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| **A study of combined targeted therapy and delivery, inducing an inhibition of PI3K/AKT/mTOR pathway in anaplastic thyroid cancer cells**  Zehra-Cagla Kahvecioglu1,2, Ami Toulehohoun1, Danièle Feudjio Tagny1, Charlotte Rogien1, Samuel Vandecasteele1, Fabrice Journé2, Sophie Laurent1,3, Sven Saussez2, Carmen Burtea1  ZEHRACAGLA.KAHVECIOGLU@umons.ac.be  1 Department of General, Organic and Biomedical Chemistry, NMR and Molecular Imaging Laboratory, Faculty of Medicine and Pharmacy, University of Mons;  2 Department of Human Anatomy and Experimental Oncology, Faculty of Medicine and Pharmacy, University of Mons;  3 Center for Microscopy and Molecular Imaging (CMMI), Faculty of Medicine and Pharmacy, University of Mons |
| 1. Background: Although rare, the anaplastic thyroid carcinoma (ATC) is the most advanced and aggressive kind of TC, presenting a median survival rate of 2 - 6 months after diagnosis. The current treatment consists of combining surgery with ionizing radiation and chemotherapy. Novel therapeutic strategies are explored and are aimed to limit the systemic undesirable effects. In this context, the EGFR and PI3K/Akt/mTOR pathway represent potent targets for improved delivery and pharmacological action of chemotherapeutic agents. 2. Aim: Our strategy consists of bringing a PIP3-targeted therapeutic peptide (TP) directly into the TC cells thanks to a vector peptide (VP) targeted to EGFR. The TP and VP peptides were identified using the phage display technology. 3. Methods and Results: The dissociation constant (Kd) of the selected VP was evaluated to confirm its specific affinity toward EGFR. EGFR overexpression and overactivation in ATC were explored on anaplastic (8505C; Cal62) and healthy (Nthy-ori 3-1) TC cell lines.   We evaluated by ELISA and confirmed by Western Blot (WB) the effect of TP on PI3K/AKT/mTOR pathway by assaying pan and phosphorylated AKT. The protein Bad (Bcl2 family), which is part of the AKT signalling cascade, was evaluated by cellular ELISA. Bad is a pro-apoptotic protein whose inactivation promotes cell survival in cancer cells. Aiming to evaluate the therapeutic efficacy of these peptides, apoptotic cell death was demonstrated by the immunofluorescent detection of activated caspase 3 on ATC cells. Apoptosis was also studied by flow cytometry, designed to detect phosphatidylserine on the external leaflet of the plasma membrane of apoptotic cells.   1. Conclusion: The peptide complex appears as a promising targeted therapy since the mortality rate was of 100% and the labelling was more localized implying that the VP delivers TP directly into the ATC cells. Our findings need to be validated *in vivo*. |