Seeing molecular vibrations: optical imaging of small molecules for biology and medicine

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Fluorescence is the most popular contrast mechanism employed in modern optical imaging. A number of versatile fluorescence-based techniques, such as single-molecule spectroscopy, two-photon excited fluorescence microscopy and super-resolution imaging, have flourished and transformed the way modern life sciences are conducted. However, fluorescence imaging faces fundamental limitations for studying the vast number of small bio-molecules such as metabolites (e.g., amino acids, nucleic acid, fatty acids and glucose), secondary messengers, neurotransmitters and drugs. This is so because (1) most of the small bio-molecules are intrinsically non-fluorescent and (2) labeling of these small molecules by the relatively bulky fluorescent probes (either organic dyes or fluorescent proteins) would strongly perturb or even destroy the native biochemical activities of these small bio-molecules inside cells. Therefore, how to visualize and study these vital chemical species inside living cells represents a grand challenge. Novel imaging techniques that accomplish this goal would enable researchers the unprecedented ability to map out distributions and to follow dynamics of a wide variety of important small bio-molecules, transforming our ability to study biochemistry and biophysics in living systems. To address this challenge, we have developed a novel optical imaging platform by coupling the emerging stimulated Raman scattering (SRS) microscopy, which is capable of producing concentration maps of chemical bonds in biological samples, with three distinct classes of small vibrational tags with characteristic Raman transitions, including alkyne moieties (i.e., C≡C triple bond, Figure), targeting these vibrational tags, SRS microscopy is well suited for probing in vivo metabolic dynamics of small bio-molecules which cannot be labeled by bulky fluorophores [1-5]. Physical principle of the SRS microscopy and emerging biomedical applications such as imaging lipid metabolism, protein synthesis, DNA replication, protein degradation, RNA synthesis, glucose uptake, drug tracking and tumor metabolism [1-5] will be presented.

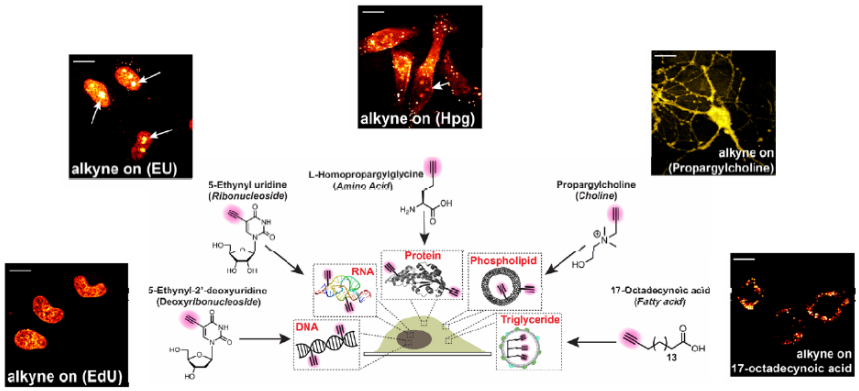

Figure. SRS imaging of *de novo* synthesis of DNA, RNA, proteomes, phospholipids and triglycerides, respectively, through metabolic incorporation of alkyne-tagged deoxyribonucleoside (EdU), ribonucleoside (EU), amino acid (Hpg), choline (propargylcholine) and fatty acid (17-octadecynoic acid) into live mammalian cells [1].

1. Wei, L., Hu, F., Shen, Y., Chen, Z., Yu, Y., Lin, C., Wang, M. C. & Min, W. Live-cell imaging with alkyne-tagged small biomolecules by stimulated Raman Scattering. Nature Methods, 11, 410-412 (2014).
2. Chen, Z., Paley, D., Wei, L., Weisman, A., Friesner, R., Nuckolls, C. & Min, W. Multicolor live-cell chemical imaging by isotopically edited alkyne vibrational palette. J. Am. Chem. Soc. 136, 8027-8033 (2014).
3. Hu, F., Wei, L., Shen, Y. & Min, W. Live-cell imaging of choline metabolites through stimulated Raman scattering coupled with isotope-based metabolic labeling. Analyst, 139, 2312-2317 (2014).
4. Wei, L., Yu, Y., Shen, Y., Wang, W. C. & Min, W. Vibrational imaging of newly synthesized proteins in live cells by stimulated Raman scattering microscopy. Proc. Natl. Acad. Sci. USA 110, 11226-11231 (2013).
5. Shen, Y., Xu, F., Wei, L., Hu, F. & Min, W. Live-cell quantitative imaging of proteome degradation by stimulated Raman scattering. *Angew. Chem. Int. Ed.* 53, 5596-5599 (2014).