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Mechanistic cell-scale modelling of ductal carcinoma in situ (DCIS): impact of biomechanics in comedonecrosis

Ductal carcinoma in situ (DCIS)—a type of breast cancer whose growth is confined to the duct lumen—is a significant precursor to invasive breast carcinoma. The presence of a central necrotic core in one or more affected ducts (comedonecrosis) indicates poorer patient prognosis. Microcalcifications—calcium phosphate deposits that gradually replace necrotic cytoplasmic debris—are critically important to detecting DCIS by mammography. Nonetheless, most models only include necrosis as a simplistic volume loss term, and none have examined necrotic cell calcification.

We present a mechanistic, agent-based model of solid-type DCIS with comedonecrosis and calcification [1]. Each agent has a lattice-free position and phenotypic state. Cells move under the balance of biomechanical forces that are exchanged with other cells and the basement membrane. Each phenotypic state has a "submodel" of changes in cell volume and composition. Necrotic cells swell, lyse, and leak cytoplasmic fluid. Their nuclei degrade (pyknosis), and microcalcifications form in their cytoplasm and deteriorate over long time scales [2]. Phenotypic transitions from the quiescent state are regulated by proteomic- and microenvironment-dependent stochastic processes. The model is fully calibrated to patient data [3].

The model predicts that fast necrotic cell swelling and lysis account for the mechanical separation of the viable rim and necrotic core seen in histopathology—a feature often assumed to be an artifact of tissue preparation. Necrotic cell lysis is a major source of mechanical relaxation, directing proliferative cell flux towards the duct centre, rather than along the duct. Due to this necrotic "flux absorbing" effect, DCIS growth is linear, and growth is slower in larger ducts, with a minimum growth rate of 7.5 mm/year—in excellent agreement with mammography [4]. These results illustrate that well-calibrated, mechanistic cell modelling can provide quantitative insight on the biophysical phenomena that drive cancer progression.

References

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