MULTISCALE MODELLING OF AVASCULAR TUMOUR GROWTH UNDER HYPOXIC MICROENVIRONMENT

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Summary A multiscale mathematical modelling system was developed to study the dynamic process of avascular tumour growth as well as the changes of microenvironments during tumour growth. We have examined the effects of hypoxic environment on the development of the tumour through three layers, including the sub-cellular layer, the cellular layer and the tissue layer. The results showed the spatial distribution of different phenotypes of tumour cells under hypoxic microenvironment.

INTRODUCTION

Solid tumour growth is a very complex pathological progress which involves multiple scales. Using scale-specific model is insufficient to uncover cross-scale mechanisms. Simulating tumour behavior across multiple biological scales in space and time is increasingly being recognized as a powerful tool to investigate tumour physiology and pathology [1].
As one of the main features of abnormal environment inside the tumour, hypoxia plays an important role in tumour growth, invasion and metastasis. It can not only upregulate various angiogenic growth factors, including vascular endothelial growth factor (VEGF) [2], but also be associated with over-expression of p27 gene to arrest the G1/S transition of cell cycle [3]. Therefore, a multiscale mathematical model involving multiple scales will be very helpful to study the influences of hypoxic microenvironment on the tumour development

METHODS

A mathematical model by coupling angiogenesis, tumour growth and blood perfusion [4], was established by our group to study the dynamic responses of tumour model to the changes of tumour microenvironment. Based on it, we extended the model to the sub-cellular layer and focused on the hypoxic microenvironment.
To be specific, in the sub-cellular layer, we consider the tumour cell life cycle and signaling dynamics of individual cell which influence microscopic tumour phenotypes. In the tissue layer, we deal with the tumour growth and the invasion of tumour cells to surrounding healthy tissues, and oxygen transport inside and outside the tumour. The dynamics of tumour cells and the formation of neo-capillaries are also influenced by certain chemical substances (oxygen, extracellular matrix, and matrix-degradating enzymes) controlled by a series of reaction-diffusion equations in the cellular layer. Also the cell-cell and cell-matrix adhesion are considered in the cellular layer. The schematic of the multi-scale model system is shown in figure 1.

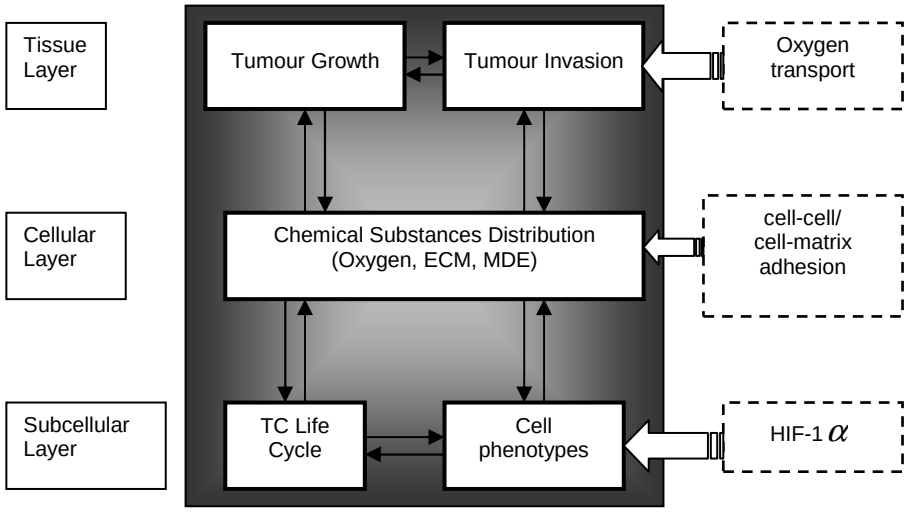

Fig. 1. Schematic of the coupled multi-scale model system.

