SENSORS AND PROBES

A thermometer for cells

A small chemical probe allows detailed spatial imaging of the temperature in single cells.

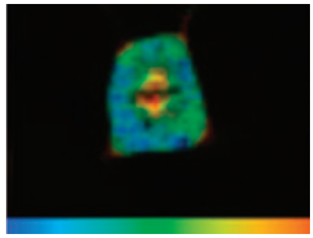
"Let me take your temperature." Children hear this numerous times and quickly learn that an increased body temperature indicates they are sick. But in spite of evidence that temperature can be indicative of cell state, the closest that thermometers in the laboratory get to cells in culture is their use to measure the temperature of the researcher's cell incubators. But recent work by Seiichi Uchiyama and colleagues at The University of Tokyo may prompt more biologists to think about measuring the temperature inside, as opposed to outside, their cells.

Many researchers have tried to make a thermometer for single cells, and there has been considerable success at creating probes that can measure the average cell temperature or the temperature in a limited volume inside a cell. But although knowing the core temperature of a person is quite useful, knowing the average temperature of a cell provides a limited amount of information. An important goal has been to create a soluble nanoscale probe that can provide a complete temperature map of a cell's interior.

But all the intracellular temperature probes reported so far had limitations that prevented reliable subcellular spatial measurement of temperature throughout a mammalian cell. Sometimes the probe was too big to obtain the necessary resolution. Sometimes it was small enough but did not distribute evenly in the cell. Other times the probe just did not have the desired sensitivity and accuracy.

Uchiyama experienced some of these difficulties himself. His group had earlier created a fluorescent nanogel thermometer that combined a thermoresponsive polymer and an environment-sensitive fluorophore so that a temperature change caused a change in fluorescence. This thermometer worked well for measuring the average temperature in a cell but ultimately proved too large and prone to aggregation above cellular temperatures of 27 °C for the more sophisticated experiments he envisioned.

In their new work Uchiyama and colleagues overcome these limitations and reduce the size of their cellular thermometer from ~62 nanometers to 8.9 nanometers measured by hydrodynamic diameter and eliminate aggregation. "The design was simple," says Uchiyama. "To prevent aggregation we wanted a more hydrophilic fluorescent thermometer, so we changed the morphology from a nanogel to a smaller linear polymer with hydrophilic moieties."



A fluorescent temperature sensor. The sensor highlights warmer (red) and colder (blue) regions of a dividing cell. Image courtesy of S. Uchiyama.

Like their older nanogel probe, their fluorescent polymeric thermometer still needs to be microinjected into cells, but once inside it readily diffuses throughout the cell, including into the nucleus. They used fluorescence lifetime microscopy to image the probe after injection into COS7 cells because lifetime imaging allowed them to ignore spatial variations in the concentration of the probe. They could resolve temperature differences of 0.18–0.58 °C in cells incubated at 30 °C.

As expected given their role as the 'powerhouses' of the cell, the area around mitochondria was warmer than the rest of the cytoplasm. They also observed increased temperature in the location of the centrosome in dividing cells.

But the surprising result was that the nucleus appeared to generate the most heat. "Moreover, the temperature gap between the nucleus and the cytoplasm was cell cycle–dependent," says Uchiyama. Could this result be unique to cancer cells, or is it a general characteristic of all cells? Uchiyama is not sure, but comparing cancer cells and non–cancer cells is certainly on his list of things to try next as he uses this probe to look for correlations between intracellular temperature distribution and specific biological reactions and organelle functions.

Daniel Evanko

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Okabe, K. *et al.* Intracellular temperature mapping with a fluorescent polymeric thermometer and fluorescence lifetime imaging microscopy. *Nat. Commun.* **3**, 705 (2012).