

Exploiting the ability of LinTT1-functionalized liposomes to target cancer cells and TAMs to improve breast cancer therapy

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Nowadays breast cancer is one of the most diagnosed cancer, accounting around 2 million of new cases per years worldwide[1]. The implication of tumor microenvironment (TME) in breast cancer progression is widely established, suggesting that the development of nanomedicine able to target specifically cancer cells as well as cancer associated cells, i.e. tumor associated macrophages (TAMs), could improve the current state of chemotherapies used in clinic.

In these attempts the aim of this work was to realize a targeted nanomedicine by the conjugation of LinTT1 peptide, a ligand of p32 receptor that results aberrantly expressed on cells' surface of both breast cancer cells[2] and TAMs[3]. Liposomes functionalization led to a higher cytotoxic effect of payloads (Doxorubicin and Sorafenib) in comparison with therapeutic bare liposomes on both mono-layer and spheroid breast cancer cellular models. The improved interaction rate of LinTT1-functionalized liposomes than bare liposomes with 3D breast cancer spheroids was also confirmed by flow cytometer and confocal laser scanning microscopy analysis. Furthermore, interaction studies between primary human M2-macrophages and LinTT1 functionalized-liposomes showed that the nanovesicles that interacted with these cells were partially (ca. 50%) internalized while the other half part resulted only strongly associated to the cells' surface. This finding suggests the opportunity to exploit the associated but not internalized nanovesicles and the intrinsic ability of TAMs to accumulate themselves in the tumor core, to enrich the hypoxic area of tumor. These results highlight the potential use of LinTT1-functionalized liposomes as a new targeted nanomedicine in breast cancer therapy.

REFERENCES

1. Bray, F., et al., *Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries*. CA: a cancer journal for clinicians, 2018. **68**(6): p. 394-424.
2. Saha, P. and K. Datta, *Multi-functional, multicompartamental hyaluronan-binding protein 1 (HABP1/p32/gC1qR): implication in cancer progression and metastasis*. Oncotarget, 2018. **9**(12): p. 10784-10807.
3. Fogal, V., et al., *Mitochondrial/cell-surface protein p32/gC1qR as a molecular target in tumor cells and tumor stroma*. Cancer research, 2008. **68**(17): p. 7210-7218.

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