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RESULTS

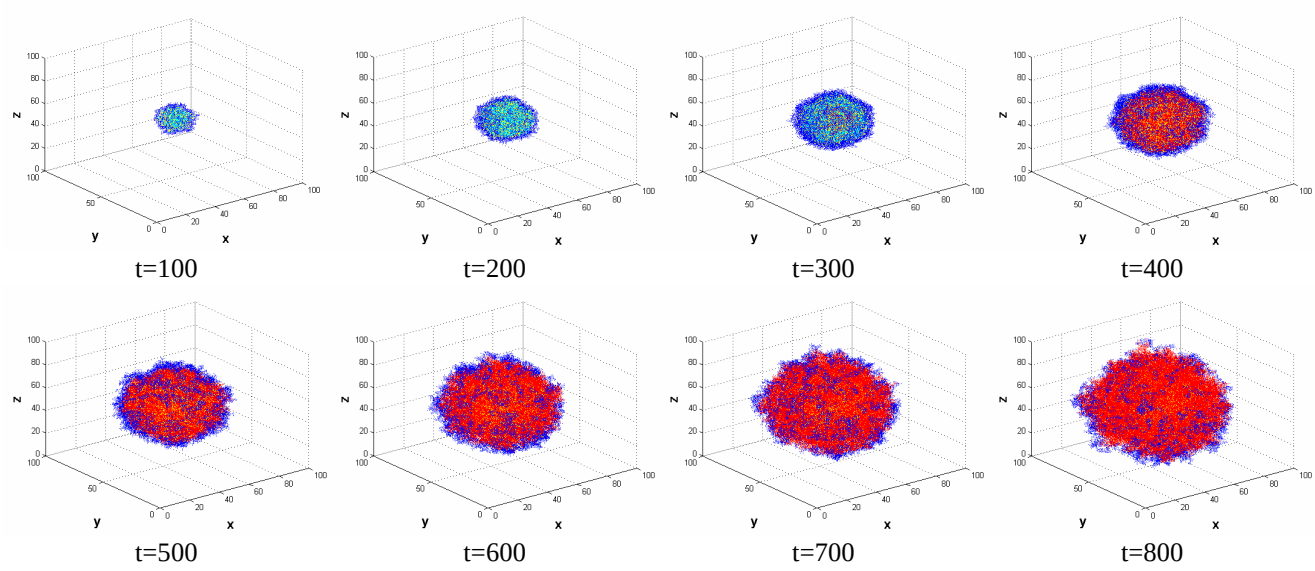

Fig. 2. The growth histories under hypoxic microenvironment. Different colours represent different phenotypes of tumour cells. See text for details.

The simulation is carried out on a 3D domain of $2mm \times 2mm \times 2mm$, divided uniformly into $100 \times 100 \times 100$ grids. We use different colours to represent different phenotypes of tumour cells, i.e., blue-proliferating cells; green-quiescent cells; red-necrotic cells; yellow-p27 over-expressed cells, as shown in figure 2. At the avascular period, the oxygen is not sufficient to support the tumour growth and invasion. Therefore, most of the tumour cells become necrotic at the late growth period. Although there are still some aggressive proliferating cells which have survived and formed a fingerlike invasion to the surrounding healthy tissues. The scattered distribution of p27 over-expressed cells (via hypoxia) exhibits hypoxia-induced arrest of the G1/S transition in cell-cycle, but not quiescence, which is the other reason for the increasing necrotic tumour cells. Moreover, the overexpression of the CDK inhibitor p27 will downregulate the activity of the cyclin-CDK complexes, which in turn prevents the normal progression of the cell.

DISCUSSION

In this study, we established a multiscale mathematical modelling system to investigate the dynamic process of avascular tumour growth under hypoxic microenvironment. Three layers are coupled in the current model, including the sub-cellular layer, the cellular layer and the tissue layer. The simulation results of the 3D model show the process of avascular tumour growth and invasion which has certain typical tumour physiological and pathological features, such as the increasing necrotic core in the centre of the tumour and the aggressive proliferating cells at the periphery of the tumour. The model can also shows the interaction of different scales including the gene overexpression in microscopic and the invasion to the surrounding tissue in macroscopic.

However, some physiological details were ignored or simplified in the model generation. Firstly, the vasculature inside the tumour is not included in the current model. Actually, the hypoxia microenvironment can stimulate the tumour cells to produce certain growth factors to start tumour-induced angiogenesis, which is known as an essential process in solid tumour growth. Secondly, tumour cells in this discrete model were treated as individual entities, but without volume. Therefore, local pressure rising due to tumour volume increasing caused by tumour cell proliferation is not included. These model potentialities will be the subjects of future studies.

References

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