Receptor surface decoration improves the anticancer activity of cannabinoid-loaded nanoparticles through delayed cell internalization

Matilde Durán-Lobato
Josefa Álvarez-Fuentes, Mercedes Fernández-Arévalo, Lucía Martín-Banderas
Dpto. Farmacia y Tecnología Farmacéutica, Facultad de Farmacia. Universidad de Sevilla. C/Prof. García González nº2 41012, Sevilla, España
mduran@us.es

Δ^9-tetrahydrocannabinol (Δ^9-THC) is known for its antitumor activity and palliative effects [1, 2]. However, its unfavorable physicochemical and biopharmaceutical properties, including psychotropic side effects due to unspecific biodistribution and resistance mechanisms associated to dosing, make mandatory the development of successful drug delivery systems [1, 2]. Hence, our team previously developed Δ^9-THC-loaded poly(lactide-co-glycolic) nanoparticles (THC-PLGA NPs) [3]. Subsequently, Tf surface-modified THC-PLGA NPs (Tf-THC-PLGA NPs) were designed and evaluated as a novel THC-based anticancer therapy with the aim of optimizing the interaction of THC-PLGA NPs with cancer cells. In addition, to assess the interaction and expected fate of both the nanocarrier and the loaded drug following exposure to the cells, a double-fluorescent strategy was applied, consisting of both the chemical conjugation of a dye to the nanoparticle polymer and the encapsulation of either a lipophilic or a hydrophilic dye. The interaction of the resulting nanocarriers with Caco-2 cells, a cancer cell model bearing both cannabinoid and transferrin receptors, was evaluated. Upon incubation with the cells, both plain THC PLGA NPs and Tf-THC PLGA NPs avoided moderate cell viability increases exerted by free THC at short incubation times, which have been associated in the literature to drug resistance mechanisms. Furthermore, Tf-THC PLGA NPs exerted higher and faster cancer cell death compared to plain nanoparticles (cell viability decrease down to 17% vs. 88). However, their internalization was significantly slower than plain nanoparticles. Uptake studies in the presence of inhibitors indicated that the nanoparticles were internalized through cholesterol-associated and clathrin-mediated mechanisms. Overall, the observations suggested that the improved Δ^9-THC antitumor effect was potentially due to increasing the presence of the nanocarriers, and hence maximizing the amount of drug locally released, at the surface of cells bearing cannabinoid receptors, instead of improving internalization. The results obtained highlight the promising potential of Δ^9-THC-loaded nanocarrier-based antitumor therapies, as well as exploring further strategies aimed at modulating the nanocarrier action at the cell surface.

REFERENCES

[1] G. Velasco, C. Sánchez, M. Guzmán, Towards the use of cannabinoids as antitumour agents, Nat. Rev. Cancer. 12 (2012) 436–444
[2] G. Velasco, C. Sánchez, M. Guzmán, Anticancer mechanisms of cannabinoids, Curr. Oncol. 23 (2016) S23–S32
[3] L. Martín-Banderas, I. Muñoz-Rubio, J. Prados, J. Álvarez-Fuentes, J.M. Calderón-Montaño, M. López-Lázaro, J.L. Arias, M.C. Leiva, M.A. Holgado, M. Fernández-Arévalo, In vitro and in vivo evaluation of Δ9-tetrahidrocannabinol/PLGA nanoparticles for cancer chemotherapy, Int. J. Pharm. 487 (2015) 205–212