Circadian clock characteristics are altered in human thyroid malignant nodules

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Due to emerging evidence on the connection between circadian oscillator, cell cycle and cellular oncogenic transformation state, we aimed to characterize the circadian clockwork in human benign and malignant thyroid nodules. The expression levels of Bmal1 were strongly up-regulated in tissue samples of Papillary Thyroid Carcinoma (PTC) nodules as compared to benign nodular counterparts, while the expression level of Cry2 was significantly down-regulated in the same PTCs. To further examine the circadian clockwork, primary thyrocytes were established from healthy thyroid tissue biopsies exhibited high-amplitude sustained circadian oscillations of Bmal1-luciferase lentiviral reporter expression, with the oscillation period length of 27.5 hours. Consistently with these results, endogenous core clock transcripts oscillated with the period length of 27.7 hours in primary thyrocytes. Circadian oscillation patterns for all the core-clock transcripts were highly reproducible among different subjects, and indistinguishable in the thyrocytes established from healthy thyroid tissue biopsy, and from benign thyroid nodules. Primary thyrocytes established from malignant nodules diagnosed as PTC, exhibited altered oscillations of Per2 transcript, in comparison to benign counterparts. Moreover, thyrocytes established from the rare type of Poorly Differentiated Thyroid Carcinoma nodule (PDTC, two cases studied), exhibited strongly ablated circadian amplitude or phase-shifts for most of the core-clock transcripts. Characterization of the thyroid clock machinery alterations upon thyroid nodule malignant transformation contributes to understanding the connection between circadian clocks and cell oncogenic transformation state, and to so far unresolved issue of the malignant thyroid nodule pre-operative diagnostics.

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