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New Doctorial Cancer Research

Hrs Makes Receptors Silent: A Key to Endosomal Protein Sorting

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The human body makes use of several control mechanisms to prevent cancer. Raiborg's thesis work reveals detailed molecular insight into one of these processes, receptor downregulation. After a growth factor receptor has received a growth stimulatory signal, the activated receptor and its ligand are taken up into cells by endocytosis and transported via endosomes to lysosomes for degradation. The activated growth factor receptors that are destined for degradation are labeled with a molecular tag, ubiquitin. By degrading the receptor and its growth factor, the cell can assure that the receptor is silenced. This is important to prevent uncontrolled signaling. In contrast to activated growth factor receptors, endocytosed nutrient receptors are recycled back to the cell surface for reuse. The fate of the receptors is settled at the level of early endosomes, which act as the main sorting stations in the endocytic pathway. A long-standing question in this field has been how the cell is able to sort the receptors in different directions from the endosome.

The hepatocyte growth factor regulated tyrosine kinase substrate, Hrs, is a protein that is localized to the cytosolic face of early endosomes. During the project period (1999–2004), we have defined the domains of Hrs that are responsible for its endosomal targeting. Furthermore, we have identified a functional clathrin-binding domain in Hrs and found that Hrs is responsible for the recruitment of this coat protein to endosomes. Moreover, we have shown that Hrs, which acts in an endosomal protein complex, can bind to ubiquitin, and functions in the sorting of ubiquitinated membrane proteins into clathrin-coated microdomains on endosomes. This seems to be a crucial step in the targeting of activated receptors for degradation in lysosomes, and cells depleted of Hrs do not degrade the receptors properly. Thus, Hrs makes receptors silent. These findings provide novel insight into the molecular mechanisms of receptor downregulation. By recognizing ubiquitinated growth factor receptors, recruiting a clathrin coat, and engaging other players in the sorting machinery, Hrs serves as a key to endosomal protein sorting.

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The dissertation focuses on a central theme in cell biology, the sorting of endocytosed proteins. The common denominator in the thesis is the Hrs; and during the

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project several components were shown to cooperate with Hrs in the sorting process: clathrin, STAM, Eps15, AIP4, etc. The work is well planned, and the methods used are excellent and always up to date and adapted to the problems investigated. The results presented in the five articles give novel, solid, and detailed information about molecular mechanisms involved in sorting and targeting of endocytosed proteins. The dissertation is a major contribution to novel insight into receptor downregulation.