Effects of De-differentiation on Waiting Time to Carcinogenesis in Stem Cell Driven Cancers

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Short Abstract — **It is unclear whether cancer originates in stem cells or in de-differentiated progenitor cells. By modeling coupled stem and progenitor populations, we show that under absolute stem cell homeostasis, de-differentiation acts like positive selection. If stem cell homeostasis is not absolute, and population size is allowed to vary stochastically with density-dependent reproduction rates, de-differentiation beyond a critical threshold can lead to exponential growth of the stem cell population, even if density-dependent reproduction rates are maintained in the stem cell population. Our results suggest that de-differentiation may hasten the time to cancer and highlight the need to understand mechanisms behind homeostasis.**

***Keywords*: cancer stem cells, cell de-differentiation, waiting time to carcinogenesis, neutral drift, mutation and selection**

I. Introduction

MANY tumors have a hierarchical organization, with short-lived cells that are maintained by a small subpopulation of cancer stem cells (CSCs), which can proliferate indefinitely and drive tumor growth [1,2]. CSCs may originate from normal stem cells that escape proliferation control after acquiring a series of mutations in a multi-step process [3]. While some cancers may require only a few mutations, solid cancers may have up to 20 driver mutations [4]. Given known division and mutation rates, theoretical studies have argued that the necessary number of mutations for carcinogenesis cannot be obtained in the stem cell population on a reasonable time scale, without assuming either significant selective advantage or elevated mutation rates [3].

The population of progenitor cells is typically several orders of magnitude larger than the stem cell population and undergoes many more divisions in which cells can acquire mutations. It has also been shown that particular mutations in progenitor cells will cause them to revert to a stem cell-like state [1]. Hence, the cancer cell of origin may occur in either the stem cell pool or de-differentiated progenitor cells that have acquired infinite proliferating potential. We are interested whether de-differentiation can speed up the time to tumor development given normal mutation rates.

II. Results

We consider a hybrid stochastic-deterministic model of mutation accumulation at both at the stem cell level (via a stochastic process) and the progenitor level (via a PDE model), as well as the effects of de-differentiation of progenitor cells to a stem cell-like state [5]. To determine if the waiting time to cancer is sped up by de-differentiation, we consider two variants of the stochastic model, with fixed and stochastically variable stem cell numbers, and we test the effect of de-differentiation on each of those models.

Because mutations in the progenitor population are washed away from the lineage, only mutations in the stem cell population can persist and rise to fixation. Normal mutation rates in the stem cell population are not sufficient to produce the number of mutations required on reasonable timescales. We perform exact computer simulations of the emergence of a tumor subpopulation with k mutations over time, and we find the waiting time distribution to fixation when the stem cell population size N_{sc} is held constant, as well as when N_{sc} is allowed to stochastically vary in time via a density-dependent stochastic process. De-differentiation of progenitor cells speeds up time to fixation of k mutations in all cases. However, the relative effect depends strongly on how de-differentiation is implemented in the model.

III. Conclusion

We find that de-differentiation of mutant progenitor cells at rate ε is equivalent to positive selection for mutant stem cells when stem cell population size N_{sc} is fixed. $\varepsilon N_{sc} > 1$ is needed to significantly shorten time to cancer acquisition, which results in a high de-dedifferentiation rate, as the stem cell pool is typically small. In a model with a stochastically variable stem cell population size, a de-differentiation rate higher than a threshold that depends on progenitor dynamics and the probability of asymmetric division of stem cells results in exponential growth, and this can significantly speed up time to cancer compared to a constant N_{sc}. We conclude that the assumption of constant stem cell population size, frequently made in population genetics cancer models, may not be adequate when considering time to cancer calculations.

References

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