A mathematical model for the emergence of intratumour metabolic heterogeneity

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Abstract

Tumours can be seen as complex ecosystems whereby spatial variations in substrates and metabolites lead to the formation of distinct local ecological niches. This allows for the coexistence of cells with different metabolic characteristics in the same tumour. In order to explore the evolutionary process underlying the emergence of such spatial metabolic heterogeneity, we present a mathematical model for the adaptive dynamics of the metabolic phenotype of cancer cells in a vascularised tissue. The model is formulated in terms of a system of nonlinear partial differential equations that describe the phenotypic evolution of cancer cells in response to dynamic variations in the spatial distribution of three abiotic factors that are key players in tumour metabolism: oxygen, glucose and lactate. The model recapitulates the eco-evolutionary spatial dynamics of cancer cells and their adaptation to hypoxic and acidic microenvironments. Moreover, the results obtained demonstrate that nonlinear interactions between cells and abiotic factors can cause the formation of environmental gradients that promote the selection of cells with metabolic characteristics that vary with distance from the blood vessels. Finally, the model enables systematic dissection of evolutionary parameters that shape the adaptive process leading cancer cells to enter into aggressive phenotypic states characterised by high levels of resistance to hypoxia and acidity, which correlates with poor prognosis, and suggests possible targets for therapeutic intervention.

References

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