Literatur-Seminar Signaltransduktion:

5. „Inaktivierung von Rezeptor-Tyrosinkinasen durch Ubiquitinierung, Internalisierung und Degradation“

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Mutation of the c-Cbl TKB domain binding site on the Met receptor tyrosine kinase converts it into a transforming protein.

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The c-Cbl protooncogene is a negative regulator for several receptor tyrosine kinases (RTKs) through its ability to promote their polyubiquitination. Hence, uncoupling c-Cbl from RTKs may lead to their deregulation. In testing this, we show that c-Cbl promotes ubiquitination of the Met RTK. This requires the c-Cbl tyrosine kinase binding (TKB) domain and a juxtamembrane tyrosine residue on Met. This tyrosine provides a direct binding site for the c-Cbl TKB domain, and is absent in the rearranged oncogenic Tpr-Met variant. A Met receptor, where the juxtamembrane tyrosine is replaced by phenylalanine, is not ubiquitinated and has transforming activity in fibroblast and epithelial cells. We propose the uncoupling of c-Cbl from RTKs as a mechanism contributing to their oncogenic activation.

Cbl: many adaptations to regulate protein tyrosine kinases.

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Responses to extracellular stimuli are often transduced from cell-surface receptors to protein tyrosine kinases which, when activated, initiate the formation of protein complexes that transmit signals throughout the cell. A prominent component of these complexes is the product of the proto-oncogene c-Cbl, which specifically targets activated protein tyrosine kinases and regulates their signalling. How, then, does this multidomain protein shape the responses generated by these signalling complexes?

Molecular ticket to enter cells

Shlomo Oved and Yosef Yarden.

Just as important as starting cellular signalling pathways is switching them off again. It seems that the Cbl protein has a dual function in accelerating the degradation of certain signalling molecules.