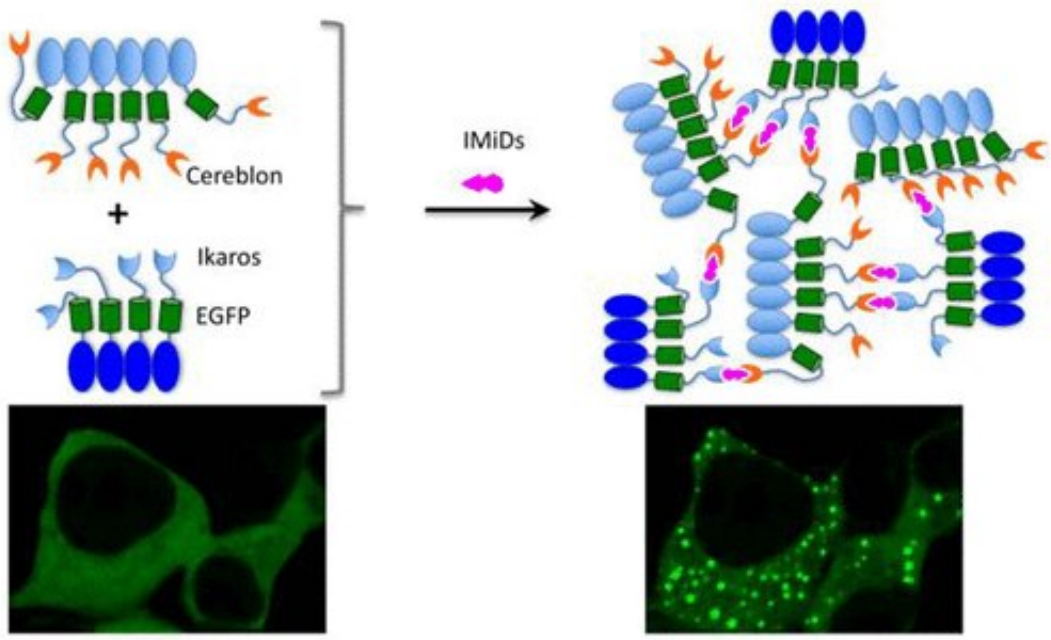
Seeing small-molecule interactions inside cells

December 12 2018



Credit: American Chemical Society

Like people in a large company, proteins in cells constantly interact with each other to perform various jobs. To develop new disease therapies, researchers are trying to control these interactions with small-molecule drugs that cause specific proteins to associate more or less with their "coworkers." Now, researchers reporting in ACS' journal *Analytical Chemistry* have developed a method to visualize whether drugs are regulating protein-protein interactions inside cells.

The ability to control interactions among proteins could be a powerful tool to treat disease. For example, a small-molecule drug called lenalidomide is used to treat multiple myeloma. It binds simultaneously to two proteins—cereblon and Ikaros—that normally wouldn't interact, bringing them together to disrupt cancer cell function. Scientists have developed several fluorescence-based assays to study such activity, but they often rely on small changes in fluorescence that can be difficult to detect in living cells. Xiaokun Shu and colleagues wondered if they could devise a new method that would produce a strong, readily observable fluorescent signal when small molecules cause proteins to interact in cells.

To develop their assay, the researchers made use of the known interactions among lenalidomide, cereblon and Ikaros. They genetically engineered human cells to produce cereblon and Ikaros, each with an attached green fluorescent protein (GFP). They also added sequences to the proteins that would cause four or six copies of each protein to associate together. This way, when cereblon and Ikaros did interact with each other, the GFP signal would be greatly amplified. In the absence of lenalidomide, the cells showed a faint, diffuse green fluorescence. However, when the team added lenalidomide to the cells, thousands of GFP-containing proteins coalesced into highly concentrated bright green droplets. And by tweaking the system, the researchers could detect when a small molecule disrupted the interaction between two other proteins by observing the disappearance of intense fluorescent spots. The ability to readily detect these interactions in cells could aid drug screening, the researchers say.

More information: Chan-I Chung et al. Dynamic Imaging of Small Molecule Induced Protein–Protein Interactions in Living Cells with a Fluorophore Phase Transition Based Approach, *Analytical Chemistry* (2018). DOI: 10.1021/acs.analchem.8b03476

Provided by American Chemical Society