

Using light as a superglue for proteins and their binding partners

Most of what happens in a cell involves fleeting interactions between proteins. Molecules briefly dock onto each other, change each other's chemistry, and then separate again. While these encounters are crucial to the health of cells, they often happen so quickly that they go unseen. In many cases, it is not clear which proteins carry out a particular process, which makes it almost impossible to study their influence on cell biology. Jörg Rademann's groups in the Medicinal Chemistry Program at the FMP and at the University of Leipzig have now found a partial solution. The scientists have built protein *ligands* that can be permanently glued to their target proteins in a reaction that is triggered by light. The lab's work appears in the International Edition of *Angewandte Chemie* (2012, 51, 9441-9447).

"Chemists and biologists have been developing probes that can be activated by light for many years," Rademann says. "These are very useful tools to study a reaction or biological process. You can precisely control when it occurs, because the reaction only takes place when you expose the molecules to particular wavelengths of light." In the past such light switches, however, have not recognized precise target proteins. This has strongly limited research into specific interactions between molecules.

In the current study, the scientists take this basic principle to a new level. The aim was to develop a novel type of molecular switch that specific proteins recognize and can be activated by light. This concept was applied to get a better handle on a type of cellular signaling called *tyrosine phosphorylation*, which is frequently disrupted during cancer and other diseases. This process loads proteins with *phosphate groups*, usually changes the molecule's architecture and activating it. This means that it recognizes new binding partners, docks onto them, and loads them in turn with the phosphates, causing new chemical reactions.

Tyrosines are one of the amino acids – building blocks of proteins – whose chemical structure permits such loading. Such *phospho-tyrosines* are often found in the active sites of molecules, creating where other proteins dock on to trigger reactions.

Rademann and his colleagues have now discovered that an artificial chemical structure called *benzoylphosphonate* is recognized by proteins just like a natural phosphotyrosine. Exposing these benzoylphosphonates to light activates them and makes them behave like a sharp hook which can snag anything in the immediate neighborhood. If this happens while another protein is attached to the benzoylphosphonate, the reaction acts like a "superglue" that permanently sticks the molecules together.

"The first benefit of this process is that we can switch off the biological activity of the target molecule by this process," Rademann says. "Additionally, we can extract the bound molecules from the test tube and analyze the components.

This means we can identify new binding partners, even when the interactions happen very rapidly."

So far the experiments have been carried out in the test tube, where the modified proteins are exposed to molecules extracted from cells. But Rademann is hopeful that proteins modified with the benzoylphosphonates can also work with entire cells. If so, scientists will have an even more powerful tool to investigate a type of cellular signaling that lies at the heart of cancer and other serious human diseases.