Super-resolution imaging breakthrough in living cells

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Edinburgh scientists have developed a new imaging technique that reveals the inner workings of living cells in stunning detail and could pave the way to a better understanding of many diseases.

The new super-resolution imaging technique—LIVE-PAINT- provides a flexible and powerful way of tracking individual proteins inside living cells, without disrupting their activity.

The game-changing advance could lead to new insights into diseases by revealing the behavior of proteins involved in disease processes and those essential to health.

Existing super-resolution techniques are limited because they cannot be used inside living cells, require complex instruments, or involve fusion of a large fluorescent molecule that can interfere with the protein of interest.

The team at the University of Edinburgh developed the LIVE-PAINT technique, and tested it in live yeast cells, by tagging a protein-of-interest with a very small protein molecule, known as a peptide.

"LIVE-PAINT offers a way to label proteins for super-resolution imaging with a very small tag, which minimizes the chance of the tag affecting the protein's natural function," explains senior author of the study, Professor Lynne Regan at the University of Edinburgh's School of Biological Sciences.

The peptide tag then temporarily binds to another protein, known as a peptide-binding protein, which is fused to a fluorescent protein.

This reversible binding drives repeated association of the fluorescent protein to the protein-of-interest, generating the necessary blinking to construct super-resolution images.

The approach could offer new insights into diseases such as motor neuron disease, ALS, and Alzheimer's, which are characterized by the harmful build-up of protein aggregates inside cells.

The proteins involved in aggregation diseases are difficult to study using existing super-resolution methods as they often behave differently when directly fused to a large fluorescent protein.

Because LIVE-PAINT only requires fusion of a small peptide, this method could be used to study many other important processes in living cells without disrupting their activity.

The approach could, for the first time, allow detailed study of a group of medically important proteins, known as transmembrane proteins, which are the target of 70% of current drugs.

Transmembrane proteins are embedded in the membrane surrounding cells and have vital roles, such as signaling between nerve cells, which often lead to disease when disrupted.

The LIVE-PAINT approach takes inspiration from another super-resolution technique—DNA-PAINT- which uses short DNA strands to reversibly associate a fluorescent molecule to a target molecule.

However, the short strands of DNA are synthesized chemically, which means that they can only be used on the outer surface of a cell, or in dead cells that have been broken up.

By contrast, in LIVE-PAINT all the components are made inside the cell, using the cell's own protein production machinery.

"We are particularly pleased that the versatility of LIVE-PAINT and its straightforward implementation means that it will be accessible to many groups, not just specialists," says senior author of the study, Dr. Matthew Horrocks at the University of Edinburgh's School of Chemistry.

More information: Curran Oi et al. LIVE-PAINT allows super-

resolution microscopy inside living cells using reversible peptide-protein interactions, *Communications Biology* (2020). DOI: 10.1038/s42003-020-01188-6