Label-free imaging of previously invisible molecules

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Technology description

MARKETS ADDRESSED:
Near-Degenerate Four-Wave-Mixing microscopy overcomes the need to bind fluorophores to substances being imaged by providing a new and easy to-use nonlinear contrast mechanism. The mechanism is based on a bulk sensitive electronic polarization which can be excited and then detected easily. This technique allows for high resolution 3D imaging of transparent live cells and tissues all without labeling. This enables sensitive detection and mapping of biologically important chromophores which have been invisible to historic fluorescence microscopy.

This technology is specifically relevant to imaging:
â€¢ hemoglobin
â€¢ beta-carotene
â€¢ cytochrome c
â€¢ rhodopsin
â€¢ melanin

Fluorescence microscopy has been the method of choice for obtaining high-resolution images of the nano-scale world. The technique takes advantage of detecting a phenomenon known as fluorescence. Fluorescence is demonstrated when unique wavelengths of light are given off from a sample after it is illuminated. However, not all substances fluoresce. Hence, various spectroscopic contrasts have been explored for imaging nonfluorescent substances. These contrasts known as fluorophores, are tagged to targets of interest with binding agents. However, many important biological molecules cannot be attached to fluorophores with existing binding agents. This renders them invisible to traditional fluorescence microscopes.
A team of Harvard chemists led by X. Sunney Xie has developed a new microscopic technique for seeing molecules with undetectable fluorescence. The technique provides a unique way to image a wide range of molecules that are currently inaccessible to today's state-of-the-art optical microscopes. The process uses multiphoton microscopy based on single-beam near-degenerate four wave mixing. One is able to detect a coherent signal generated by a sample at frequencies close to the edge of the spectrally truncated incident femtosecond pulses. This technique allows for label-free biomedical imaging with high sensitivity and spatial resolution. In particular, by achieving a nearly perfect phase

matching condition, near-degenerate four wave mixing generates the highest nonlinear coherent signal in a bulk medium possible and provides a contrast mechanism different from other nonlinear imaging techniques. Most importantly, the technique provides an electronic resonant version of near-degenerate four wave mixing for absorbent, but nonfluorescent molecules.

Above is a shot of live human lung cancer cells (cultured A549 cell line) imaged with near-degenerate four wave mixing microscopy captured by this technology. Note that cellular organelles such as nucleus and mitochondria are clearly visible.

Institution

Harvard University

联系我们

叶先生

电 话：021-65679356

手 机：13414935137

邮 箱：yeyingsheng@zf-ym.com