Department of Molecular Brain Science

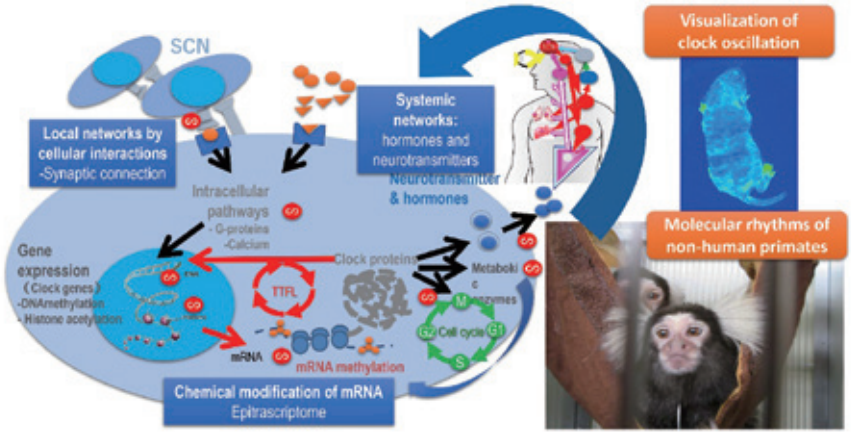
Specially Appointed Professor: Hitoshi Okamura

Research Projects:

Organisms live in a spatiotemporal world. Even for humans, regular diet and sleep are the basis of a healthy life. Epidemiological studies have demonstrated that the incidence of life-style related disorders such as diabetes, hypertension and obesity has increased in parallel with the development of our 24-hours society.

We are researchers of the suprachiasmatic nucleus (SCN) where the master clock of the mammalian circadian rhythms localizes. In the past decades, we have been pioneers in the exploration of molecular mechanism underlying the biological clock since the isolation of the mammalian *Period* genes (Nature 1997; Cell 1997; Science 1999; Science 2001, Science 2003a). In recent years, we have shown that the methylation of mRNA determines the period length of the clock (Cell 2013; PNAS 2018), that novel orphan G protein-coupled receptors and their regulation are critical for the function of the SCN and the synchronization to the light/dark cycles (Nature Comm 2011, 2016). We have also examined the impact of a disrupted clock on the development of diseases including hypertension (Nature Med 2010), jet lag (Science 2013; iScience 2018), and on the timing control of cell division, especially during the development and regeneration of hepatocytes (Science 2003b; Nature Com 2017).

The disruption of circadian rhythms cannot be explained simply based on the transcription-translation feedback loop (TTFL), since metabolism also greatly influences the formation and adjustment of rhythms, and so is the ability of cells to synchronize their intracellular rhythms. In nocturnal animals, synchronization to the environmental cycles mostly occurs via light exposure, while non-photic information (darkness, melatonin, etc.) is critical in diurnal animals such as humans. Therefore, to understand sleep rhythm disorders in humans, it is important to develop experimental paradigms in non-human primates. In 2018 we set up the first Japanese biorhythms measurement room for marmosets, and observed their strong circadian rhythms and social synchronization, as well as how their rhythms can be reset by dark-pulses. At the molecular level, we now try to visualize gene expression oscillations in marmoset brain, and compare this to that of mice brain.



Recent publications

- Doi M et al. Non-coding cis-element of Period2 is essential for maintaining organismal circadian behaviour and body temperature rhythmicity, ***Nature Commun*** 10: ***, 2019.
- Yamaguchi Y & Okamura H Vasopressin signal inhibition in aged mice decreases mortality under chronic jet lag, ***iScience*** 5: 118–122, 2018.
- Fustin, JM et al. Two Ck1δ transcripts regulated by m6A methylation code for two antagonistic kinases in the control of the circadian clock. ***Proc Natl Acad Sci USA*** 115:5980-5985, 2018.
- Chao H-W et al. Circadian clock regulates hepatic polyploidy by modulating Mkp1-Erk1/2 signaling pathway. ***Nature Commun*** 8: 2238, 2017.
- Yamaguchi Y et al. Mice genetically deficient in vasopressin V1a and V1b receptors are resistant to jet lag. ***Science*** 342: 85-90, 2013.
- Fustin JM et al. RNA-methylation-dependent RNA processing controls the speed of the circadian clock. ***Cell*** 155: 793-806, 2013.
- Doi M et al. Salt-sensitive hypertension in circadian clock-deficient mice involves dysregulated adrenal Hsd3b6. ***Nature Med*** 16: 67-74, 2010.
- Yamaguchi S et al. Synchronization of cellular clocks in the suprachiasmatic nucleus. ***Science*** 302: 1408-1412, 2003.
- Matsuo T et al. Control mechanism of the circadian clock for timing of cell division in vivo. ***Science*** 302: 255-259, 2003.
- Shigeyoshi Y et al. Light-induced resetting of a mammalian circadian clock is associated with rapid induction of the mPer1 transcript. ***Cell*** 91: 1043-1053, 1997.