Monitoring the dynamics of thousands of protein complexes simultaneously within intact cells

June 8 2018

Protein-protein interactions are at the heart of all cellular functions and biological processes. These interactions are carefully regulated in space and time to meet the cell's requirements and are often disrupted in disease states.

An international study led by Chris Soon Heng Tan at the A*STAR Institute of Molecular and Cell Biology (IMCB) describes a new technique that uses powerful data analytics to infer protein-protein interaction dynamics from the melting behavior of protein complexes inside cells.

Methods to capture snapshots of protein-protein interaction networks in cells have been described before, but as Tan explains, "until now there has been no way of monitoring the dynamics of these protein complexes in a high-throughput and untargeted manner".

Exposing proteins to increasing temperature causes them to precipitate out of solution. Thermal proximity coaggregation (TPCA) is based on the idea that proteins that are part of a stable protein complex will coprecipitate, by virtue of close proximity, and have a similar precipitation profile across different temperatures (or melting curve).

In isolation, different proteins are likely to have different melting curves, but the team showed that in more than 350 well-characterized

human protein complexes, the melting curves of interacting proteins are statistically similar. Thus, by quantifying similarity between melting curves, the TPCA method can be used to determine which proteins are likely to interact with each other and form stable complexes across different samples.

"We were quite surprised that the TPCA signatures were so strong and detectable," admits Tan. TPCA signatures were found to correlate with the amount of interaction between two proteins. Accordingly, they show that some complexes change their melting curves depending on the cell type or cell cycle stage, suggesting that TPCA could be used to identify changes in protein interactions under different conditions.

When explaining the advantages of TPCA, Tan says that when compared with current methods, TPCA does not rely on the availability of appropriate affinity reagents, such as antibodies, nor does it require genetic engineering. This allows it to be applied to tissues and clinical samples to identify protein complexes that are driving disease progression and that could serve as potential prognosis markers or therapeutic targets.

The team is already using the technique to study the molecular effects of drugs and synthetic chemicals, and plans to extend the technique to study the progression of selected human diseases.

More information: Chris Soon Heng Tan et al. Thermal proximity coaggregation for system-wide profiling of protein complex dynamics in cells, *Science* (2018). DOI: 10.1126/science.aan0346

Provided by Agency for Science, Technology and Research (A*STAR), Singapore