Quantum sensing system measures intracellular temperature over long periods

Intracellular temperature in biological cells is a key parameter influencing cellular functions and activities. To study cellular functions, thermometry techniques capable of measuring intracellular temperature over long periods of culturing and incubation are required. Hiroshi Yukawa of Nagoya University, Japan, and his research colleagues from various universities and institutes in Japan have now developed a novel quantum thermometric sensing and analysis system (QTAS) that uses fluorescent nanodiamonds (FNDs) for this purpose. This QTAS enables the intracellular temperature of cells to be detected over several days of incubation. The team also demonstrated that this QTAS can be used to study the relationship between intracellular temperature and cellular functions. Their research was published in a recent issue of *Nanoscale Advances* (<https://doi.org/10.1039/d0na00146e>).

“The novelty of this paper is [the detection of] intracellular temperature of stem cells stably by using nitrogen-vacancy (NV) centers in nanodiamonds,” says Hiroshi Yukawa, lead author of the study. The QTAS uses FNDs to label cells and exploit the quantum coherence of NV centers in the diamonds for its temperature sensitivity. NV centers

have spin-triplet ground and excited states with a long electron spin coherence time. This electron spin can be optically detected with a technique known as optically detected magnetic resonance (ODMR). As the frequency of ODMR is temperature-dependent, the local temperature in the cells can be measured by measuring the frequency shift of the ODMR peak of the FNDs. Here, the peak was reported to be at 2.87 GHz.

To ascertain that the FNDs can be used to label cells for use in this quantum thermometry technique, studies were conducted using FND-labelled adipose tissue-derived stem cells (ASCs). ASCs are mesenchymal stem cells derived from adipose tissue with the ability for self-renewal and multipotent differentiation. Data showed that ASCs could be labelled with FNDs with high efficiency. Under $500 \mu\text{g mL}^{-1}$ of FNDs, no cytotoxicity was observed. Additionally, results showed that the FNDs did not affect the stem cell abilities of the ASCs. These findings highlight the low cytotoxicity and non-influence of FNDs on cellular function.

The researchers also further validated the QTAS for use over several days. Using the QTAS, intracellular temperatures between 24.0°C and 40.9°C could be precisely measured over several days of culturing ASCs. As temperature decreased, the ODMR peak shifted to the high-frequency side, giving a mean temperature dependence of $-(77.6 \pm 11.0) \text{ kHz } ^\circ\text{C}^{-1}$, allowing for continuous temperature changes to be detected.

The QTAS also has other potential applications. “The implication of this research is to clarify the influence of the intracellular temperature of stem cells on stem cell abilities,” Yukawa says. “We newly clarified that stem cell abilities such as self-propagation and the production of growth factors were affected by the intracellular temperature of stem cells,” Yukawa says. He also notes that this technology can be applied to other kinds of cells such as cancer cells.

David Simpson of The University of Melbourne, Australia, whose research includes diamond-based quantum sensors for use in biological systems, says, “The work by Yukawa et al. extends ... the growing body of work into intracellular thermometry using nanoscale quantum probes.” Simpson was not involved in this study. “Nanodiamonds (NDs) have shown significant promise for nanoscale thermometry in biology. High-pressure, high-temperature (HPHT) synthesized NDs are biocompatible and can be introduced via a number of pathways into cellular systems. The photostable fluorescence properties of NDs, in particular the NV center, enables high resolution, long-term imaging, and sensing,” Simpson says.

Simpson says that the capability of this novel QTAS for long-term culturing and recording will be critical for longitudinal cell culture studies. “It is critical from a biological standpoint that sensors themselves do not compromise the functions of the biological system under investigation. This validation is an important step for future applications of

ND sensors in biological systems,” he says.

Simpson also points out considerations for use of NDs in quantum thermometric sensors, in particular that reaching the theoretical limits of temperature sensitivity in the living cell represents a significant technical challenge. “The speed at which the ODMR signal, which reports the temperature, is currently a

Schematic of the measurement of temperature change inside living adipose tissue-derived stem cells (ASCs) labelled with fluorescent nanodiamonds (FNDs) using the quantum thermometric sensing and analysis system (QTAS). The QTAS consists of an in-house-crafted cell culture dish with a heater and a three-axis scanning piezo stage of a confocal fluorescence microscope built in-house. Credit: *Nanoscale Advances*.

limiting factor. In the present work, the full ODMR spectrum is obtained, which can take up to a minute depending on the scan parameters. Unless bound to particular cellular compartments, freely diffusing NDs will move away from the imaging spot over that time scale.”

Yukawa and his research team continue to improve this technology and aim to achieve detection of intracellular temperature *in vivo*. Simpson reflects, “This is an exciting time to be working in quantum sensing with ND materials. The technical maturity of NDs coupled

with the opportunity of nanoscale sensing in biology provides a unique opportunity for these two disciplines to come together and solve some of the fundamental questions regarding how temperature regulates life.”

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