Vibrational Spectroscopic Imaging of Molecular Dynamics in Living Systems

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Cell metabolism involving uptake and conversion of small biomolecules is the foundation for cell survival and proliferation. Quantitation of metabolic conversions in live tissues and in real time is essential to determining how a cell responds to an intervention such as drug treatment or exposure to a risk factor. Nevertheless, most of our knowledge about cellular content is derived from in vitro analysis of isolated cells or measurement of tissue homogenates, either by biochemical assays, omics or sequencing technologies. This gap highlights a need of developing new techniques that are able to repetitively assess the same single cell in a vital organism.

Raman scattering based vibrational spectroscopy has been traditionally used for quantitative analysis of biomolecules and biochemical reactions in solutions by detecting the molecular vibrations induced by laser pulses. Raman spectral imaging of live cells has been limited by the very small cross section of Raman scattering. It still takes tens of minutes for the most advanced Raman spectroscopy to acquire an image. Recently coherent Raman microscopy focusing on a specific Raman band has improved imaging speed to real-time with no spectral information. Hyperspectral coherent Raman microscopy based on either fast laser wavelength tuning or pulse shaping technique has been demonstrated with an integration time of several milliseconds per pixel or minutes per image, which still does not allow for imaging of a highly dynamic living system.

Here we developed microsecond hyperspectral coherent Raman techniques that enable repetitive assessment of single cell metabolism in a vital organism. By multiplex excitation and parallel detection in space or in frequency domain, we demonstrated spectral acquisition of one coherent Raman spectrum within several microseconds. This speed is 100 times faster than the state-of-art technology. We demonstrated several applications, including compositional analysis on single cell level, study of lipid metabolism in C. elegans and histological assessment of cancerous tissues.