The role of tumour heterogeneity and TGF-β mediated stromal interactions in prostate cancer

David Basanta[1], Simon W. Hayward[2] and Alexander R. A. Anderson[1]

***Abstract* — Prostatic adenocarcinomas are complex diseases in which progression towards malignancy depends the interactions of tumour cells with stroma and the microenvironment as much as on the genetic mutations that enable those tumour cells to escape homeostatic control. In this abstract we introduce a hybrid discrete-continuum cellular automaton model (HCA) to study the role of cell-cell interactions mediated via extrinsic factors such as TGF-β to explain different stages of prostate tumour progression. Crucially, we also explore the role of tumour cell heterogeneity in driving adaptation to changing microenvironments.**

***Keywords* — Hybrid Cellular Automaton, Stroma, Cancer, Prostate, Heterogeneity.**

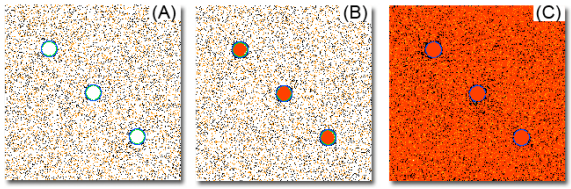
I. Introduction

PROSTATE cancer is one of the most commonly diagnosed cancers in the US but paradoxically, not one of the most deadly ones. In many cases, prostate tumour progression takes decades, so it is comparatively easier to diagnose and treat before it can become life threatening. The architecture of the prostate is maintained in a homeostatic equilibrium by interactions between the stroma (e.g. fibroblasts, monocytes) and epithelium (luminal and basal) within the microenvironment (TGF-β, Matrix degrading enzymes, extracellular matrix). TGF-β is a key growth factor produced by various cells (including the tumor) in the prostate and is vital for tumour cell survival and proliferation. For a prostate tumour to progress it must disrupt this homeostasis and the balance of TGF-β and basal membrane production. This disruption will be influenced by any preexisting heterogeneity (in terms of cellular traits e.g. variations in proliferation, adhesion, growth factor processing etc) within the prostate cell population. Traditionally it is assumed that there is a genetic source for this heterogeneity, however, recently non-genetic mechanisms have been discovered (1).

Here we develop a Hybrid Discrete Continuum Cellular Automaton (HCA) model to study how tumour cell heterogeneity is influenced by TGF-β, other microenvironmental elements and stromal interactions in driving tumour progression towards either malignancy or stagnation (2). HCA models are a class of cellular automata (CA) model in which continuous equations and discrete elements are solved together on the same grid. In this implementation the PDEs define the mE variables and a CA defines the tumor, stromal and epithelial cell behaviours and have previously been applied to tumour invasion (3). While in most HCA models the source of heterogeneity is not considered here we explicitly consider the role of non-genetic trait heterogeneity, specifically TGF-β production, in the tumour cell population.

II. Results and Discussion

Our model recapitulates key aspects of prostate cancer progression towards malignancy, including the importance of prostatic architecture, the balance of MDE production by tumour cells and the timescales involved. Some of the model predictions such as the role of TGF-β overexpression in PIN tumours, have been experimentally confirmed. Three specific tumour outcomes are observed: (A) dies out, (B) is contained (PIN) and (C) invades. These are dependent upon stromal configuration and the aggressiveness of the tumour phenotype (in terms of MDE and TGF-β production levels).



Whilst trait heterogeneity across the tumour population (in terms the diversity of TGF-β production) would not change these outcomes it does alter the capacity of the tumour to adapt to a changing microenvironment. For example, by dropping the TGF-β levels significantly the tumour compensates by up regulating production. This adaptive response emerges naturally as a result of survival of higher TGF-β.

References

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[1]Integrated Mathematical Oncology. H. Lee Moffitt Cancer Center, Tampa, FL 33612, E-mail: david.basanta@moffitt.org
[2]Department of Urologic surgery, Vanderbilt University Medical Center, Nashville, TN 37232, USA.