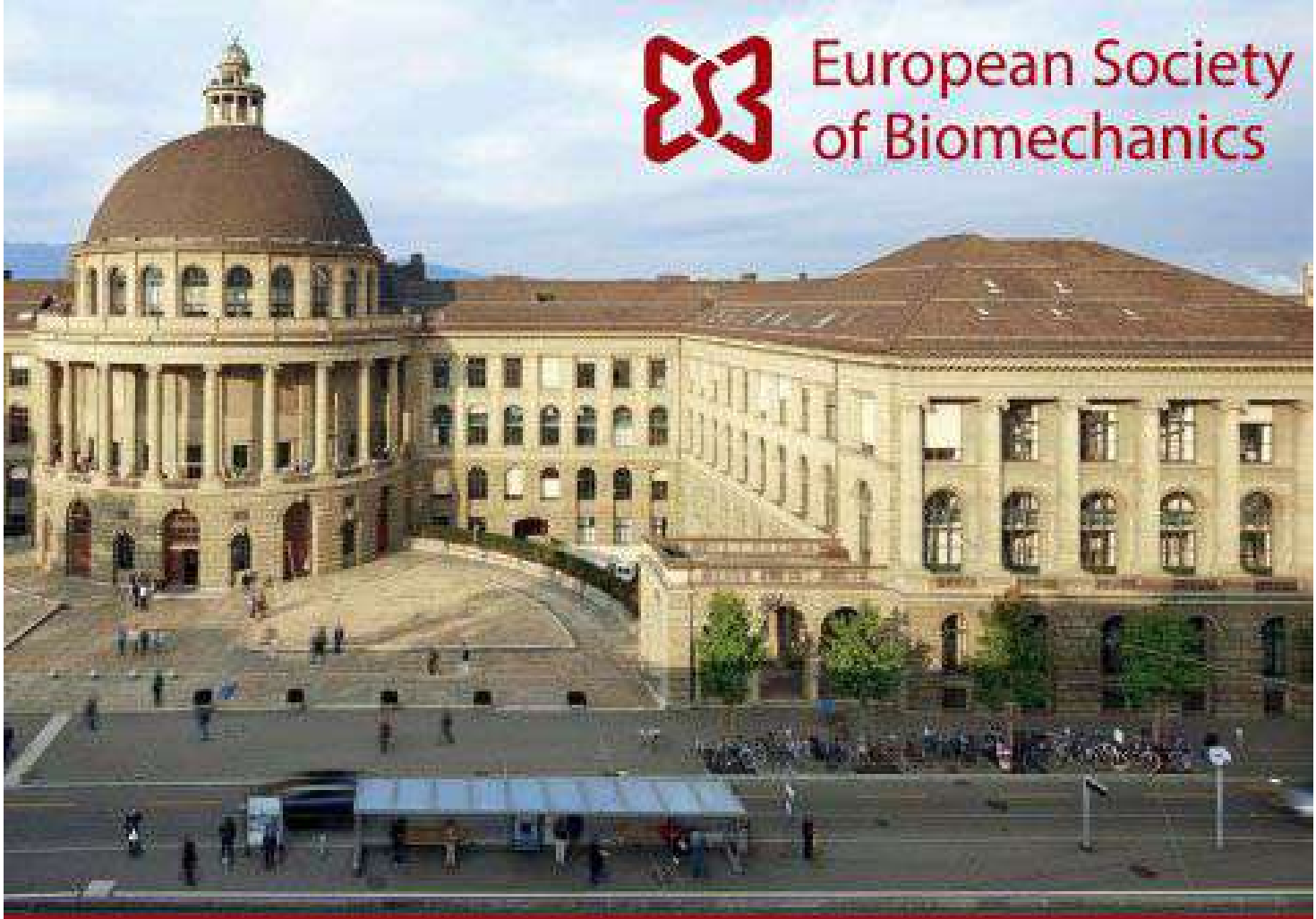

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THE ROLE OF MECHANICAL TRANSDUCTION IN DRUG RESISTANCE: NEW INSIGHTS FROM MICROSTRUCTURED 3D MODELS

