Core-shell breast cancer models: mimicking the tumor matrix for drug screening

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1 Introduction

Breast cancer is one of the most common cancers globally and a major cause of cancer-related deaths [1]. During tumor progression, the remodeling of the extracellular matrix (ECM) supports cancer cell proliferation and drug resistance. Therefore, developing **biomimetic 3D breast cancer models** that replicate the key features of the tumoral ECM is critical to better study malignancy and predict drug response [2].

The main objective of this study was to fabricate a 3D *in vitro* breast cancer model based on **core-shell** hydrogel beads composed of alginate, gelatin, and collagen I (Col1), with the aim of replicating the mechanical properties and elevated Col1 content of *in vivo* breast tumors, thereby enhancing the model's physiological relevance and translatability.

2 Materials and Methods

Core-shell hydrogel beads were fabricated via extrusion through a coaxial needle (Figure 1), with controlled flow rates of the pre-gels. MCF-7 cells were encapsulated within the core.

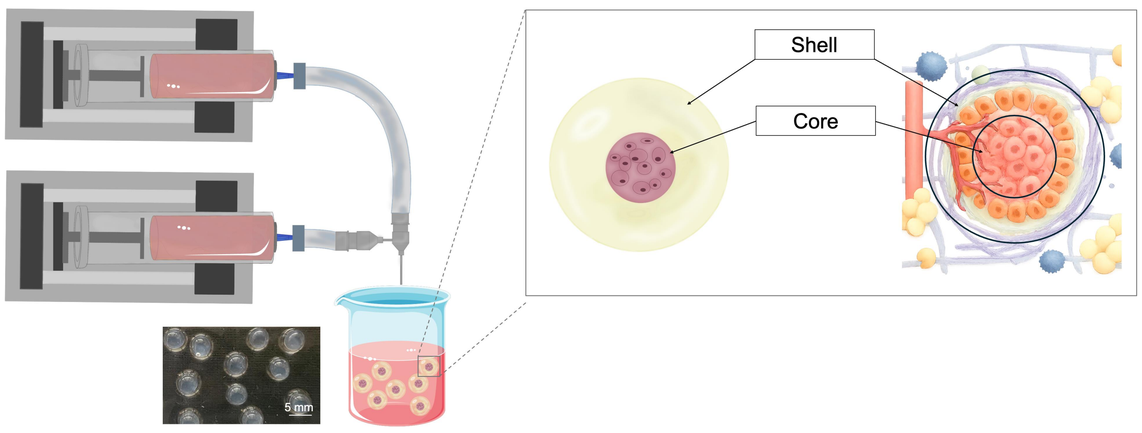


Figure 1. Scheme of production of core-shell hydrogel beads [3].

3 Results and Discussion

G3A1C0.4 and G3A0.5C0.4 (prototypes with Col1 in the core) present high porosity as observed in the SEM images (Figure 2A). Also, **Col1** incorporation to the cores increased stiffness to values comparable to *in vivo* tumors (Figure 2B).

