





Role of the NEU3 sialidase in colorectal cancer EGFR-targeted therapies

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The Epidermal Growth Factor receptor (EGFR) pathway plays a pivotal role in colorectal cancer (CRC) pathogenesis, leading to the activation of the MAP kinase signalling, implicated in cellular duplication, and the PI3K-AKT-mTOR axis, which is involved in cell survival. In the absence of ligand, this pathway could be triggered by the membrane-associated NEU3 sialidase, which desialylates EGFR promoting the receptor dimerization and is also found to be overexpressed in CRC. Due to the fact that CRC is the third most frequently diagnosed malignancy and the second leading cause of cancer death in the world, the attention was focused on the introduction of improved diagnostic methods and the adoption of newer targeted therapies, such as the development of monoclonal antibodies. Among them cetuximab binds the extracellular domain of EGFR, inhibiting its downstream signalling. However alterations in this pathway cause a negative response to cetuximab; in order to better understand the mechanisms of pharmacological resistance we investigated the role of NEU3 in cetuximab EGFR-specific therapy.

To this end we evaluated the sensitivity to cetuximab of CCD841 healthy cell line and CACO-2, E705, DIFI and MICOL24 tumor cell lines, showing that only the E705, DIFI and MICOL24 lines are sensitive. Further analysis on cell viability, conducted in the presence of NEU3 overexpression and cetuximab, revealed a drug efficacy implementation only in CACO-2 cell line.

EGFR pathway analysis in the presence of NEU3 and/or cetuximab showed no effect on the healthy cell line; while on the tumor cell lines the pharmacological treatment reduced P-EGFR, P-AKT and P-ERK levels and NEU3 overexpression enhanced P-ERK levels and reduced the phosphorylation of AKT.

Taken together these results confirm NEU3 role of promoting cell proliferation in CRC cell lines by hyperactivation of the EGFR pathway. Furthermore, a combination of NEU3 sialidase with cetuximab unexpectedly seems to increase the therapy's efficacy in CACO-2 resistant cell line, carrying out an antitumor action.

