A MODELING STUDY OF METASTATIC INITIATION AND TUMOR-TUMOR SPATIAL INTERACTIONS

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Abstract

Poor is known about the detailed mechanisms of metastasis establishment in a distant organ, due to lack of experimental means to observe the process at this early stage. To resolve this further, we conducted a theoretical study based on data from an orthotopic murine experimental system of metastatic renal cell carcinoma. We first confronted longitudinal data of total number of cells in the lungs with a mathematical model for the total metastatic burden dynamics. The results demonstrated that, despite being able to fit the total metastatic burden dynamics, the classical view of metastases formation (dissemination from the primary tumor and then independent growth) was unable to explain data of number of lesions (observed by magnetic resonance imaging) and growth velocity of individual metastatic tumors.

Instead, we propose that metastatic germs growing from one or a few cells could be aggregating, resulting in a similar total mass but a lower number of metastases. This led us to investigate the effect of tumor-tumor spatial interactions on the global metastatic burden dynamics. A novel mathematical model based on pressure-mediated growth was derived and shown able to fit the growth of metastatic lung nodules retrieved from magnetic resonance imaging data. As a non trivial outcome from this analysis and under our modeling assumptions,

the model predicted that total growth of two neighboring tumors was considerably impaired (of 31% $\pm$ 1.5%, mean $\pm$ standard deviation), as compared to the growth of two independent tumors. Our results provide a quantitative assessment of how much individual tumors growth is suppressed when tumors are in contact interactions. Moreover, they have implications for theories of metastatic development and suggest that global metastatic dynamics could emerge from the combined effects of fractionation of the total mass and spatial interactions between metastatic germs.