TRPM8 channel-functionalized halloysite nanotubes to target tumor vascularization

TRPM8 CHANNEL-FUNCTIONALIZED HALLOYSITE NANOTUBES

TO TARGET TUMOR VASCULARIZATION

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Cancer growth and metastasis are strictly dependent on tumor angiogenesis, which is promoted by tumour cells upon secretion of a number of growth factors. Vessel formation is a complex multistep process during which 'activated' endothelial cells (ECs), the first mechanical and functional interface between blood and tissues, proliferate, migrate, differentiate and are stabilized in a new circulatory network. Being involved in nearly all of the 'hallmarks of cancer', there is an increasing consensus on the idea that ion channels play a significant role in driving cancer progression at all stages. Accumulating evidence tends to demonstrate that the development of some cancers could also involve such ion channel aberrations. In this context ion channels may be seen as potential novel therapeutic, diagnostic, and prognostic targets for anti-cancer therapies. The discovery of Transient Receptor Potential (TRP) superfamily of channels provided putative candidates for non-voltage-gated Ca2+ entry mechanisms. Notably, several TRP proteins are up regulated in cancer cells and have been suggested as valuable markers in predicting cancer progress and as potential targets for pharmaceutical therapy. In particular, the cold/menthol-sensitive TRPM8 (belonging to the 'melastatin' TRP subfamily) has emerged as an important factor in cell migration and prostate cancer (PCa) progression[1]. TRPM8 channel activation by menthol could be used to induce apoptosis of TRPM8-expressing prostate cancer cells and to inhibit angiogenesis. A great advancement in anti-angiogenic therapy has come from the use of nanotechnology since several nanovectors have been used as drug delivery systems (DDS) to efficiently target and kill tumor-associated vasculature. In this project we pursue a strategy of drug delivery using Halloysite nanotubes (HNTs) functionalized to target tumor angiogenesis in PCa, conjugating these nanomaterials with a selective TRPM8 activator such as menthol. We evaluated the cytotoxic effect of functionalized HNTs on Human Endothelial Microvascular Cells (HMECs) trough cellular toxicity in vitro assay. HNTs were then functionalized with fluoresceine isotiocyanate (FITC) to study their cellular localization and finally we decided to non-covalently functionalize HNTs with menthol through vacuum cycles to selectively activate TRPM8 in HMECs. [2] Consequently, menthol-functionalized HNTs' antiangiogenic role compared to free menthol was tested on HMEC through ECs migration and tubulogenesis in vitro assays. Menthol release was studied by GC-MS and the functionalized nanomaterials were characterized by TGA, SEM and TEM.

[1]Fiorio Pla A., Munaron L. (2014). Functional properties of ion channels and transporters in tumour vascularization. Phil. Trans. R. Soc. B, 369.

[2] Vergaro V., Lvov Y. M., Leporatti S. (2012) Halloysite Clay Nanotubes for Resveratrol Delivery to Cancer Cells. Macromol. Biosci. 12, 1265–1271.