Department of Systems Biology

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Research Projects:

The major interest of our lab is and has been centered on Research and Development of Innovative Chronomedicine and Therapies Based on Circadian Clock. Research topics undergoing in our lab are characterized as follows:

Fig. Drug discovery based on TIME:
Let's tune the world for better health!

1) Clock Gears: State-of-the-art research on circadian rhythms began with a seminal finding of "clock genes" that are common to human beings and other mammals. The field since then has expanded into a rich and diverse interdisciplinary academic field that deals with both basic sciences and clinical interrogations of daily rhythms in physiology. There are still a number of mysteries in the molecular clock gears, which would reveal as yet undeciphered molecular links between daily physiologies and circadian clock.

2) Central Clock: A section of the hypothalamus called the suprachiasmatic nucleus (SCN) lies at the center of the body's master clock and gets input directly from light sensors in the eyes, keeping the rest of the body on schedule. My lab studies the molecules, cells, and circuits underlying these circadian rhythms in the SCN using techniques that include real-time cellular imaging and multiple genetic manipulations, i.e. mutants, knockouts, transgenics, optogenetics, etc. This approach is producing insight into the roles of specific neuropeptides and G-protein-coupled receptor-mediated signaling circuits in the rich repertoire of daily behaviors and physiologies.

3) Time Medicine: What will be a representative medical application of time control medicine? Sleep-wake cycles are profoundly influenced by the abnormalities of the circadian clock. We have recently demonstrated that Gpr176 is an orphan G-protein-coupled receptor that sets the pace of the central clock in the brain. Gpr176 is thus a potential drug target to treat sleep-wake cycle dysfunction. Development of a chemical modulator of Gpr176 function is our next on-going challenge.

4) Lark vs. Owl: Do you usually wake up early or sleep in the morning? Genome-wide association studies featured RGS16 as a "morning person"-associated gene. These human studies corroborate our original research finding using knockout mice. RGS16 shows strong circadian expression in the brain's pacemaker neurons and its deletion leads to elongation of period of circadian locomotor activity rhythm. We are currently interested in defining brain G-protein signaling that sets the time to go to sleep and wake up every day.

5) Clock Disorders: One of the most significant conceptual changes brought about by the analysis of circadian clock-deficient mice is that abnormalities in the circadian clock are linked not only to sleep arousal disorder but also to a wide variety of common diseases, including hypertension, diabetes, obesity, and cancer. We previously revealed a molecular mechanism linking circadian malfunction to salt-sensitive hypertension. Elucidation of clock dysfunction behind diseases will continue to be a main project of our lab.

6) Circadian Therapies: The development of anti-cancer drugs and therapies for lifestyle-related illnesses, such as cardiovascular disorder, obesity, and diabetes mellitus, would not solely involve manipulation of the core clock proteins *per se*, but will also be equally facilitated by manipulating the function of the group of "output" genes, which are regulated by the circadian clock. Manipulating the "input" signals that adjust the phase and amplitude of the circadian clock will also expand the path to drug discovery for circadian disorders. Symptoms of illness and efficacies of drugs are known to change according to time of our body and therefore can be predicted. It is hoped that the body time information will be used as clinical evidence to maximize the effectiveness of existing drugs and also to reduce their potential adverse side-effects.

Recent publications

- Doi et al. Salt-sensitive hypertension in circadian clock-deficient *Cry*-null mice involves dysregulated adrenal Hsd3b6. **Nature Medicine** 16, 67 (2010)
- Doi et al. Circadian regulation of intracellular G-protein signaling mediates intercellular synchrony and rhythmicity in the suprachiasmatic nucleus. **Nature Commun**. 2, 327 (2011)
- Yamaguchi et al. Mice genetically deficient in vasopressin V1a and V1b receptors are resistant to jet lag. **Science** 342, 85 (2013)
- Doi et al. Gpr176 is a Gz-linked orphan G-protein-coupled receptor that sets the pace of circadian behaviour. **Nature Commun**. 7, 10583 (2016)
- Chao et al. Circadian clock regulates hepatic polyploidy by modulating Mkp1-Erk1/2 signaling pathway. **Nature Commun**. 8, 2238 (2017)
- Goda, Doi et al. Calcitonin receptors are ancient modulators for rhythms of preferential temperature in insects and body temperature in mammals. **Genes Dev**. 32, 140 (2018)
- Doi, Shimatani et al. Non-coding *cis*-element of *Period2* is essential for maintaining organismal circadian behaviour and body temperature rhythmicity. **Nature Commun**. 10, 2563 (2019)
- Miyake and Doi, Reconstitution of organismal liver clock function requires light. **Trends Endocrinol Metab**. in press