True Cell Simulations Inc.
cell blog
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19. Oscillation of a cell

Jet lag is caused by the difference in the phase between our circadian rhythm and the day–night cycles in a visiting country. Our circadian rhythm adapts to the environment over several days to a week. On the other hand, there is a famous experiment where we lived almost a 24-hour cycle, even in constant light intensity, such as in a cave. This strongly suggests that we have an autonomous generator of a 24-hour cycle, the circadian rhythm. It was found that a single cell also showed a 24-hour cycle. Extensive research during the 1990s and early 2000s has revealed its molecular mechanisms.

A cell also displays several other oscillations, including gene expression triggered by an external stimulus. In addition, a protrusion or expansion grows and retracts from and to a cell on the culture dish. This is a kind of spatial oscillation. Here, we discuss these oscillations of a cell.

First paper on cell oscillation? : Oscillating phenomena have mainly attracted physicists and neuroscientists, and many works have been published, from pure theoretical to molecular-based models. Among them, a research work published in 1965 may be the first on the possible oscillation in the gene expression. In this model, a simple mechanism was proposed, in which a gene expression is activated, followed by the expression of an inhibitory gene suppressing the activated gene. If the gene activation continued, the cycle continued, and thus an oscillation was generated (Goodwin, B.C., Adv. Enzyme Regul., 1965). In that period, the molecular mechanisms of gene expression and suppression were totally unknown. I was impressed by the author's insight into the intracellular oscillation mechanism. This paper, however, has been ignored by descendant researchers.

Circadian rhythm: As described above, the circadian rhythm is the most famous oscillatory phenomenon, and its single-cell-level molecular mechanisms were described, in which the transcription factor CLOCK/BMAL1 promotes the expression of *Per*/*Cry* genes, which leads to the inhibition of CLOCK/BMAL1 activities. This negative feedback with a time delay generates a 24-hour oscillation (Okano, T., et al., J. Biochem., 2003). This is the same mechanism proposed by Goodwin, B.C. in 1965.

Oscillation of transcription factor NF-κB: Oscillation mechanism of NF-κB is also the same as that by Goodwin B.C. in 1965. Activated transcription factor NF-κB by external stimulus translocates from the cytoplasm to the nucleus, promoting the expression of IκB, an inhibitor of the activated NF-κB. When external stimulus still exists, NF-κB translocates to the nucleus again. Thus, this cycle is repeated, generating the damped oscillation of NF-κB (Hoffuman,A., et al., Science, 2002). The period of the oscillation is around 2 hrs, which is shorter than that of the circadian rhythm.

Oscillation in a MAPK pathway: Oscillation of p38 MAPK, which plays important roles in regulating many functions of a cell, including stress responses, was also reported (Tomida, T., et al., Nat. Comm., 2015). This is evoked by IL-1β stimulation, resembling damped oscillation with a period of about 2 hrs. The essence of the molecular mechanism is similar to that of NF-κB, where activated p38 is inhibited by MKP-1 with a time delay, thus generating oscillations by a sustained stimulus. The difference to the NF-κB mechanism exists in that p38 MAPK oscillation does not involve gene expression.

Oscillation of Ca^{2+} : The concentration of intracellular Ca^{2+} (60 nM) is only $1/10^5$ that of extracellular Ca^{2+} (2 mM). Ca^{2+} concentration in ER and inside the mitochondria is higher than that of the cytoplasm. Apoptosis is closely related to the increase in the intracellular Ca^{2+}. An increase in Ca^{2+}

concentration in synaptic terminals is required for the release of transmitter molecules, and Ca^{2+} acts as a critical regulator of the long-term change in the synaptic transmission efficacy (synaptic plasticity). Although it is not discussed frequently recently, intracellular Ca^{2+} oscillates. Ca^{2+} oscillations in astrocytes are known to increase the dysfunction of neurons.

Spatial oscillation (pseudopodia and filopodia): Cell shape also oscillates. Although a periodical cell-shape change is not regarded as an oscillation, lamellipodia and/or filopodia, which are protrusions from a cell, protrude and retract, resembling morphological/spatial oscillations. Extensive research has revealed its molecular mechanisms, including dynamic changes in actin filaments. Dynamic change in the cell-adhesion molecules and the supply and release of phospholipids will also be included. Although many seem to be left behind in understanding, the formation/fusion of lipid droplets and the lipid transfer at membrane contact sites (MCSs) should be recruited to this activity.

Oscillations of a cell discussed above are a part of cell oscillations. Techniques for investigating a single cell accelerated the finding of cell oscillations, because a cell population doesn't always oscillate synchronously in a culture dish.

Why does a cell oscillate? Is it needed for any function of a cell? Or, is it just a consequence of cellular mechanisms? It is natural to assume that the circadian rhythm is advantageous to living species on Earth[*1]. But what functions are realized by the oscillations of NF-κB and MAPK pathways? Why are their oscillation periods around 2 hrs? How about for the oscillation of pseudopodia or filopodia?[*2] Translocation of NF-κB to the nucleus leads to the expression of many genes. Since a prolonged expression of a specific gene will be harmful to a cell, an inhibiting mechanism must exist. However, oscillation is not essential just for inhibiting the expressed genes. This may raise a possibility that the oscillation of NF-κB is just a consequence without any specific role[*3].

*1 In the early period when cells emerged, "oscillation" might be just a consequence. But cells might find it advantageous to utilize it on Earth. This will be an eternal mystery.

*2 The oscillation of pseudopodia and filopodia may emerge from the combination of chance and necessity. A part of a cell protrudes to investigate its outside randomly. If a reached position is not favorable or does not fulfill the cell's demand, the protrusion is retracted, and the cell generates a protrusion in a different direction. The protruding direction may be determined randomly by an intracellular condition. If so, what is the intracellular condition, and what is the extracellular condition and mechanism for fixing the protrusion?

*3 One report described that the oscillation frequency and persistency determined the expressed genes (Ashall, L. et al., Science, 2009). This can explain the requirement of NF-κB oscillation.

There are multiple types and mechanisms in the oscillations of a cell. Why a cell oscillates and what function is realized are not clear yet, except for some oscillations like the circadian rhythm. Such a question might be nonsense if a mere consequence is changed into active use. Cells are interesting and, at the same time, formidable.