Novel Cell-Friendly Microscopy

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“Measure what is measurable, and make measurable what is not so” quoted the famous Galileo Galilei, and indeed, mankind has pushed forward science through new measurement and observation technologies. The development of telescopes and satellites has deepened our understanding of space, whereas measurement technologies for quantum mechanical matter have brought us closer to quantum computing. A more familiar innovation for us is cell observation technology, an essential tool when developing vaccines for fighting diseases, such as COVID-19.

While there exist multiple cell observation methods and each has its pros and cons, mid-infrared photothermal (MIP) microscopy is a novel cell imaging technique. Although not yet common, without perturbing intrinsic functions, the chemical compositions of cells can be estimated, and the intracellular distribution can be imaged [1]. This leads to further understanding of cellular function and additionally to the development of new therapeutic agents for currently incurable diseases.

MIP microscopy, as the name implies, is an imaging method for the photothermal effect of cells in the mid-infrared region. When cells are exposed to light, they absorb a portion of the light inducing a phenomenon called the photothermal effect which changes the speed of light passing through the cell, or in other words the refractive index, a value indicating how slow light passes through an object, inside the cell. This change is known to depend on the amount of light absorbed, thus by measuring the change in refractive index, the amount of light absorption by cells can be determined [2]. Because different biomolecules show different responses to light, measuring the light absorption of cells helps us estimate and measure the chemical compositions of cells.

The mid-infrared region is a useful region in light for observing cells. Each color of light has a different wavelength. In the visible region, violet has the shortest wavelength while red has the longest. Mid-infrared is a region with longer wavelengths than red, therefore invisible to the human eye, at the same time, however, includes rich information on biological molecules, meaning that different biological molecules show different absorption rates in the region. Therefore, by measuring MIP signals at multiple wavelengths in the mid-infrared region, to be

more specific measuring the change of refractive index when mid-infrared light is illuminated to cells, the intracellular distribution of biological molecules can be estimated. This is like when you have yellowish green colored ink in front of you that you know was made by mixing yellow and green ink, you can calculate the ratio that the two inks were mixed.

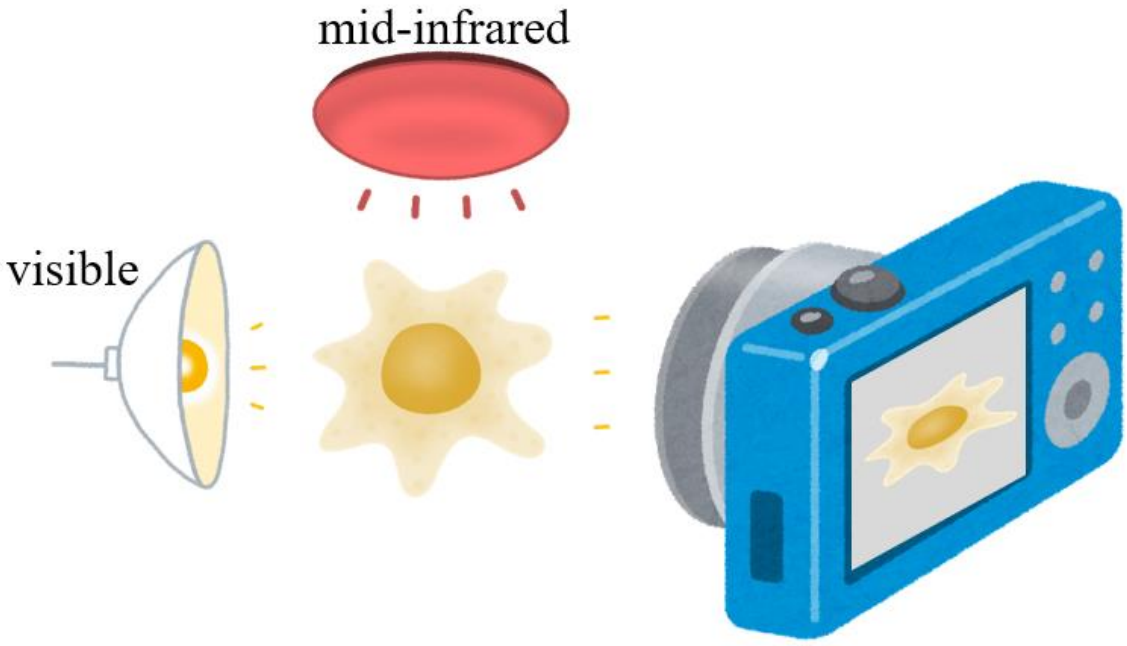
One interesting aspect of MIP microscopy is that visible light is used to capture the change in the refractive index caused by mid-infrared light, instead of using the mid-infrared light itself. Cells and the water around them show less absorption in the visible light region compared to the mid-infrared region, which is known to result in lower noise when measuring the refractive index. It is also known that measuring refractive indices using light with shorter wavelengths leads to higher spatial resolution, another advantage of using visible light for measurement.

MIP microscopy shows some advantages when compared to other methods, for example, fluorescence microscopy. Fluorescence microscopy is the current gold standard of live single-cell imaging where usually specific cellular structures are stained or modified to emit fluorescence. Although being a powerful tool for imaging specific intracellular structures, fluorescence microscopy suffers from inevitable problems originating from its methodology; the risk of impairing cell functions. As fluorescence microscopy requires the labeling of biological molecules with fluorescent labels, there is little guarantee that the natural functionality of the cell will not be compromised at all, becoming a challenge in regenerative medicine where the cell is required to be put back into the human body. On the other hand, MIP microscopy is a label-free imaging technique that does not introduce fluorescent labels, thus there is no need for these worries.

Despite these advantages, MIP microscopy still faces some challenges for practical applications. One challenge is its complex setup. MIP microscopy demands two powerful light sources and a refractive index measurement system, requiring a careful setup. Another challenge is its sensitivity. Coming back to the previous analogy of colorful inks, MIP microscopy can currently estimate the ratio of yellow and blue ink but has difficulties estimating with three or more colors, for example when red ink is added. The original issue is a little bit more complex, but the essence is the same. A more precise measurement is desired.

When the issues are resolved, MIP microscopy's ability to image intercellular distributions of chemical composition at high resolution without damaging cell functions will provide new approaches to solving challenging cytological problems. MIP microscopy has the potential for real-time tracking of the accumulation of drugs and how it is processed in cells, which leads to not only a deeper understanding of cell functions but also applications in pharmaceuticals, for example, in the development of new drugs for cancer treatment. As mentioned earlier, fluorescence microscopy has the risk of impairing the original function cells, hence observing cells in a label-free matter is preferable, as in the case of MIP microscopy. MIP microscopy is also expected to be applied to regenerative medicine. MIP can provide quantitative images of individual cells without compromising cell function, assisting the selection of suitable cells for regenerative medicine from a large number of candidate cells.

In a word, MIP microscopy is a new imaging technique that can map the distribution of chemical compositions in cells. Hopes are high for not only academic science but also for pharmaceutical applications benefiting our lives. The time may soon come when current incurable diseases can be easily cured!



Reference

[1] Zhang, D., Li, C., Zhang, C., Slipchenko, M. N., Eakins, G., & Cheng, J. X. (2016). Depth-resolved mid-infrared photothermal imaging of living cells and organisms with submicrometer spatial resolution. Science advances, 2(9), e1600521.

[2] Bai, Y., Yin, J., & Cheng, J. X. (2021). Bond-selective imaging by optically sensing the mid-infrared photothermal effect. Science Advances, 7(20), eabg1559.