Press Release

Polymeric Nanomicelles Improve Internalization of Lipid Metabolism Modulators in Brain Cells

Summary:

Fatty acid (FA) metabolism is the critical link between obesity and cancer progression, making it an attractive target for the central appetite regulation for obesity and glioblastoma therapy. (±)-C75-CoA and its enantiomers are effective modulators of FA metabolism but are anionic and have low cellular permeability. We thus developed charge-neutralizing poly-ion complex (PIC) nanomicelles to efficiently deliver such molecules into glioma cells and neurons in 2D and 3D cultures.

https://pubs.rsc.org/en/Content/ArticleLanding/2021/BM/D1BM00689D

August 3, 2021, Kawasaki (Japan) and Barcelona (Spain): Innovation Center of NanoMedicine (Director General: Prof. Kazunori Kataoka, Abbreviation: iCONM) and the Basic Sciences Department, Faculty of Medicine and Health Sciences of the International University of Catalunya (Abbreviation: UIC Barcelona) jointly announced that a research paper “Poly-ion complex micelle effectively delivers CoA-conjugated CPT1A inhibitors to modulate lipid metabolism in brain cells” was published on July 27 in Biomaterials Science (Impact Factor: 6.843 in 2021). This paper was accomplished by the joint project between iCONM and UIC Barcelona led by Dr. Sabina Quader (Senior Research Scientist, iCONM) and Dr. Rosalía Rodríguez (Associate Professor, Department of Basic Sciences, Faculty of Medicine and Health Sciences, UIC Barcelona) to report that PIC micelles carrying CPT1A inhibitors can effectively ferry their drug cargoes inside brain cells such as neurons and glioma cells, leading to reduced fatty acid oxidation (FAO). Several researchers from the University of Barcelona (Barcelona, Spain) also participated in this research project.

Recent evidences suggest that FA metabolism serves as the critical link between obesity and cancer progression. FAs are important substrates for energy metabolism and are the building blocks for lipids. It is becoming increasingly apparent that intermediary lipid metabolism within the brain is a major contributor to the regulation of systemic metabolism. Lipid metabolism within the brain is tightly regulated to maintain neuronal structure and

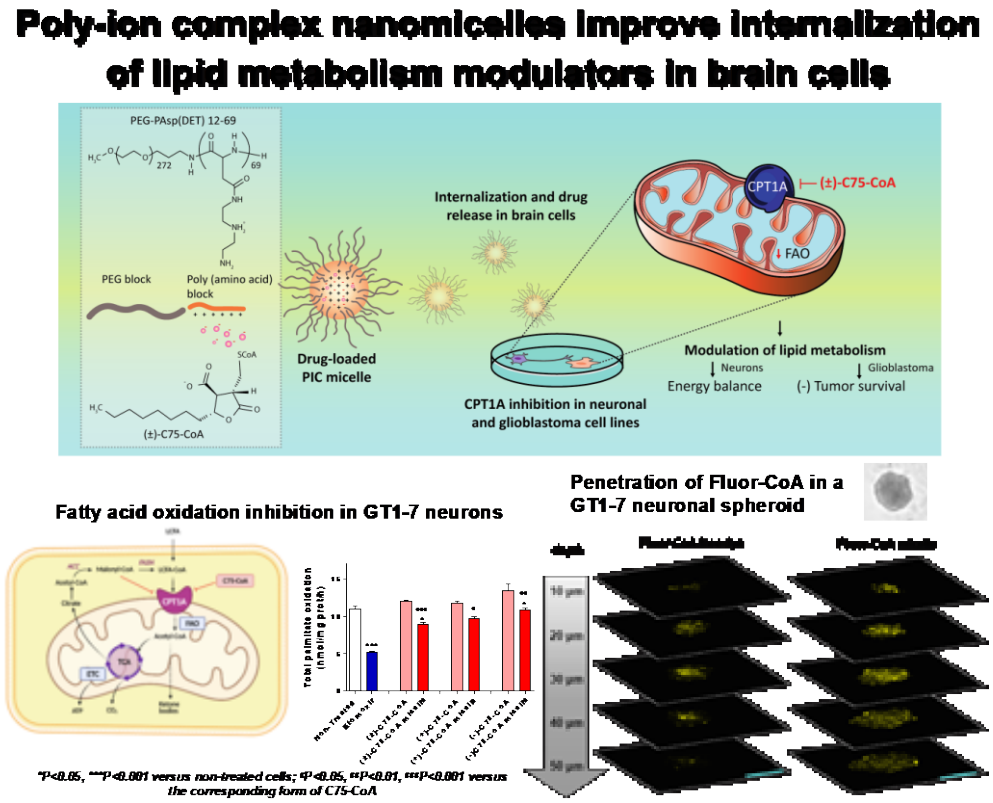
function to modulate peripheral tissues. Central levels of malonyl-CoA act as a molecular messenger of nutritional status. Therefore, pharmacological manipulation of malonyl-CoA levels in the brain, results in changes in food intake and energy expenditure. In addition, many types of tumor cells, including glioma cells, show alterations in FA metabolism. Glioblastoma (GBM), in particular, has been connected with increased expression of CPT1. While tumor molecular heterogeneity is emerging as a critical concern in oncology, homogeneous elevated expression of CPT1 in GBM is indeed an attractive molecular target for therapy. Accordingly, FA metabolism in the brain is an attractive target for the central regulation of obesity and glioblastoma therapy.

