A nanomedicine approach for treatment of glioblastoma

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Glioblastoma multiforme (GBM) is the most common, aggressive and lethal primary brain tumor in humans. Recurrence is unavoidable and fatal, with only a few patients (less than 5 %) surviving beyond 5 years [1]. The radio- and chemo- resistance of GBM stem-like cells (GSCs) together with their innate tumor-initiating aptitude, make this cell populatiion a crucial target for the design of effective therapeutic strategies. Due to the infiltrative nature of GBM and the presence of the Blood-Brain Barrier (BBB), reaching GSC niches dispersed into the brain parenchyma is hardly difficult and complex. Using multifunctional liposomes as carriers for doxorubicin, we provide the proof of concept for an innovative strategy able to improve BBB crossing and to ensure GSCs targeting. Liposomes, composed of sphingomyelin and cholesterol (1:1 molar ratio) and embedding doxorubicin, were functionalized with a modified fragment of human Apolipoprotein E (mApoE, CWGLRKLRKRLLR) as a BBB ligand [2], and with Chlorotoxin (CTX), a scorpion-derived toxin with a tumor binding activity [3], for the GBM cell targeting. The in vivo results on healthy mice indicate that DOXO encapsulation into liposomes allows drug crossing of the BBB and enhances its accumulation into the brain. Moreover, in vitro experiments using a BBB cellular model indicate that encapsulated-DOXO preserves endothelial cells viability while retaining, after BBB crossing, a significant cytotoxic activity against GBM cells. Experiments with different GBM cell lines, stem lines included, showed that cell targeting and uptake are sustained by receptor-mediated endocytosis involving the Low Density Lipoprotein Receptor and that the presence of CTX improve the GBM targeting, reducing also the cell migration. Thus, these multifunctional liposomes can be proposed as promising drug nanocarrier for GBM treatment.

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Acknowledgments. This work was supported by a grant from the European Centre for Nanomedicine (CEN Foundation) to Prof. Michela Matteoli.