A Cellular Automaton Model of the Effects of Maspin on Cell Migration

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Abstract. Maspin (Mammary Serine Protease Inhibitor) is a non-inhibitory serpin with multiple cellular effects that is a type II tumour metastasis suppressor. Maspin has been shown to reduce cell migration, invasion, proliferation and angiogenesis, and increase apoptosis and adhesion. In this paper, we report the development of a mathematical model of the effects of maspin on cellular proliferation and migration. An artificial neural network has been used to model the unknown cell signalling to determine the cells fate. Results show that maspin reduces migration by between 10-35%; confirmed by published in vitro data. From our knowledge, this is the first attempt to model maspin effects in a computational model to verify in vitro data. This will provide new insights into to the tumour suppressive properties of maspin and inform the development of novel cancer therapy.

Keywords: Maspin, Serpin, Cell migration, Mathematical model, Neural Network.

1 Introduction

Maspin (SERPINB5) is a member of the serine protease inhibitor (serpin) superfamily which has been characterized as a type II tumour metastasis suppressor in multiple cancer types. Metastasis is a complex and multi-step process involving cell migration, invasion through the lamina propria, and growth in an extraneous microenvironment. Maspin decreases tumour growth and metastasis in vivo [1] and invasion in vitro [2]. This is achieved by the ability of maspin to influence aspects of cell behaviour including migration, invasion, proliferation, angiogenesis and apoptosis. These effects are proposed in many in vitro and in vivo models to involve both intracellular and extra-cellular activities of maspin. This diversity motivates us to build a computational model of the effects of maspin to show its potential engagement with multiple cellular phenomena using cellular automata modelling techniques.
The cellular mechanisms that maspin uses to influence cellular behaviour are not yet clearly defined, but have been reviewed recently [3]. There are reports that maspin works inside and outside the cell. It is possible that extracellular maspin directly affects cell migration, adhesion and angiogenesis, while indirectly affecting tumour cell proliferation and apoptosis. Maspin has been reported to bind to integrin cell adhesion receptors [4] or to the extracellular matrix [5]. Intracellular maspin binding partners have been identified, including the transcription factor IRF-6[2, 6], and histone deacetylase 1 influencing the Bcl-2/Bax signal axis [7, 8]. To date there have been no reports of mathematical and computational models to support these data. In this paper we have taken the migration raw data from [9], where it was reported that the G-helix is essential and sufficient for the influence of maspin on cell migration.

This paper presents an investigation into the development of a mathematical model of the effects of maspin on cellular proliferation and migration. The main objective of this investigation is to model proliferation and migration to investigate the unknown effects of maspin; this will allow us to verify the in vivo or in vitro experiments. The proposed model was implemented, tested and verified through a set of experiments to demonstrate the merits and capabilities of the scheme.

2 The Model

Mathematical models have been developed for tumour growth, tumour invasion and considerations of the different stages of tumour pathogenesis. Much work has been done to model the different aspects of tumour development. The majority of modelling approaches have considered all cancer cells as having the same properties. They considered the whole tumour mass as a single entity and defined the global parameters for every cell [10]. There are some attempts to model tumour growth characteristics at the cellular level as well, but considered cells as static entities. A cell is a complex living structure and its behaviour is not completely understood, especially when considering what has done wrong to allow the development of cancer. It evolves during both the growth process and therapy. A model discussing the evolutionary aspects of tumours at the cellular level has been presented [11]. Author considered the cell as an individual entity and modelled its decisions making processes based on the tumour microenvironment using a neural network. The model explored the consumption of oxygen, glucose concentration and hydrogen ions production but passed over some important growth constraints. In our previous model we established an in silico model to calculate tumour mass with the consideration of oxygen, glucose, extracellular matrix (ECM), cell-cell adhesion and cell movement as key micro environmental parameters. We also integrated the information regarding protein expression, growth promoters and growth inhibitors as tumour growth constraints and a bioreductive drug (TPZ) transport model for the hypoxic tumour cells [12]. In this paper we modified our neural network to show the effect of maspin presence/absence on tumour growth in respect of proliferation and migration [12].

A tumour tissue was developed starting with one cell at the centre of a two dimensional grid. In this cellular automaton model, each grid element was either occupied