In this paper, poly-ion complex (PIC) nanomicelles loaded with the CPT1A inhibitors (±)-, (+)-, and (–)-C75-CoA have been developed. The CoA adducts' chemical structure presents challenges to cellular entry, being small, polar, and charged metabolites. They have low permeability across the cell membrane, and as a consequence, need a delivery system for intracellular transport. The anionic state of CoA, together with its long aliphatic side-chain enables CoA to interact with cation-conjugated polymers through a combination of electrostatic and hydrophobic interactions. Therefore, forming a poly-ion complex (PIC) micelle with racemic C75-CoA or its enantiomers is a sound approach in designing a delivery system since this neutralizes the overall negative charge that would hinder its cellular entry.

The cationic block-copolymer PEG-PAsp (DET) provided a platform by neutralizing the negative charge of the cargo molecules, generating micelles with optimal physicochemical properties (55-65 nm size range). Through targeting CPT1A, fatty acid oxidation (FAO) was effectively inhibited in both U87MG glioma cells and GT1-7 hypothalamic neurons, which led to overall decreased metabolism of radioactively-labeled palmitate into CO2 and acid-soluble products. The final product of FA metabolism, ATP, was also effectually reduced by the micelles up to 5-fold, in comparison with the free drug counterparts.

The dye-loaded model particle, Fluor-CoA micelle, showed a statistically increased internalization in both brain cells. This higher cellular internalization corroborated the FAO inhibition results, that delivery through PIC micelle resulted in increased cellular concentration of the cargo, which further led to increased biological activity. Effective cellular entry of Fluor-CoA micelle was further confirmed in 3D spheroids, especially in neurons where uptake reached up to 3-fold over the free dye, inferring the superior activity of CoA adducts when loaded in micelles in a biological model that is transitional in complexity between standard 2D in vitro and diseased tissue in vivo. The size range of these PIC micelles, combined with their efficient penetration in 3D spheroids, imply that this platform is ideal in navigating through the brain parenchyma. This justifies additional exploration of its in vivo properties in subsequent works and further development into effective brain therapeutics, especially those that involve the delivery of CPT1A inhibitors and other

negatively-charged molecules for management of diseases where modulating lipid metabolism is a key emerging strategy.



