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CURRENT TOPICS IN BREAST PATHOLOGY

Environmental factors in breast cancer invasion: a mathematical modelling review

Alex Simmons[1], Pamela M. Burrage[1], Dan V. Nicolau Jr[1,2,3], Sunil R. Lakhani[4] and Kevin Burrage[1,5]

[1]*School of Mathematical Sciences, and ARC Centre of Excellence for Mathematical and Statistical Frontiers, Queensland University of Technology, Gardens Point, Brisbane, Qld, Australia;* [2]*Mathematical Institute, University of Oxford,* [3]*Molecular Sense Ltd, Oxford, United Kingdom;* [4]*The University of Queensland, Centre for Clinical Research and School of Medicine and Pathology Queensland, The Royal Brisbane and Women's Hospital, Brisbane, Qld, Australia; and* [5]*Department of Computer Science, University of Oxford, United Kingdom*

Summary

This review presents a brief overview of breast cancer, focussing on its heterogeneity and the role of mathematical modelling and simulation in teasing apart the underlying biophysical processes. Following a brief overview of the main known pathophysiological features of ductal carcinoma, attention is paid to differential equation-based models (both deterministic and stochastic), agent-based modelling, multi-scale modelling, lattice-based models and image-driven modelling. A number of vignettes are presented where these modelling approaches have elucidated novel aspects of breast cancer dynamics, and we conclude by offering some perspectives on the role mathematical modelling can play in understanding breast cancer development, invasion and treatment therapies.

Key words: Breast cancer; mathematical modelling; ductal carcinoma *in situ*; mathematical oncology.

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INTRODUCTION

Breast cancer is a highly heterogeneous disease that incurs seemingly random and numerous changes in the genome of specific cells over extended time periods. These mutations, alongside an array of other interactions from local and non-native environments, disrupt a normal cell's physical characteristics, behaviour and communication pathways, leading to the initiation of complex behaviours, reciprocating interaction pathways and other phenomena that deviate significantly from their non-cancerous counterparts.[1] As a result of this complexity, investigators face a multitude of challenges in their attempts to study the driving forces that modulate the transition of normal breast cells into cancer cells.

The transition from ductal carcinoma *in situ* (DCIS), a non-invasive non-obligate precursor lesion, to invasive ductal carcinoma (IDC)[1,2] has come under considerable investigation from this genetic and molecular perspective.[3] Another facet and the basis for this review that has been recently brought to the forefront is how an altered microenvironment affects cancer,[4] including breast cancer.[5,6] Essentially, the notion is that altered cellular behaviours of tumour cells are brought about from the altered chemical or cellular microenvironments.[7] These altered local 'ecosystems' act as necessary driving forces that, in conjunction with mutations in the genomic profiles of epithelial cells, modulate the initiation of invasive behaviour. Mentioned in the review by Bissel and Hines is the perspective that these disturbed microenvironments can act as both promoters and inhibitors of cancer. In fact, in this view, the development of local tumours is unavoidable but the progression to malignancy should be controllable through the microenvironment.[4]

As with most biological systems, the microanatomy of the terminal duct lobular unit (TDLU) is complex and multifaceted, changing over the life span of an individual to suit the particular growth and lactation needs.[8] Understanding the genetic and molecular malfunctions in signal transduction pathways brought about by genomic mutations and their effect on cell population has been a major focus of research effort. However, this research mostly addresses just one (important) facet of cancer progression. Connecting how these breakdowns in signal transduction pathways of cell populations with the modulating or restraining effects of the microenvironment will enhance our understanding of breast cancer in an integrative way, ensuring clinical relevance of research findings, particularly as they relate to treatment options. To accomplish the aim of unravelling the complexity of this system, we must construct comprehensive modelling and computational tools to work synergistically alongside robust experimental techniques.

Computational methods are a rapidly evolving field of research, now used to investigate many aspects of cancer amongst myriad other biological systems. In spite of this, a significant portion of research output is targeted at model construction and calibration. While this is a vital process, its significance to pathology and clinical based research has been modest to date. In this review we set out to illustrate how mathematical techniques could be applied, complementarily to experiments, to elucidate pathophysiological features of breast cancer that are difficult to illuminate through experimental work alone. We note, however, that mathematical models have other uses besides this, for instance in designing new therapies or better structured clinical trials.

