Innovative drug delivery system using EGFR-targeted engineered peptides in anaplastic thyroid cancer treatment

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Abstract: Anaplastic thyroid carcinoma (ATC) represents the most aggressive and deadliest thyroid cancer in humans. Mostly affected signaling pathways in ATC are those of MAP kinase and PIP3/AKT/mTOR. The median survival of patients with ATC is of about 4 months after diagnosis. Currently, there is no cure for this cancer. The targeted therapy developed in the present work aims to inhibit the PI3K/AKT/mTOR signaling pathway, thereby inducing apoptosis of cancer cells with a therapeutic peptide (TP) developed in our laboratory. The epidermal growth factor receptor (EGFR) is commonly studied in oncology as it is overexpressed in cancer cells and is actively investigated in the framework of receptor-mediated drug delivery. The EGFR has been associated for years with worse prognosis.

Therefore, an EGFR-targeted peptide (vector peptide, VP) was developed by our group and coupled to TP in a peptide complex (PC) to enable the specific drug delivery to ATC cells. The molecular mechanism of binding of our PV to EGFR has been analyzed *in silico* by peptide-protein docking studies using the HPEPDOCK web server. VP has a long half-life and binds to the interface between domains I and III of EGFR, in the large hydrophobic pocket exposing the binding sites to EGF. VP is endocytosed independently of the EGF presence and without activating the EGFR. Within cells, VP is colocalized with EGFR, following its trafficking pathway. Moreover, 10 µM of PC induces cell apoptosis after 1h of incubation. To conclude, our studies confirmed that VP is a good EGFR-targeting candidate to deliver TP to cancer cells.