Key points of this press release:

1. Carnitine palmitoyltransferase 1A (CPT1A) is a central player in lipid metabolism, catalyzing the first committed step to fatty acid oxidation (FAO). Inhibiting CPT1A, especially in the brain, can have several pharmacological benefits, such as in obesity and brain cancer.
2. C75-CoA is a strong competitive inhibitor to CPT1A. However, due to its negatively-charged nature, it has low cellular permeability.
3. PIC nanomicelles were formed through charge-neutralization of C75-CoA with the cationic side chain of PEG-Pasp (DET), forming particles with 55 to 65-nm diameter
4. Nanomicelle-entrapped CPT1A inhibitors resulted in up to 5-fold reduction of ATP synthesis compared to the free drug. Nanomicelle treatment showed a marked decrease in 14C-palmitate oxidation into CO_2 and acid-soluble metabolites.
5. To measure cellular uptake of these CoA-adduct loaded PIC nanomicelles, we synthesized a fluorescent CoA derivative and prepared Fluor-CoA nanomicelle, which showed efficient internalization in brain cells, both in 2D and 3D culture models, especially in neurons where uptake reached up to 3-fold over the free dye.
6. This press release is about the first academic paper by the CPT Obesity Cancer Drug Delivery (COnCorD) project for the treatment of obesity and cancer, which is being jointly

promoted by iCONM and UIC Barcelona. See the following site to find this original paper:

W. K. D. Paraiso, J. Garcia-Chica, X. Ariza, S. Zagmutt, S. Fukushima, J. Garcia Gomez, Y. Mochida, D. Serra, L. Herrero, H. Kinoh, N. Casals, K. Kataoka, R. Rodriguez-Rodriguez and S. Quader, Biomater. Sci., 2021.
DOI: 10.1039/D1BM00689D.

Kawasaki Institute of Industrial Promotion (KIIP)

Kawasaki Institute of Industrial Promotion was established in 1988 funded 100% from Kawasaki City for the purpose of coping with the hollowing out of industry and changes in the demand structure. In order to realize a higher level of market development, transforming R&D type companies, training technological capabilities to support it, human resources development, understanding market needs, etc., by utilizing the functions of the Kawasaki, KIIP has been contributing to revitalize the local economy by promoting exchanges of local industry information, advancing technology and corporate exchanges with establishment of a R&D institutions, developing creative human resources through workshops and promoting businesses such as expanding sales channels through exhibition business.
https://www.kawasaki-net.ne.jp/

Innovation Center of NanoMedicine (iCONM)

Innovation Center of NanoMedicine (iCONM) started its operation in April 2015 as a core research center in life science field at King SkyFront on the request of Kawasaki city that KIIP utilized national policies as a business operator and proposer. It is a unique research center that the world has ever seen which is designed for the purpose of promoting open innovation through industry-academia-government/medical-engineering collaboration, prepared with state-of-the-art facilities and experimental equipment, that enables comprehensive research and development from organic synthesis / microfabrication to preclinical testing.
iCONM: https://iconm.kawasaki-net.ne.jp/en/index.html
Kataoka-Kinoh Lab: https://iconm.kawasaki-net.ne.jp/en/laboratory_kataoka.html

The International University of Catalunya (UIC Barcelona)

The International University of Catalunya (UIC Barcelona: The Universitat Internacional de Catalunya) was founded in 1997 with the aim of offering outstanding university education and promoting research that benefits society. With strong ties to the world of health, business and a highly international profile, the institution offers 16 bachelor's degrees, 8 double degrees, around 30 international double degrees and a wide range of postgraduate programs across both campuses, located in Barcelona and Sant Cugat del Vallès.
UIC Barcelona: https://www.uic.es/en
R. Rodríguez's Lab: https://www.uic.es/en/research/research/research-groups/health-sciences/grc-

research-group-regulation-lipid-metabolism-0

CPT Obesity Cancer Drug Delivery (COnCorD)

COnCorD was one of the three bilateral projects awarded by the Spanish State Agency for Research (AEI) and the Japan Agency for Medical Research and Development (AMED) as a result of invitation for joint project proposals from early-stage researchers in Japan and Spain in the "Nanomedicine" research area in 2018. The main objective of this project is the development and use of novel nanomedicine-based therapeutic approaches directed to specific cells of the brain and to fight against obesity and brain tumors focusing on the brain lipid metabolism's key enzyme CPT1. This project signifies a tremendous biomedical challenge, principally in the field of nanomedicine, since drug delivery into specific brain cells has not yet been thoroughly investigated. This bilateral endeavor enables boosting collaboration between institutions in the two countries and significantly strengthens the international nature of research at the Innovation Center of Nanomedicine (iCONM), Japan and UIC Barcelona, Spain.