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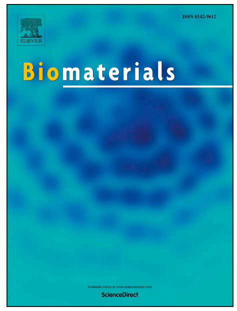

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3D organizational mapping of collagen fibers elucidates matrix remodeling in a hormone-sensitive 3D breast tissue model

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Abstract

Hormones play an important role in normal and diseased breast tissue development. However, they can also disrupt cell-matrix interactions and their role in extracellular matrix reorganization during epithelial morphogenesis remains poorly understood, partly due to a lack of sensitive approaches for matrix characterization. Here, we assess the hormonal regulation of matrix reorganization in a three-dimensional (3D) breast tissue culture model using a novel metric, i.e., 3D directional variance, to characterize the 3D organization of collagen fibers visualized via high-resolution, second harmonic generation imaging. This metric enables resolving and quantifying patterns of spatial organization throughout the matrix surrounding epithelial structures treated with 17β-estradiol (E2) alone, and E2 in combination with either promegestone, a progestogen, or prolactin. Addition of promegestone results in the most disorganized fibers, while the E2 alone treatment leads to the most organized ones. Location-dependent organization mapping indicates that only the prolactin treatment leads to significant heterogeneities in the regional organization of collagen fibers, with higher levels of alignment observed at the end of the elongated epithelial structures. The observed collagen organization patterns for all groups persist for tens of micrometers. In addition, a comparison between 3D directional variance and typical 2D analysis approaches reveals an improved sensitivity of the 3D metric to identify organizational heterogeneities and differences among treatment groups. These results demonstrate that 3D directional variance is sensitive to