

Circadian Endocrinology Group

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Research focus

Circadian control of physiology and behavior is driven by a master pacemaker located in the suprachiasmatic nucleus (SCN) of the hypothalamus, orchestrating subsidiary slave oscillators in peripheral organs. Rhythmicity in the SCN is entrained by external *Zeitgeber* cues, such as daily changes in light intensity. Remarkably, obesity and high-fat feeding reciprocally affect the circadian system in rodents, indicating that metabolism and circadian rhythms are interconnected through complex behavioural and molecular pathways. Despite the obvious difficulty of human studies, it is well established that insulin is released from pancreatic islets in a strongly circadian manner, and thus glucose homeostasis and insulin secretion are tightly controlled by the circadian system. An outstanding goal is therefore to provide further insights into the emerging roles of circadian genes in the regulation of body metabolism and in etiology of obesity and T2D in human beings, and to translate this knowledge to clinic (projects 2,3).

A number of studies in cultured fibroblasts by us and others suggested that these cellular clocks represent an excellent experimental system to analyze mammalian circadian oscillator functions. Bioluminescence profiles from primary or immortalized cell lines expressing luciferase driven from different circadian regulatory sequences can be continuously recorded at the population level using photomultiplier tubes, or at the single cell level using highly sensitive photon-counting microscopy (see the illustration below). Recent studies (S. Brown and colleagues) have demonstrated that cultured primary human skin fibroblasts represent an excellent experimental system allowing to assess circadian clock function in human. One important implication of this rather unique and innovative approach could be getting the significant insights into human circadian rhythms upon different health conditions (project 3).

In addition to intrinsic circadian oscillator, another fundamental attribute of a cell is its ability to divide and multiply. While the circadian clock is the body's molecular time-keeping system, the cell division clock executes a precise temporal control mechanism with multiple checkpoints for proper cell division. Studies aimed to unravel the molecular mechanisms of the circadian clocks gave rise to a hypothesis that cell circadian oscillation profile might change as the cell overcome oncogenic transformation changes. An important challenge will be to explore the emerging roles of circadian genes in the regulation of cellular transformation, to characterize the cell oscillation profile upon the malignant transformation, and to apply these profile characteristics for the diagnostics purposes (project 1).

Research Projects

1. A new approach to predict malignancy in suspicious thyroid nodules

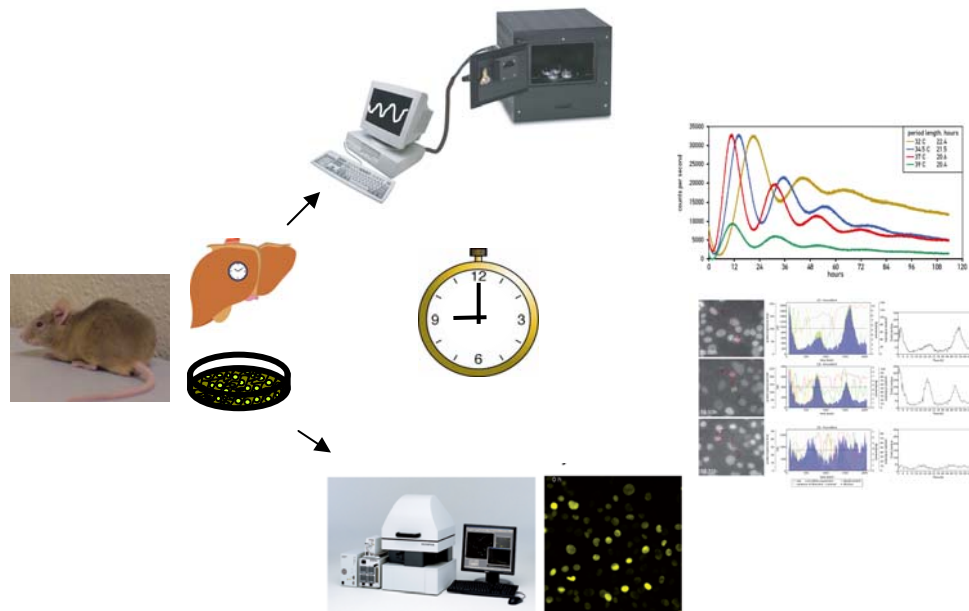
In this study we aim to develop a new method for clear differentiation between benign thyroid nodule lesions and malignant nodules before undergoing surgery. Circadian pattern change of the thyroid cells upon transformation will be analyzed.

2. Pancreas clock input on insulin secretion and glucose homeostasis regulation in human and rodent models

We have developed the real-time bioluminescence recording system for long term circadian rhythm studies in living human and mouse islet explants. We apply this approach to study the islet circadian oscillator and its impact on endocrine pancreas gene expression and function in rodents and in human.

3. Studies of human circadian clocks in normal conditions, high-fat diet, and type 2 diabetes

This study is aimed to characterize human circadian clockwork in healthy individuals in comparison to obese and type 2 diabetic subjects. Human circadian oscillator function has been addressed by unique non-invasive approach allowing to establish primary fibroblast culture from tiny skin biopsy, and to obtain the oscillation profile employing circadian bioluminescent reporter. The outcome of this analysis will contribute to the understanding of circadian clock impact in metabolic disorders development in human beings.



Experimental systems for the analysis of circadian gene expression in tissue explants, cell populations or single cells by *in vivo* bioluminescence recording. *Upper picture:* Actimetrics Lumicycler device allowing the long term continuous bioluminescence recording in living cells and tissue explants; *Lower picture:* Combined fluorescent/ bioluminescent time-lapse microscopy, recently developed and unique approach for single cell oscillation recordings.

Selected recent publications

1. Gosmain Y. et al., **Diabetes Obes Metab.** (2011) Oct;13 Suppl 1:31-8.
2. Sage D, Unser M, Salmon P, **Dibner C., Cell Division** (2010) Jul 6;5:17.
3. **Dibner C., Schibler U. and Albrecht U., Ann. Rev. Physiol.** (2010) Mar 72, 517-549.
4. **Dibner C. , Cell Cycle** (2009) Mar 27;8(5).
5. **Dibner C. et al. EMBO J.** (2009) Jan 21;28(2):123-34.
6. Asher G. et al., **Cell** (2008) Jul 25;134(2):317-28.