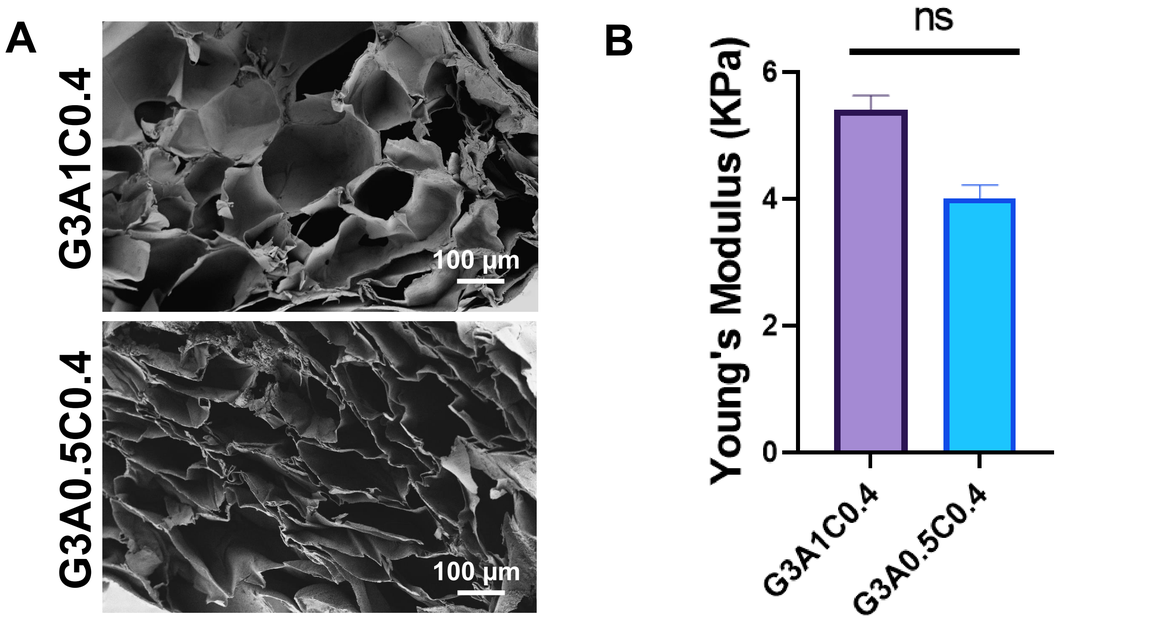


Figure 2. (A) SEM images of G3A1C0.4 and G3A0.5C0.4. Scale:100 µm. **(B)** Young's modulus measured by compression testing [3].

All prototypes promoted cell proliferation and viability, and supported spheroid formation within their cores. MCF-7 **morphology** and organization was observed via confocal microscopy (Figure 3A,B)

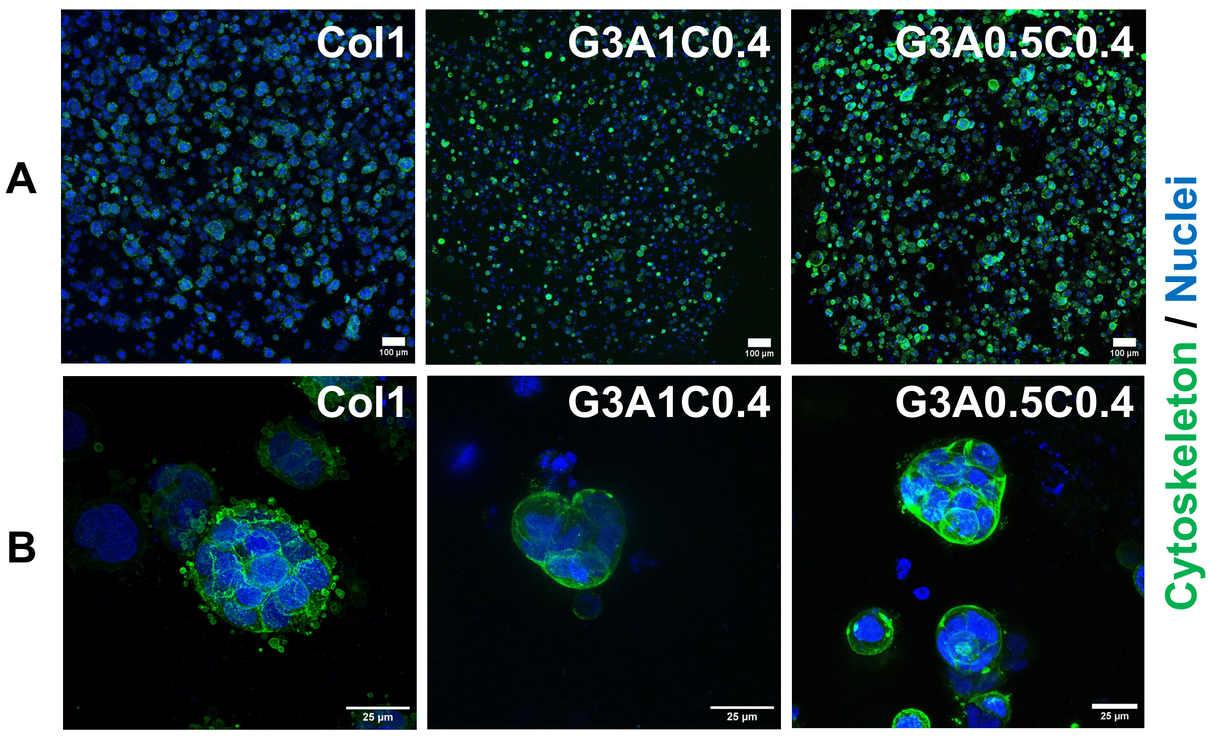


Figure 3. (A) Confocal microscopy images of Col1, P1, and P2. Scale bar: 100 µm. **(B)** Close-up images of individual spheroids in Col1, P1, and P2. Scale bar: 25 µm.

Col1 addition also promoted the expression of **drug resistance** (CYP1A1) and **invasion** (COL1A1, WWTR1, MENA) markers in MCF-7 cells (Figure 4A). G3A1C0.4 and G3A0.5C0.4 also showed a significantly higher resistance to doxorubicin than the 2D control (Figure 4B).

