Role of Stem Cell Niche Structure in Cancer

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***Short Abstract* — Using recent modern imaging techniques, scientists have found evidence of collaboration between different types of stem cells (SCs), and proposed a bi-compartmental organization of the stem cell niche. Here we create a class of stochastic models to simulate the dynamics of cells at the stem cell niche. We examine this model in the context of 2-hit mutant generation, which is a rate-limiting step in the development of many cancers. We discover that a cooperative pattern in the stem niche with two groups leads to a significantly smaller rate of double-hit mutant production compared with a homogeneous and one-compartmental SC niche. Furthermore, the optimal architecture (which minimizes the rate of 2-hit mutant production) requires a large proliferation rate of stem cells which are close to the transit amplifying (TA) cells along with a small, but non-zero, proliferation rate of the central stem cells. This result is remarkably similar to the niche structure described recently by several authors, where one of the two stem cell compartments was found more actively engaged in tissue homeostasis and turnover, while the other was characterized by higher levels of quiescence (but contributed strongly to injury recovery).**

***Keywords* — Stem cell niche, Mutation, Cancer, Tumor suppressor genes, Stochastic process, Moran process.**

I. Purpose

Anatomical and molecular heterogeneity has been reported to be a common feature between mammalian SC niches across different tissues [1, 2, 3]. In [4], it was suggested that SCs in many tissues are characterized by a bi-compartmental organization. One SC group engages more readily into new growth, while the other one contributes more to the long-term turnover and regeneration of the tissue. Such patterns have been identified in several adult SC niches, such as hair follicles, blood, intestine, and brain [4]. So SC populations exhibits a certain degree of complexity that cannot be captured by simple, one-compartment models. More details of the bi-compartmental niche structure were recently uncovered by [5]. Researchers were able to follow the fate of individual intestinal stem cells and their progeny over time *in vivo*. In particular, two distinct groups of SCs have been identified: the "border cells" located in the upper part of the niche at the interface with TAs, and "central cells" located at the crypt base. The proliferative potential of the two groups was unequal and correlated with the cells' location (central or border). Further, it was reported that the central SCs could divide and migrate downstream replacing SCs in the border part. A similar dependence of self-renewal potential on proximity to the niche border was reported in the hair follicle, in an *in vivo* live-imaging study [6].

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II. Stochastic Model of the Stem Cell Niche

Here, we incorporate the bi-compartmental structure in our modeling approach, to see how this complexity might affect the evolutionary forces that shape the cells' division patterns. We focus on the stem cell niche and create several general models of the architecture, which include the model of [7] as a special case. Following evidences of collaboration between cells in the niche and their neighboring cells [5, 6], we divide SCs in the niche into two groups. One stem cell group S1 (the border cells) regulates the number of TAs and SCs, and the group S2 (the central cells), is only responsible for controlling the total number of SCs. We also include a possibility of migration of cells from one group to the other. In particular, we investigate which architecture type lead to the maximum delay in 2-hit mutant production. We obtain the optimal niche structure and the division patterns for each group, which minimize the rate of 2-hit mutant production.

III. Conclusion

We found that a certain pattern of cooperative stem cells in the bi-compartmental niche, along with symmetrically dividing SCs, leads to a significantly lower rate of two-hit mutant generation compared with the architecture that involves only one group of stem cells. In the optimal niche architecture, most divisions happen in the S1 group, with an occasional symmetric division in the S2 compartment followed by a S2 to S1 SC migration.

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