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Functionalization of a self-assembling peptide with bioactive sequences for 3D culture of cancer cells toward anticancer drug tests

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Tissue-engineered tumor models that mimic the *in vivo* tumor microenvironments have contributed greatly to understanding dynamic tumor development and studies of cancer therapy. Self-assembling peptides can form various nanostructures to provide biomaterials for 3D cell culture and drug delivery. Conventional 2D cancer cell culture systems often poorly present tumor conditions, while 3D cancer cell culture systems can provide tumor tissue models in vitro with a better understanding of the tumor microenvironments.

In this study, a short self-assembling peptide $(FFiK)_2$ was designed to assemble into networked nanofibers in water and form a hydrogel. $(FFiK)_2$ was functionalized with four bioactive sequences, RGDS and PHSRN derived from fibronectin and AG73 and C16 derived from laminin. Functionalized $(FFiK)_2$ hydrogels could be applied to 3D culture of breast cancer MCF-7 cells without significant cytotoxicity. MCF-7 cells proliferated and formed spheroids in the hydrogels that displayed the RGDS, PHSRN, or C16 sequences. On the other hand, MCF-7 cells migrated in a 3D hydrogel that displayed the AG73 sequence, which is helpful for the elucidation of breast cancer cells and drug screening against cancer cells in a metastatic state. The spheroid and metastasis models of MCF-7 cells in peptide hydrogels were used to test the anticancer drug, doxorubicin (DOX). The spheroid model exhibited high resistance to DOX due to up-regulation of P-glycoprotein, a drug efflux pump. On the other hand, the metastasis model was sensitive to DOX. Therefore, functionalized $(FFiK)_2$ hydrogels with various bioactive sequences can be used to regulate cancer cell function for tumor engineering and drug screening in the future.