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DYSREGULATION OF THE CIRCADIAN CLOCK BY EXTERNAL FACTORS DISRUPTS CELLULAR PROCESSES AND IMPACTS IN PHYSIOLOGY AND HUMAN HEALTH

Abstract

Circadian rhythms are essential to the temporal regulation of molecular processes in living systems and as such to life itself. These endogenous rhythms are generated by the circadian clock, which allows organisms to synchronize to the geophysical time, and are accountable for 24 hours oscillation in the expression of about 40% of all genes. In mammals, disruption of oscillations leads to failures in biological processes and eventually to pathological phenotypes including cancer. From the analysis of several cancer cell lines we observed weak and strong oscillator-phenotypes. In an attempt to unravel the elicitors of such disrupted clocks, we applied a systems biology approach to correlate experimental, bioinformatics and modelling data. We identified key genes which discriminate different oscillator strengths within the same type of cancer. Most of the discriminative genes play important roles in cell cycle regulation, DNA repair, immune system and metabolism. To further investigate the potential impact of circadian disruption on biological processes we use cellular models together with computational mathematical modelling to simulate in vitro and in silico diverse cellular scenarios. Our systems approach allowed us to bridge the gap between the circadian clock the cell division cycle and metabolic rewiring, and to analyse the effects of several perturbations on the circadian system. Our data demonstrate that perturbations induced by a single oncogene, and/or by external desynchronization factors, are sufficient to deregulate the mammalian circadian clock, that such clock-induced alterations result in malignant proliferation and metabolic variations, and pave new ways in which the circadian clock can influence disease. Our work highlights the role of our biological clock as a guardian of a healthy physiology, and forewarns to the potential dangers of its dysregulation.