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Cancer spatial evolution in a changing microenvironment

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Abstract: Cancer development as an ecological and evolutionary process is poorly understood, which includes early cancer evolution, malignancy and metastasis. It was hypothesised that the tumour microenvironment (TME) plays a critical role in this process. Unfortunately, in most cancer modelling studies the TME is ignored or considered static and different cancers are often studied in isolation. There is a lack of a general theory of cancer adaptive evolution (CAE). Here I establish a genetic and phenotypic model of cancer three-dimensional (3D) spatial evolution in a changing TME. With 3D individual-based simulations I show how cancer cells adapt to diverse changing TME conditions and selection intensities. I am able to capture key histological characteristics of various cancer forms including complex dynamics of spatial-temporal heterogeneity of subclonal fitness and subclonal mixing, ball-like and non-ball-like subclonal structures. Moreover, I identify key evolutionary and phylogenetic patterns of CAE under various combinations of phenotypic, genetic, population genetic and changing TME conditions. I show classical drivers, mini drivers, Darwinian and neutral/nearly neutral evolution and cost of complexity. I demonstrate the importance of ecology in CAE. I show that there are fundamental differences in the mode of CAE when the TME is changing, which is the limiting factor of CAE. Finally, I discuss important implications for cancer evolution theories and cancer personalised medicine.

Expanded summary*: In this work, I rethink cancer development from the ground by developing a three-dimensional (3D) spatial model of CAE in a changing TME. I use a formal adaptation theory—the Fisher’s geometric model, which originated from the great R.A. Fisher. Fisher invented his phenotypic geometric model in his 1930 original work “The genetic theory of natural selection” to understand the nature of adaptation in Darwin’s theory of evolution by Natural selection. In almost a century this model has been extended into a general form, which includes parameters such as biological complexity, epistasis, robustness and changing environment. This framework now can be used to explore many fundamental evolutionary processes and theories and can even incorporate seemingly competing theories, such as the neutral/nearly neutral and selection theories of molecular evolution. However, it has never been applied to understanding cancer development as an ecological and evolutionary process. In my results, the whole adaptive process can be visualised and recorded in real-time, which includes a front-end 3D graphic interface and background spatial adaptation model based on Fisher’s framework. To my surprise my model is able to capture many important evolutionary patterns, such as complex dynamics of spatial-temporal heterogeneity of subclonal fitness and subclonal mixing, selection driven and neutral/nearly neutral evolution, classical drivers and mini drivers. I predict the TME is the limiting factor for CAE although mutation, mitotic recombination and chromosome instability can facilitate adaptation. Using my model, I can also demonstrate several fundamental theories in cancer, e.g., cancer cell origin, namely, cancer stem cell and non-cancer stem cell. For latter, our lab has provided experimental evidence published in Nat. Med. Finally, I show that there is a cost of complexity associated with CAE, which is the rate of adaptation (as well as the mean fitness of the population) decreases and the mean selection coefficient increases during adaptation when the cancer cell has an increased number of traits and the TME changes. This is consistent with a cancer reverse evolution theory that cancer removes non-essential multicellular life traits by random mutations and only focuses on few important traits for unicellular life adaptation. Ideally these few traits may be cancer’s Achilles’ heel. I show that there are fundamental differences regarding cancer spatial-temporal evolution when the TME changes, which is not possible in any previous cancer models. I think my work is of high importance and of general interest.

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