Ectodomain shedding of epidermal growth factor receptor by cysteine cathepsins

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Cysteine cathepsins are lysosomal proteases, also known to be secreted to the extracellular space. Secreted cysteine cathepsins can cleave ectodomains of membrane proteins including receptors, growth factors, cytokines, and adhesion proteins. Among the receptors, the epidermal growth factor receptor (EGFR) was identified as a cysteine cathepsin substrate candidate with high physiological relevance. EGFR belongs to the ErbB family of receptor tyrosine kinases and plays an important role in cell differentiation, migration, proliferation, and metabolism. This receptor is found to be overexpressed in many cancers, showed to be consequently more aggressive and resistant to chemotherapeutics. Signaling through EGFR is commonly triggered by ligand binding, however, deletions in the extracellular region of EGFR can also cause ligand-independent constitutive activation.

Using mass spectrometry-based proteomics, we determined that extracellular cysteine cathepsin L cleaves domain II of EGFR. Moreover, our results revealed that this ectodomain truncation activated the receptor and changed the phosphorylation profile of cellular kinases. By phosphoproteomic analysis, we were able to identify and quantify significant differences in cellular phosphorylation in cells expressing truncated EGFR. Significant pathways suggest that expression of truncated EGFR causes changes in mitogen-activated protein kinases (MAPK) pathway, connected with cell cycle and proliferation, and changes in RNA metabolism.

Since EGFR is one of the important anticancer drug targets, our finding could lead to a better understanding of EGFR and possibly to more effective strategies in anticancer therapy. Additionally, our results confirm the increasingly recognized important role of extracellular cysteine cathepsins in cancer.