

Science Highlights

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CIRCADIAN RHYTHMS IN THE SPOTLIGHT

The 2017 Nobel Prize in Physiology for circadian rhythm discoveries is exciting news for Bedford Research.

Almost a decade ago, Bedford Research scientists discovered circadian rhythm genes were turned on as early as three days (the 8-Cell stage) after a human egg was activated by sperm (1).

Although circadian rhythms were discovered over a century ago, their importance and their molecular basis is a fast-growing field in the past 20 years.

Circadian Rhythm: a behavior that repeats every 24 hours

Bedford Research scientists became aware of circadian rhythm genes while researching ways to improve the efficiency of developing therapeutically valuable stem cells from human eggs activated without sperm (parthenotes).

The new Nobel Laureates, Jeffrey Hall and Michael Rosbash of Brandeis University, and Michael Young of Rockefeller University, simultaneously discovered a protein, "PER," in fruit flies over 30 years ago that increased after dark and decreased during the day. The key finding was that although the rise and fall of "PER" was entrained by cycles of light and dark, the circadian pattern persisted even after the fly was kept in solid darkness for several days. Hence, production of the protein wasn't directly stimulated by light exposure, but had become its own internal, circadian mechanism.

We now know that all cells are regulated by circadian rhythms, a fundamentally important process that controls both behavior, e.g. sleep, and cellular processes, such as release of hormones.

Mammalian circadian rhythm genes are different from those in fruit flies, and were discovered by several investigative teams in the 1990's:

Takahashi and colleagues identified the mammalian gene, CLOCK, as essential for normal circadian rhythms. Mammalian cells have three "PER" genes: PERIOD 1, -2, -3, plus two forms of a gene, CRYPTOCHROME discovered by Sancar and colleagues to form a complex with PERIOD.

Hogenesch, Ikea and Nomura discovered ARNTL (also known as BMAL), which was shown to form a complex with CLOCK by Weitz and colleagues, including Fred Davis, Bedford Research Advisor.

The picture has now emerged of an elegantly simple feed-back loop that takes 24 hours to complete, is thought to control about 12% of mammalian genes, and is maintained by stimuli from the supra-chiasmatic nucleus in the hypothalamus.

Core circadian oscillators: CLOCK/ARNTL stimulates PER/CRY which feed-back inhibits CLOCK/ARNTL, which decreases PER/CRY allowing CLOCK/ARNTL to increase again, in a 24 hour cycle

Bedford Research scientists, however, have more recently reported(2,3) that approximately 70% of key regulatory genes expressed at high levels at the 8-Cell stage of development are circadianly controlled(4), and that in contrast to the 8-cell stage, the core circadian oscillators in human stem cells in long term culture are silent, calling into question the normality of their responses during experiments.

There is a pressing need to support circadian rhythms during the derivation, long term culture and study of human stem cells. Bedford Research scientists began to develop such methods a decade ago, the importance of which is supported by this year's Nobel Prizes. Hearty congratulations to Jeffrey Hall, Michael Rosbash and Michael Young.

(1) *JARG* 26:187; (2) *JARG* 27: 265; (3) *SCD* 25:160; (4) *circadb.hogeneschlab.org*