhythmicity and non rhythmicity.

Results 1

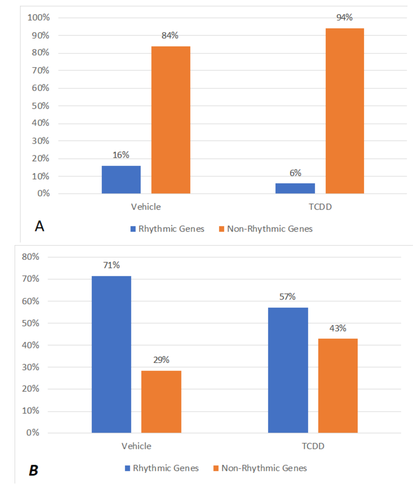

Figure 3: The effect of TCDD on the diurnal rhythmicity of hepatic gene expression in male C57BL/6 mice orally gavaged with sesame oil vehicle or 30 μg/kg TCDD every 4 days for 28 days.

Results 2

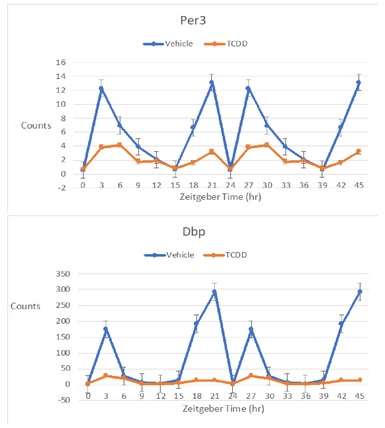

Figure 1: The effect of TCDD on core hepatic clock regulators in male C57BL/6 mice orally gavaged with sesame oil vehicle or 30 μg/kg TCDD every 4 days for 28 days.

Even though most clock related genes retained their rhythmicity following treatment, TCDD had an effect on these genes by dampening their rhytmicity. TCDD caused a reduction in amplitude in most of the clock gene. One of the clock activator genes Clock had an increase in its amplitude after treatment.

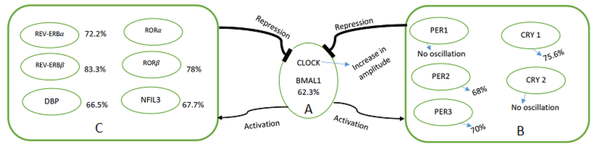

Figure 2: The percentage of amplitude reduction confirmed by JTK-CYCLE in the clock regulated genes. This figure also shows the positive and negative feedback loop involved in the clock mechanism

Conclusion

The current research explored the impact of TCDD on the rhythmicity of the hepatic transcriptome and metabolome in mice specifically clock regulated genes

- TCDD activation of AhR dampened the rhythmic expression of 12 hepatic core clock genes, causing either a reduction in amplitude or total oscillation loss.
- TCDD cause changes in the amplitude, phase and period of the hepatic transcriptome and metabolome in mice.
- TCDD also increased the number of hepatic gene expression.

References

[1] Fader. A. Kelly and Nault. Rance... *2, 3, 7, 8-Tetrachlorodibenzo-p-dioxin abolishes circadian regulation of hepatic metabolic activity in mice* , 2019.

[2] Hughes, Michael, ... JTK_CYCLE: an efficient nonparametric algorithm for detecting rhythmic components in genome-scale data sets, 2010.

Future Research

To check for DRE-AHR-peaks and AHR binding sites within the promoter region of the clock related genes. This will help investigate the question of whether TCDD prevents Bmal1 to bind to the promoter regions of the clock genes that decreased in amplitude by sitting on the AHR binding sites in the promoter region of these genes or there are other factors involved.

Contact Information

lab Bhattacharya Lab MSU IQ
Email marridan@msu.edu