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Normal breast

The entire breast tree, including the functional unit (the TDLU), is lined by two types of epithelial cells. Surrounding the lumen of each duct are cuboidal or columnar epithelial cells, often referred to as the luminal cells. These epithelial cells differentiate to produce milk during lactation. Surrounding the luminal cells are the basal/myoepithelial cells that provide support and contract the duct to move milk during breast-feeding.[9]

There are in fact two distinctly different structures for the myoepithelial layer: around the ducts, the myoepithelial cells form an almost continuous layer,[10] while around the lobules, the myoepithelial cells form a discontinuous mesh-like structure best seen on scanning electron microscopy.[9] This potentially leads to two distinctly different phenomena, since the luminal epithelial cells in the lobule, but not the duct, have direct contact to the basal lamina. Surrounding the epithelium is the basement membrane that secures it to the stroma. The basement membrane is separated into two layers, the basal lamina and the lamina reticularis (Fig. 1). Mammary stem cells are believed to be important in both the maintenance and development of the ductal epithelium.[11]

Multistep progression

Breast cancers are traditionally classified using morphology[12] but there is an increasing trend of using molecular classification based on gene expression and DNA sequencing.[13,14] Considerable work over the last two decades has indicated that breast cancers arise through a 'multistep' process with low grade and high grade disease arising via distinct pathways.[15]

There is an increasing recognition that in the transition from DCIS to IDC, the myoepithelial cell layer plays an important role in regulating and facilitating invasion.[16–18] This is supported by molecular studies revealing that myoepithelial cells associated with DCIS are not phenotypically normal.[19] That same study also demonstrated that DCIS-associated myoepithelial cells have increased levels of ECM-degrading enzymes, such as matrix metalloproteinase (MMPs).[19]

Breast tumours are highly heterogeneous, both between and within patients and with multiple subclones within an individual patient's tumour.[20,21] There exist two competing but necessarily mutually exclusive models that attempt to explain breast cancer intra-tumour heterogeneity.[22] The first is the cancer stem cell (CSC) hypothesis[23] that presupposes the existence of a hierarchical organisation of cancer cells, where only a few cells drive tumour progression. The second theory is the clonal evolution/selection model[24] in which cells are bound by Darwinian evolutionary rules and the emergence of tumour progression is a response to selective pressures imposed locally by the micro-environment and externally such as through therapies.

Differentiation and proliferation

It is known that the stiffness of the extra cellular matrix (ECM) is an important component in the differentiation of stem cell lineages.[25] Hypoxia-inducible factors were also found to alter the function of myeloid-derived suppressor cells, redirecting their differentiation towards tumour-associated macrophages.[26] In recent work, the cell niche and integrin dynamics (transmembrane receptors for cell-cell and cell-ECM interactions) were found to be central to cell cycle and fate decisions. 3D cultures, which remove some of the limitations of strictly 2D microenvironment studies, have provided evidence that breast epithelia retain plasticity in their response to microenvironmental cues.[27] They have also indicated that the cellular microenvironment dictates the nucleolar complexity of breast epithelia independently of differentiation.[28] This plasticity, especially in the cell-cycle arrest, is similar to the glycolytic phenotype.[28,29]

Although hyperproliferation can be driven by oncogenic mutations, the 'angiogenic switch' has long been known as a well-established extrinsic modulator of proliferation.[30] Recently, these angiogenic vascular cells have been shown to express and secrete growth-promoting trophic factors independently in addition to blood-borne growth factors. Furthermore, endothelial cells depositing complex ECM into vascular niches establish a specialised basement membrane that could be responsible, in part, for tumour progression by providing support for organogenesis.[31] This vascular niche could be responsible for increased proliferation by endothelial cells secreting cytokines that accelerate tissue repair,[32] activated during inflammation and neo-angiogenesis.[33]

The ECM also plays an important role in controlling the proliferation of cells. A vascular endothelial growth factor binds to specific domains in the ECM and these associations promote cell proliferation.[33] The transforming growth factor beta (TGF-β) is a cytokine that can arrest the cell cycle, stop proliferation and initiate the apoptosis cascade. Together with its propeptide [the latency-associated peptide (LAP)], they can bond non-covalently in a complex called the small latency complex.[34] These latent TGF-β bind to other ECM

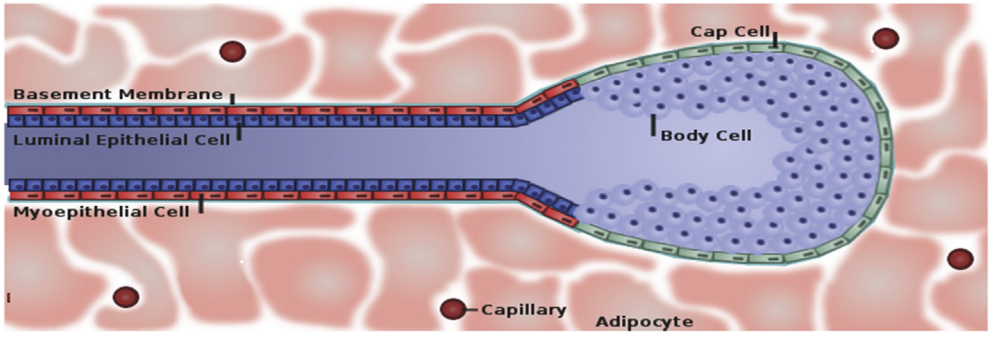

Fig. 1 Schematic diagram of mature ductal epithelium with luminal epithelial cells, myoepithelial cells terminating at an end-bud.

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