Anticancer Activity of Anti-cancer Drug-Conjugated Sulfobetaine Polymers against Cancer Cell Spheroids

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Introduction

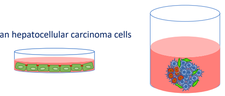
Tumor cell spheroid: as a mimicry of tumor microenvironment in the body

Spheroids

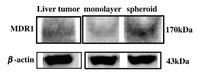
Decreasing concentration of drug, nutrients, and oxygen

The permeation of the substances could be influenced by cell-cell junctions and ECM deposition.

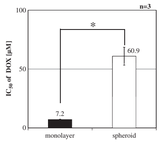
HepG2 in monolayer *vs* in spheroids



Overexpression of transporter such as multidrug resistance 1 (MDR1)



Increased IC_{50} against DOX

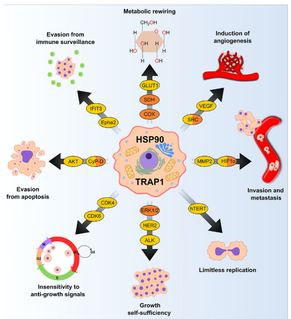


Oshikata *et al. J. Biosci. Bioeng.* **2011**, 111, 590.

Cells in spheroids could gain the function to excrete drugs.

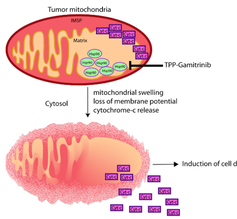
Spheroids have been recognized as a mimicry of in vivo tumor microenvironment and showed us the importance of tumor-permeable drug delivery systems.

Neoplastic Progression vis HSP90



A. Rasola et al, *Front. Oncol.,* 2020

HSP90 inhibition in mitochondria causes cancer cell death



Inhibition of HSP90 by Tanespimycin (17AAG)

Summary

P(SB-PEG) conjugation allows drugs to be effectively delivered to cells in spheroids. The anticancer activity of 17AAG in spheroids was enhanced by the conjugation.

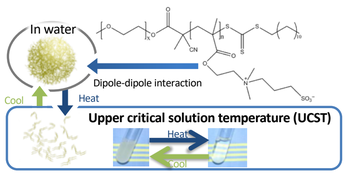
Objective

Cell-cell and/or cell-extracellular matrices interactions seen in spheroids allow cells to mimic in vivo cellular microenvironments, resulting in recapitulating in vivo-like cell functions in culture. However, the microenvironments could also function as a barrier to deliver drugs to cells in spheroids. To tackle this drawback, a sulfobetaine polymer was investigated as a drug delivery system for spheroids by conjugating with anticancer drugs.

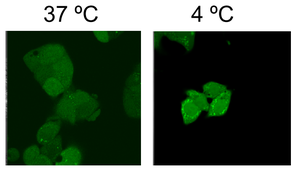
Result & Discussion

Conjugation with P(SB-PEG) allows drugs to be delivered into mitochondria of A-172 cells even in spheroids

Sulfobetaine copolymer



Membrane permeable sulfobetain polymer



Uptaken through non-endocytotic pathways and accumulated into organelles by cooling

Drugs used in this study

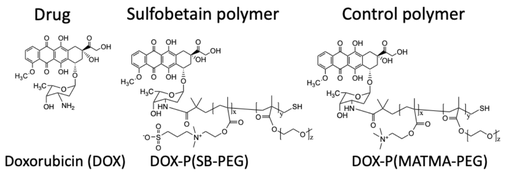
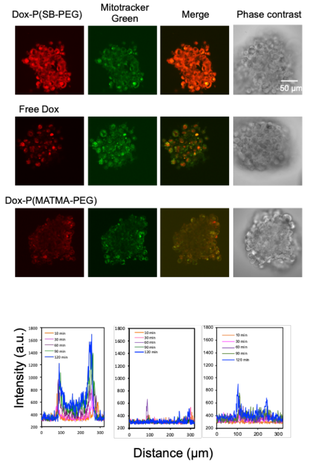


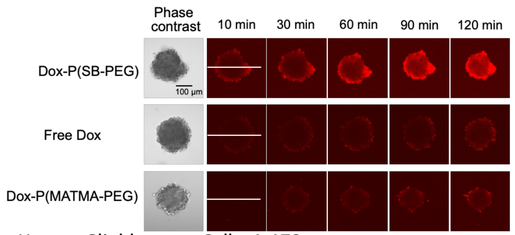
Table 1. Characterization of Drug-Conjugated Polymers

	M_n	M_w/M_n	mol % of PEGMA in copolymer	% modification of drug in the terminus end	hydrodynamic diameter (nm)	ζ-potential (mV)
Dox-P(SB-PEG)	17 000	1.3	2.5	30.2	54.6 ± 2.0	−3.4 ± 1.5
17AAG-P(SB-PEG)	17 000	1.3	2.5	44.0	105.1 ± 5.3	−1.2 ± 3.4
Dox-P(MATMA-PEG)	23 000	1.3	2.6	29.6	13.1 ± 0.3	0.8 ± 0.4

Mitochondrial accumulation in spheroids



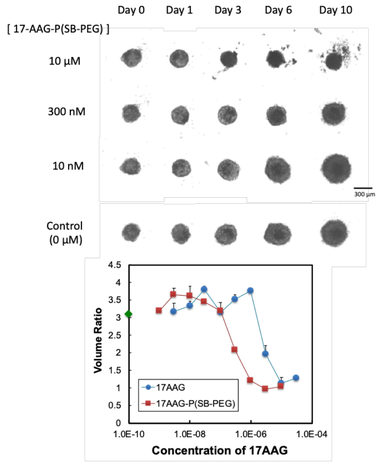
Permeation of the drugs into A-172 spheroids

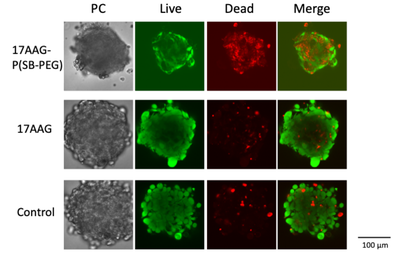


Human Glioblastoma Cells: A-172

Enhanced cell death of 17AAG for A-172 spheroids by conjugating with P(SB-PEG)

Growth suppression

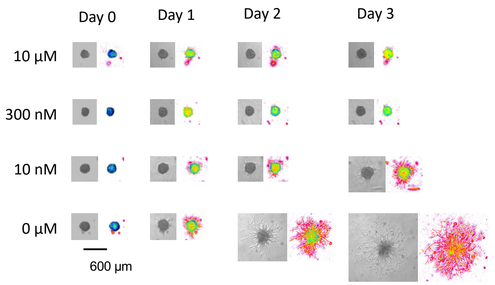


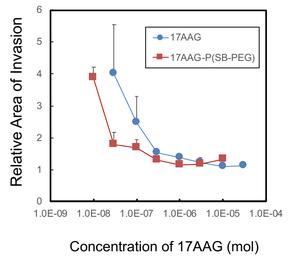


17AAG alone: cell death was observed for cells on the surface of spheroids

17AAG-P(SB-PEG): cell death was observed for cells homogeneously in spheroids

Matrigel invasion suppression





Delivery of 17AAG by conjugation with P(SB-PEG) suppressed the invasion of A-172 cells from spheroids