IMAGING

Gold glitters in transparent tissue

Through scattering, *in situ* metal particle growth enables biomolecule visualization within tissue.

Three-dimensional optical imaging of biological tissue is challenging. Optical clearing can be used to reduce scattering and thereby enable deep-tissue imaging; however, optical microscopy still heavily relies on fluorescent labels which often suffer from poor photophysical properties. Optical imaging deep into tissue requires stable, bright optical signals. A team led by Warren C. W. Chan from the University of Toronto has demonstrated the *in situ* size amplification of small metal nanoparticle biolabels. Because of their scattering nature, the resulting larger particles enable the three-dimensional visualization of features within optically cleared tissue.

Taking advantage of the scatter-free environment of optically cleared tissue, the team aimed to introduce scattering particle labels. Metal nanoparticles, which have a scattering efficiency similar to that of fluorescent molecules but a significantly larger extinction cross-section, can be millions of times brighter than fluorescent molecules. Additionally, nanoparticles do not suffer from photophysical artifacts such as blinking or bleaching.

The scattering cross-section of a metal nanoparticle scales with the sixth power of its radius, therefore a big particle is significantly brighter than its smaller counterpart. The team began with *in vivo* labeling using 15-nm gold nanoparticles. In order to increase the scattering of the nanoparticles for imaging, researchers put the optically cleared tissue into a mild reducing environment, which facilitated the slow and uniform growth of the nanoparticles. As the nanoparticles grew, the optical scattering increased to be up to 1.4 million times greater than that of a fluorescent molecule, making the scattered light sufficiently bright for the direct visualization of each nanoparticle in three dimensions with dark-field optical microscopy. The size, shape and material of the nanoparticle can also tune its spectral response, potentially enabling multispectral imaging.

The researchers applied their metal nanoparticle imaging approach to imaging mouse kidney vasculature, visualizing rare nanoparticles in a xenograft mouse tumor model, as well as characterizing lesions in a mouse model of multiple sclerosis. While challenges such as the simultaneous *in situ* growth of different particles remain, researchers are working towards developing methods for multispectral labeling. In his words, Chan plans to apply these techniques to study the "mechanism of how nanoparticles transport into tumors."

Zachary J Lapin

RESEARCH PAPERS

Syed A.M. *et al.* Three-dimensional imaging of transparent tissues via metal nanoparticle labeling. *J. Am. Chem. Soc.* **139**, 9961–9971 (2017).