The Therapeutic Effect of Epigenetic Drug-encapsulating-lipid Nanoemulsions for Triple Negative Breast Cancer Cells

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Opportunity
The plasticity of cancer epigenetics make them plausible candidates for therapeutic intervention. Decitabine (DAC) and Panobinostat (PAN) were shown to reverse abnormal methylation of DNA and altered chromatin structure, respectively, leading to the increased expression of tumor suppressor genes. Although DAC and PAN have therapeutic benefits, their use is limited by chemical instability and hydrophobicity to achieve effective therapeutic doses. We took advantage of elevated expression of lysophosphatidic acid receptors (LPARs) in advanced breast cancer tissues to target DAC and PAN to breast cancer cells. Herein, we present LPAR1-targeted lipid nanoemulsions (LNEs) encapsulating both DAC and PAN. Our results showed that the uptake of LNEs was dependent on LPAR1 expression in triple negative breast cancer (TNBC) cell lines. DAC/PAN-LNEs were significantly more cytotoxic to TNBC cells than non-TNBCs. DAC/PAN-LNEs were effective in inhibiting the growth and migration of mesenchymal breast cancer cells that overexpress mFOXM1 by restoring mCDH1/E-cadherin and suppressing mFOXM1 expression while ineffective to epithelial breast cancer cells that inherently express low mFOXM1 and high mCDH1. Overall, we successfully designed LPAR1-targeted LNEs that can selectively suppress mCDH1(low)/mFOXM1(high) TNBC cell lines.

Data or Results
1. LPAR1 and G2A Expression Levels in Different Cell Lines and Uptake of Rho-LNEs presenting LPA and LPC
2. Characterization of LNEs
3. The Effect of LNEs on Cell Viability on Migration
4. Screening of the Methylation Status in the Promoter Regions of MDA-MB-231 after DAC/PAN LNEs Treatment
5. Restoration of CDH1 and Surface E-Cadherin upon DAC/PAN LNEs Treatment
6. Suppression of FOXM1 upon DAC/PAN LNEs Treatment

Impact
In summary, we developed LPAR1-targeted LNEs encapsulating DAC and PAN to selectively induce cytotoxicity to TNBCs. For the first time, we showed that LPAR1-overexpressing TNBCs can be a targeted using LPA-presented LNEs. Nanopackaging improved the stability of DAC, further suppressing the cell growth of MDA-MB-231. DAC/PAN delivery through LNEs restored mCDH1/E-cadherin expression and suppressed the mFOXM1 expression in MDA-MB-231, leading to a decrease in cell migration and cell viability. We also showed that DAC/PAN-LNEs selectively killed mCDH1(low)/mFOXM1(high) aggressive TNBCs. In vivo experiment may be required to further validate the therapeutic efficacy of LPAR1-targeted LNEs encapsulating DAC and PAN. However, our study showed that DAC/PAN treatment using LNEs may be a good alternative to Dox treatment for TNBCs.

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References
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