Self-generated intracellular heat drives neuronal differentiation

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Abstract

Temperature is one of the most fundamental physical quantities governing all biochemical reactions, and cellular functions are highly dependent on intracellular temperature. We focused on "cell differentiation," where cells dramatically alter their gene expression patterns and morphology, and examined the effects of intracellular temperature on the differentiation process using a neural model cell. Our findings revealed that neural cells experience an approximately 1°C increase in intracellular temperature during differentiation. Furthermore, inhibiting transcription or translation causes intracellular temperature to decrease, suppressing neurite outgrowth. Additionally, heating the cell nucleus by several degrees after differentiation induction promotes differentiation. Furthermore, we clarified that inhibiting the rise in intracellular temperature after differentiation induction suppresses differentiation, and this inhibitory effect can be recovered by heating the nucleus. These results suggest the existence of a novel mechanism whereby spontaneous heat production within cells drives cell differentiation via the activation of transcription and translation reactions.

Background & Results

Temperature is one of the most familiar physical factors for humans. However, the effects of temperature on the function of cell remain poorly understood. Therefore, we attempted to directly measure intracellular temperature. We developed a method to visualize temperature distribution within a single cell with high sensitivity and quantitatively. This was achieved by introducing a fluorescent polymer temperature sensor, which exhibits a characteristic increase in fluorescence lifetime with rising temperature, into cells via microinjection. Observation using fluorescence lifetime imaging microscopy enabled this visualization. Our results revealed that intracellular temperatures are not uniform: the cell nucleus is approximately 1°C warmer than the cytoplasm; the temperature difference between the nucleus and cytoplasm changes with the cell cycle; and some mitochondria are warmer than their surroundings. Next, to clarify the effects of temperature changes on cellular function, we focused on "cell differentiation," a process where gene expression patterns and morphology change dramatically. Adding nerve growth factor (NGF) to a neural model cell initiated differentiation, with neurite outgrowth observable within hours. Twenty-four hours after NGF addition, both the nucleus and cytoplasm showed a temperature increase of approximately 1°C. However, when a transcription inhibitor was added simultaneously with NGF, neurite outgrowth was suppressed to about 60%, and both nuclear and cytoplasmic temperatures dropped below pre-NGF levels. When a translation inhibitor was added simultaneously, neurite outgrowth was completely inhibited. While the nuclear temperature remained unchanged, the cytoplasmic temperature decreased. These results are thought to reflect that transcription occurs in the nucleus and translation occurs in the cytoplasm. Furthermore, to verify whether the temperature increase accompanying differentiation is merely a consequence or an active factor controlling differentiation, nuclear heating experiments were performed. Focusing an infrared laser to a diameter of several micrometers and locally heating the cell nucleus by several degrees immediately after NGF addition resulted in longer neurite outgrowth and accelerated differentiation after 24 hours. Interestingly, heating the nucleus alone, without NGF addition, also increased the differentiation rate. Conversely, introducing heat-absorbing polymers after differentiation induction to inhibit intracellular temperature rise suppressed differentiation. This suppression effect was restored by nuclear heating with the infrared laser. Furthermore, experiments using mouse embryonic neural cells confirmed that intracellular temperature rises during the processes of neurite outgrowth and network formation. These results strongly suggest that intracellular temperature may play a crucial role in developmental processes within the brain, including neural differentiation.

Significance of the research and Future perspective

This study revealed that during cell differentiation, heat generated by the activation of transcription and translation reactions further promotes intracellular transcription and translation, accelerating neuronal differentiation. We propose this phenomenon as a "temperature signaling" mechanism. Temperature signaling may be widely present not only in neural differentiation but also in other diverse and dynamic biological phenomena. Going forward, this concept is expected to provide new perspectives for understanding biological functions. Furthermore, the control of neural cell function by heat is anticipated to contribute to the development of therapies involving neural regeneration.

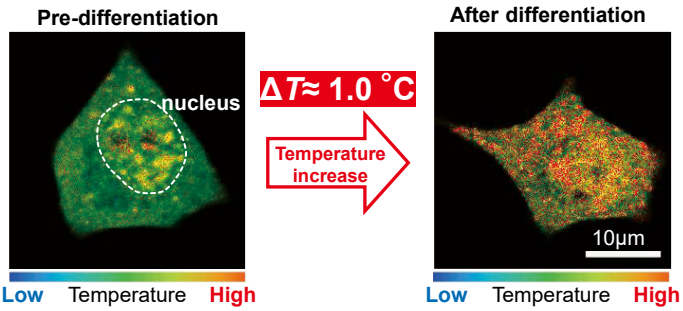

Fig1. Intracellular temperature imaging during neural differentiation
Twenty-four hours after nerve growth factor addition, the temperature of the nuclei and cytoplasm in differentiated neural model cells was approximately 1 degree higher than before differentiation.

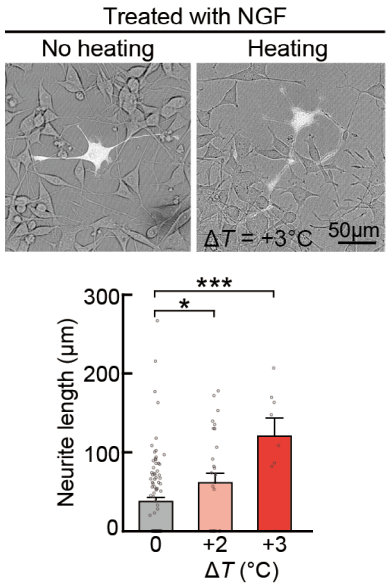

Fig2. Promotion of Neurite Outgrowth by Intracellular Heating
Compared to non-heated cells, the neurite length of heated cells increased proportionally to the heating temperature.

Patent

Treatise Chuma, Shunsuke et al. Implication of thermal signaling in neuronal differentiation revealed by manipulation and measurement of intracellular temperature. Nature Communications. 2024, 15(1), 3473-3473. doi: 10.1038/s41467-024-47542-8

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