

Characterizing breast capsular contracture: a translational study of primary fibroblast behaviour

Wu K, Kim S, Yazdani A, DeLyzer T, and Turley E

Purpose: Breast capsular contracture is a difficult complication occurring in up to 17% of implant-based breast surgeries. The pathological switch that propels a ‘healthy capsule’ towards contracture is multifactorial and remains incompletely characterized. The objective of this study is to define the fibrotic signature and characterize primary fibroblast behaviour in different grades of breast capsular contracture

Methods: Sixteen breast capsular tissue samples from 11 patients (9 primary augmentation, 7 breast reconstructions with 4 patients receiving radiation) undergoing capsulectomy or capsulotomy were collected and grouped according to the Baker classification (Grade 1 to 4). Capsular tissue was processed for histological analysis (H&E, Masson’s Trichrome) to visualize tissue architecture. Capsular tissue was sectioned into 0.5cm² pieces and incubated in DMEM media with FBS to allow outgrowth of primary fibroblasts. Fibroblasts were stained for alpha-smooth muscle actin (αSMA) and fibroblast activating protein (FAP) immunofluorescence and INK4a to identify fibroblast subtypes.

Results: Capsular tissue demonstrates densely organized parallel collagen architecture by Masson’s Trichrome staining and Grade 4 capsules had decreased capsule thickness ($p < 0.001$). Primary fibroblast outgrowth occurred by day 5-14. Fibroblasts from all capsule grades were successfully cultured and passaged, except from patients with previous radiation treatment. Immunofluorescence identified αSMA+ myofibroblasts within all capsule grades and an increased proportion of SMA+:FAP+ hybrid activated myofibroblasts in higher capsule grades ($p < 0.01$). Two distinct populations of bi-polar and stellate fibroblasts were identified with a higher proportion of bi-polar fibroblasts in higher capsule grades ($p = 0.07$). Grade 3 capsules show significantly higher staining for senescence marker, INK4a.

Conclusions: Higher capsule grade was associated with a higher proportion of hybrid activated myofibroblasts positive for both αSMA and FAP. Higher capsule grades also contain a higher population of INK4a+ senescent fibroblasts. These are non-replicative cells distinct from myofibroblasts, that contribute to fibrosis by secreting pro-inflammatory/fibrotic cytokines. This is the first demonstration of senescent fibroblast populations contributing to breast capsular contracture formation.