CANCER

Thyroid circadian clock—altered in cancer?

Changes in the human thyroid circadian clock upon malignant transformation have been characterized in a study by Swiss researchers.

The search continues for markers of thyroid malignancy that can improve thyroid nodule preoperative diagnostics. A new study has examined circadian clock function in normal and malignant human thyroid tissue.

“An increasing body of evidence suggests a strong link between cellular circadian cycle, DNA damage, apoptosis control and carcinogenesis,” explains senior researcher Charna Dibner of the University of Geneva. “Thus, the essential question we addressed in our study was whether circadian clockwork is altered upon thyroid malignancies.”

The researchers studied the expression of circadian clock genes in thyroid biopsy samples from normal or nodular (benign or malignant) thyroid tissue. In human primary thyrocytes established from these tissues *in vitro*, circadian oscillations of the expression of clock genes over time was assessed. The circadian rhythms of the cells were synchronized by a pulse of dexamethasone.

In tissue samples from follicular and papillary thyroid cancers, expression levels of the circadian clock gene *ARNTL* (also called *BMAL1*) were upregulated and those of *CRY2* were downregulated, compared with the expression levels in normal thyroid tissue and benign thyroid nodules.

Around-the-clock analysis of endogenous transcript levels of various clock genes in synchronized human primary thyrocytes from normal thyroid tissue revealed circadian oscillations of *ARNTL*, *PER1–3* and *NR1D1*. In addition, high-amplitude circadian oscillations in the expression of a *ARNTL*-luciferase reporter gene were observed with a period length of ~27 h in synchronized thyrocytes from normal thyroid tissue.

In both bioluminescence and endogenous transcript analyses, similar circadian oscillator function was reported for thyrocytes established from benign thyroid nodule samples or follicular thyroid samples as for normal thyroid tissue. Thyrocytes established from papillary thyroid cancer tissue also had similar circadian oscillator function in endogenous transcript analysis, although expression of *PER2* was altered. By contrast, thyrocytes

established from a single case of poorly differentiated thyroid cancer displayed altered circadian oscillations.

“From the clinical perspective, the finding of alterations in the expression levels of core clock genes in thyroid malignancies might help improve thyroid nodule preoperative diagnostics,” concludes Dibner.

Carol Wilson

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