Mutual coupling between circadian clock and cell cycle in single mammalian cells

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***Short Abstract* — Previous work in mammalian fibroblast cells suggested that the circadian clock can gate cell division, and some proteins mediating this interaction have been proposed. Here, we further quantify the mutual interactions between the two oscillators by time-lapse imaging single mammalian cells during several days. We combine automatic segmentation and tracking of single cells with minimal mathematical model to provide new quantitative insight into the interplay between the two cycles.**

***Keywords* — Circadian clock, cell cycle, oscillator synchronization, single cell imaging**

The circadian clock and the cell cycle are two fundamental biological processes. The circadian clock is a self-sustain oscillator with a 24h hour period that regulate many cellular processes. In growing conditions the successive divisions and progression through the cell cycle can also be thought as a periodic process. Strong evidence for cell cycle and circadian clock interaction has been found in cyanobacteria (1), zebrafish (2) or mammalian cells (3,7). The influence of the circadian clock on the cell cycle has been proposed to occur both at the G1/S and G2/M transitions (7). Another study reported no strong coupling (phase locking) between the two cycles in rat fibroblast (4). Disruption of the circadian clock has also been linked to cancer (6).

Even though many molecular interactions between cell cycle and circadian clocks have been reported (5), it is not clear under which conditions these molecular interactions lead to entrainment of one cycle by the other, or possibly synchronization between the two cycles in mammalian cells. Moreover, a more precise characterization of the temporal relationships between circadian and cell cycle phases is lacking.

Here we study the coupling between cell cycle and circadian clock by imaging mouse fibroblasts containing a fluorescent reporter under the control of the circadian clock during three days. Semi-automatic segmentation and tracking of circadian rhythms in single cells, and estimation of the timing of divisions in different growth conditions allows us to gather large amounts of data to quantitatively study the coupling between the two processes under a wide set of conditions.

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We then model those data using stochastic phase models for the two oscillators. These models contain a minimal number of parameters, including the mean periods and fluctuations, and functions that embody the mutual couplings between the cycles. Our observed phase responses indicate that then coupling between the two cycles is indeed bi-directional, leading to a tendency for division times to occur at specific circadian phases.

Together, our single cell analysis allows us to shed light on the respective contributions of noise and coupling in controlling the relationships between circadian and cell cycle phases in mammalian cells.

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