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Molecular ticket to enter the cell

In the recent Nature Cell Biology report (2006; 8:163-169) scientists at the Institute of Biochemistry II, Goethe University Medical School and their collaborators have described a novel mechanism controlling intracellular trafficking of transmembrane receptors. When the cell is stimulated with a growth factor or an antibody the receptors are removed from the cell surface and sorted via a network of luminar vesicles into either the degradative compartment known as lysosome or they are recycled back to the cell membrane where they become again accessible to stimulation by extracellular factors. Keeping the right balance between these two pathways is of great importance to ensure proper functioning to the cell.

Many of the processes responsible for this balance are regulated by the attachment of a small protein modifier ubiquitin, which acts as a molecular signature for receptor sorting to the lysosome. A class of protein, called adaptors, which are able to temporarily bind to ubiquitin attached to the receptors are crucial in the sorting process. However, in this report Dikic and colleagues have shown that these proteins are also themselves monoubiquitinated and that an intramolecular interaction between monoubiquitin and the ubiquitin-binding domain of the adaptors inhibits their ability to bind and direct trafficking of ubiquitinated cargo.

By combining experimental, mathematical and bioinformatical approaches, the scientists were able to describe the behaviour of ubiquitinated adaptor proteins in detail.

“It was intriguing to see how efficient this auto-inhibition functioned. By attaching ubiquitin to different kinds of adaptor proteins we were able to block their activity by nearly 100%. It will be very important now to understand how the ubiquitination status of these proteins can be modulated in cells since this could be the key to control diverse cellular processes for example in tumor cells” says Daniela Hoeller, the first author on this report.

The scientists were quite surprised to find that the described mechanism was applicable to all tested Ub-binding proteins including proteins like DNA polymerases that are completely unrelated to protein trafficking. “This indicates a broader and more general importance of ubiquitin signaling in regulation of cell functions. Detailed understanding of these principles may help in explaining the action of several modern therapeutics such as monoclonal antibiodies,” explains Ivan Dikic, a senior author on this study and Professor of the Institute of Biochemistry II.

“This study marks a major breakthrough in our understanding of the fine-tuning of ubiquitin-dependent pathways and represents a fine example of nature´s efforts to keep this powerful effector system in check”, adds Werner Müller-Esterl, Professor of Biochemistry and Director of the Institute of Biochemistry II. “It will open novel avenues for target identification and development of interfering drugs”.

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