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Introduction

Multi-drug resistance (MDR) is a major challenge in cancer therapy, leading to treatment failure and poor outcomes [1]. MDR arises from mechanisms like efflux pump overexpression, regulated by mechanosignaling cues that traditional 2D models fail to replicate. The two-photon polymerization technique [2] enables the creation of 3D microstructured scaffolds to better study mechanotransduction in drug resistance [3-4]. This work investigates how culture conditions deregulate key mechanotransduction elements, focusing on β-catenin nuclear translocation, which controls ABC efflux pumps. Additionally, we examine cytoskeletal remodeling and MICAL2 localization in response to 3D culture. We aim to assess how our 3D model replicates tumor architecture and drug resistance, providing an innovative platform to study MDR mechanisms and improve cancer drug development.

Methods

The custom-made organic-inorganic polymeric scaffold, Niche, features cubic pores (15×15×15 μm³) fabricated via two-photon polymerization in biocompatible resin SZ2080 [2]. MCF7 and MDA-MB-231 cells, representing primary and aggressive breast tumors, were cultured on glass coverslips, collagen-based hydrogel, the 3D Niche, and conventional spheroids to study their impact on mechanotransduction and pump activity. Cell viability was assessed after 24h under a Doxorubicin gradient (0.1 nM–40 μM) ± Verapamil (40 μM). Immunofluorescence characterized β-catenin, cortical actin, and MICAL2, while Western blot and PCR quantified MICAL2 expression.

Results

Doxorubicin-treated cells exhibited lower viability in 2D than in 3D cultures. Inhibiting efflux pump activity reduced IC50 by ~99% in 3D cultures but only ~2% in 2D, demonstrating that MDR is effectively recapitulated in our 3D microscaffold (Figure 1.a). Significant nuclear β-catenin accumulation was observed, suggesting a correlation with efflux pump activity. Additionally, MICAL2-mediated actin depolymerization led to thick, homogeneous cortical actin formation exclusively in the Niche scaffold (Figure 1.b, 1.c), influencing cytoplasmic stiffness and efflux pump function.

Discussion

These results confirm that the 3D Niche scaffold successfully mimics in vivo mechanosignaling mechanisms underlying MDR. The observed β-catenin nuclear translocation and cytoskeletal remodeling highlight key mechanotransduction pathways contributing to drug resistance. The scaffold's ability to replicate these features underscores its potential as a robust model for investigating MDR and advancing cancer drug development.

Figures

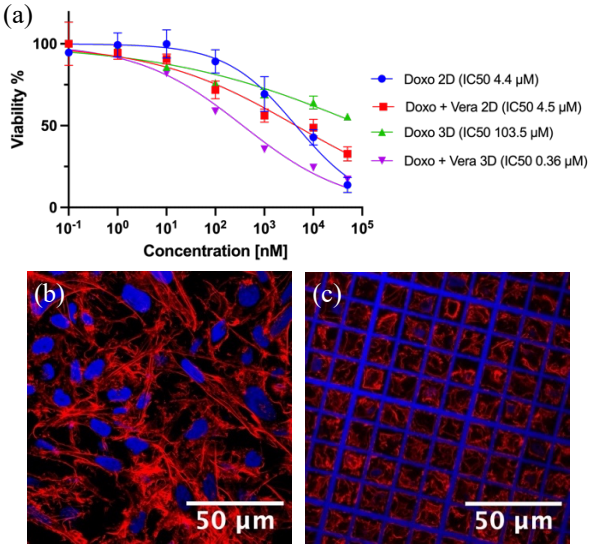

Figure 1: (a) Viability curves of MDAMB231 treated with Doxorubicin ± Verapamil for 24h. Efflux pump inhibition increases drug sensitivity only in 3D models. Immunofluorescence images of MDAMB231 in (b) 2D and (c) 3D Niche show distinct actin organization (blue: nucleus/Niche, red: actin).

References

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