Deleterious mutations in cancer progression

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***Short Abstract* — Evolutionary models of cancer almost exclusively focus on the acquisition of driver mutations, which are beneficial to cancer cells. The driver mutations, however, are only a small fraction of the mutations found in tumors. The other mutations, called passenger mutations, are typically neglected because their effect on fitness is assumed to be very small. Recently, it has been suggested that some passenger mutations are slightly deleterious. We find that deleterious passengers significantly affect cancer progression. In particular, they lead to a critical tumor size, below which tumors shrink on average, and to an optimal mutation rate for cancer evolution.**

***Keywords* — cancer, evolution, deleterious mutations, passenger mutations, mutational meltdown, Muller's ratchet.**

I. Introduction

Cancer is an outcome of somatic evolution [1-3]. To outcompete their benign sisters, cancer cells need to acquire many heritable changes (driver mutations) that enable proliferation. In addition to the rare beneficial drivers, cancer cells must also acquire neutral or slightly deleterious passenger mutations [4]. Indeed, the number of possible passengers exceeds the number of possible drivers by orders of magnitude. Surprisingly, the effect of passenger mutations on cancer progression has not been explored. To address this problem, we developed an evolutionary model of cancer progression, which includes both drivers and passengers. This model was analyzed both numerically and analytically to understand how mutation rate, population size, and fitness effects of mutations affect cancer progression.

II. Model

We adopted the model of cancer progression that incorporates both driver and passenger mutations [4]. Driver mutations have a much larger fitness advantage compared to the fitness cost of deleterious passenger mutations. Indeed, a driver mutation turning on an oncogene affects fitness more than a passenger mutation increasing the rate of misfolding of a particular protein. The target size for mildly deleterious passenger mutations is however orders of magnitude larger than the number of possible driver mutations; therefore the rate of passenger mutations is much larger than the rate of driver mutations. We assume that mutations affect only the growth rate of cancer cells and that the effects of mutations multiply. The death rate is assumed to increase linearly with the population size. The balance between the birth and the death rates sets the "equilibrium" population size. Since the birth rates are changing due to somatic evolution, the tumor size is also changing. This change is crucial for many of our results, but it is missing in many evolutionary models that assume a constant population size.

III. Results

Upon including passengers in our model, we found that cancer is no longer a straightforward progression to malignancy. In particular, there is a critical population size such that smaller populations accumulate passengers and decline, while larger populations accumulate drivers and grow. The transition to cancer for small initial populations is, therefore, stochastic in nature and is similar to diffusion over an energy barrier in chemical kinetics. We also found that there is an optimal mutation rate for cancer development, and passengers with intermediate fitness costs are most detrimental to cancer. The existence of an optimal mutation rate could explain recent clinical data [5] and is in stark contrast to the predictions of the models neglecting passengers. We also show that our theory is consistent with recent sequencing data.

IV. Conclusion

Deleterious passenger mutations significantly affect evolutionary dynamics of cancer. Including passenger mutations in evolutionary models is necessary to understand the role of genetic diversity in cancer progression and to create new treatments based on the accumulation of deleterious passenger mutations.

References

[1] Michor F, Iwasa Y, and Nowak MA (2004) Dynamics of cancer progression. Nature Reviews Cancer 4, 197-205.
[2] Crespi B and Summers K (2005) Evolutionary biology of cancer. Trends in Ecology and Evolution 20, 545-552.
[3] Merlo LMF, et al. (2006) Cancer as an evolutionary and ecological process. Nature Reviews Cancer 6, 924-935.
[4] McFarland C, et al. "Accumulation of deleterious passenger mutations in cancer," in preparation.
[5] Birkbak NJ, et al. (2011) Paradoxical relationship between chromosomal instability and survival outcome in cancer. Cancer Research 71,3447-3452.

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