Circadian clock induction or disruption in cancer therapy

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Background Cellular metabolism and proliferation are rhythmically controlled by the Circadian Timing System (CTS). The CTS is constituted with molecular clocks in each cell, which are reset and coordinated by the supra-chiasmatic nuclei, a central hypothalamic pacemaker through the generation of circadian physiology. These molecular clocks give time to the cells through interwoven translation/transcription feedbacks loops involving a dozen of specific genes, among which *Rev-erbα, Per2* and *Bmal1* play an essential role. As a result, circadian changes characterize both tolerability and efficacy of more than 40 anticancer agents in experimental models.

Methods and results Using rest-activity and body temperature rhythms as non invasive biomarkers of the CTS in mice, anticancer drugs disrupted the Circadian Timing System (CTS), as a function of dose and circadian time of administration. The extent of drug-induced circadian disruption was associated with that of known drug-related toxicities for vinorelbine (a mitotic inhibitor), gemcitabine (an antimetabolite), irinotecan (a TOP1 inhibitor) or seliciclib (a CDK inhibitor), as well as with chemical carcinogen exposure (diethylnitrosamine). Furthermore, anticancer agents, including interferons, γ-radiations, or seliciclib could disrupt the rhythmic patterns in clock gene transcription in SCN and/or peripheral organs, including liver, thus contribute to circadian disruption. On the contrary, the circadian clocks of malignant tumors such as mouse Glasgow osteosarcoma, are usually disrupted. In this experimental model, seliciclib restored near normal circadian rhythms in core clock genes mRNA expression or had no effect on the clock, pending upon dosing time. The induction of the molecular clock was associated with a near doubling of antitumor efficacy of seliciclib. The clinical relevance is illustrated with the disruption or amplification of the rest-activity circadian rhythm in cancer patients on chemotherapy or gefitinib(an EGFR inhibitor) respectively.

Conclusions and perspectives The outcome of patients on chemotherapy can be influenced by disruption or induction of circadian clocks in host or tumor cells. Such novel effects of anticancer agents could play an important role in the optimal scheduling of chronotherapeutic delivery. Mapping the mechanistic relations between circadian clocks, cell cycle and pharmacologic pathways should enable the modelisation of optimal chronotherapeutic delivery schedules and their personalization.

References

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