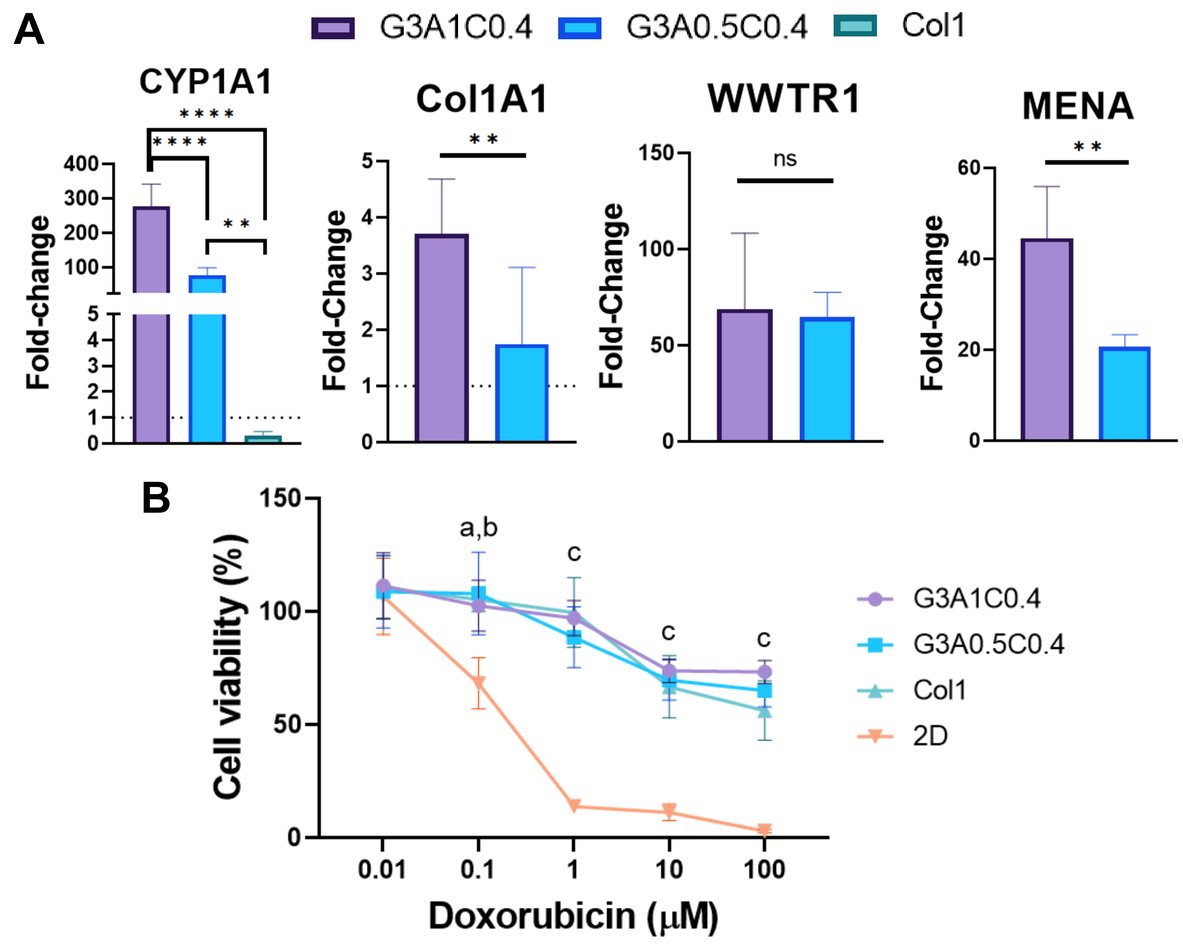


Figure 4. (A) Expression of CYP1A1, COL1A1, WWTR1, and MENA, measured by RT-qPCR. $2^{-\Delta\Delta Ct}$ values of CYP1A1 were calculated using ΔCt values from the 2D model, while $2^{-\Delta\Delta Ct}$ values of COL1A1, WWTR1, and MENA were calculated using ΔCt values from the Col1 model. (**: p<0.01, ****: p<0.0001). **(B)** Cell viability (%) after incubation of G3A1C0.4, G3A0.5C0.4, Col1, and 2D with different concentrations of doxorubicin for 48 h. a: G3A1C0.4, Col1 vs. 2D: p<0.01; b: G3A0.5C0.4 vs. 2D: p<0.001; c: G3A1C0.4, G3A0.5C0.4, Col1 vs. 2D: p<0.0001 [3].

Acknowledgements

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