

Effects of DNA damage on the cell cycle through the circadian clock

Zsófia Bujtár^{1*}, Judit Zámboreszky², Toru Matsu-ura², Christian I. Hong², Attila Csikász-Nagy^{1,3}

¹Pázmány Péter Catholic University, Budapest, 1083, Hungary

²University of Cincinnati, Cincinnati, OH 45267, United States

³King's College London, London, SE1 1UL, United Kingdom

*E-mail: bujtar.zsofia@hallgato.ppke.hu

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Most cancer treatment induces DNA damage to eliminate highly proliferative cells. This process, however, also affects healthy cells creating numerous side effects ranging from infertility to heart problems. Cells respond differently to DNA damage depending on where they are in their cell cycle at the time of the treatment. Intriguingly, circadian rhythms provide temporal information to the cell cycle machinery to control the timing of cell divisions. Personalized chronotherapy based on this: the time of the treatment based on the patient's natural daily rhythm.

To understand the impact of DNA damage in altering the timing of cell divisions via circadian rhythms, we built a mathematical model and performed in-silico experiments for the proposed system that integrates circadian rhythms, cell cycle, and DNA damage response in *Neurospora crassa*.

One part of the model is the main mechanism of the circadian rhythm in *Neurospora*, which is a negative regulatory feedback loop, because FRQ protein inhibits its own transcription factor, White Collar Complex. The other part of the model based on the interactions of CLB1 (CycLinB), because it takes the main role in the coupling between the 2 cycles. STK-29 (homologue of mammalian Wee1) inhibits CLB1 in the cell cycle before mitosis and its concentration is influenced by White Collar Complex, the core molecular clockwork. When we do not introduce any coupling between the cell cycle and circadian rhythm, the duration of a single cell cycle is about 3 hours. But when the circadian rhythm influences the cell cycle, the duration of each cell cycle is different: their length depends on the circadian time. The reason is that WCC stops the cell cycle through STK-29, right before mitosis. Meaning that if the concentration of WCC is higher, the duration of the cell cycle is longer. This happens in the middle of the subjective days of our simulations.

We composed a unified code for the analysis in the Matlab programming language to simplify examinations. We simulated the perturbation of the circadian clock and the cell cycle upon DNA damage and analysed the consequences of this perturbation on the following cycles using phase-response curves. We can observe that in the subjective day the phase shift is near to 0, but in the subjective night, high phase advance appears.

We analysed the behaviour of the cell cycle, where the strength of connection between the cell cycle and circadian rhythm was noisy. We wanted to examine the number of nuclei in mitosis after perturbation in the subjective day and night. According to the results, perturbation upon DNA-damage in the subjective day did not lead to relevant changes in the cell cycle. But, when the effect of the perturbation upon DNA-damage was in the subjective night we got other conclusions. Immediately after the disturbance we observed a perturbed system when cell cycles are not synchronised. After some days, the amplitude of the oscillations resets, but a high phase-advance appears.

In summary we can see, that it matters, when perturbation upon DNA-damage occurs: it can result in high shifts in the timing of the cell cycle or have almost no effect. This consequence may have relevance to cancer treatment as well. Depending on the timing of the induction of DNA-damage, the healthy cells reacts differently: they can continue their normal division or they can be perturbed as the side-effect of the treatment.

In the future, we would like to add to the model the direct effect of the DNA-damage on the cell cycle as well, to be able to analyse the general effect of the DNA-damage on the cell cycle.

References

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