Symmetric vs. Asymmetric Stem Cell Divisions

Leili Shahriyari[1] and Natalia L. Komarova[2]

***Short Abstract* — We study the ability of stem cells to produce double-hit mutants (such mutants are often responsible for cancer initiation). We compare and contrast symmetric and asymmetric (and mixed) stem cell divisions, and focus on the rate at which double-hit mutants are generated. It turns out that symmetrically-dividing cells generate such mutants at a rate which is significantly lower than that of asymmetrically-dividing cells. We argue that symmetric stem cell divisions in mammals could be an adaptation which helps delay the onset of cancers.**

I. Purpose

In this work we examine the symmetric and asymmetric divisions in the context of producing mutations. An important advance in quantification of symmetric vs asymmetric divisions became possible with the invention of inducible genetic labeling [1]. Ref. [2] provides a review of the recent evidence of symmetric divisions in mammalian intestinal stem cells, spermatogenesis and epithelial tissues such as hair follicles [3], [4]. These new findings reveal that contrary to the previous thinking, adult tissue stem cells are often lost and replaced in a stochastic manner. This notion challenges the traditional concept of the stem cell as an immortal, slow-cycling, asymmetrically dividing cell [1]. In paper [2], an important question is raised: Why should mechanisms of tissue maintenance so often lean toward symmetric self-renewal? One answer comes from recognizing the ability of symmetrically-dividing stem cells to respond to injury. It however could be argued that the symmetric divisions are "switched on" in response to a sudden stem cell loss, and the asymmetric division strategy is employed in the course of normal homeostasis.

We explore an alternative hypothesis, which gives an additional reason for the tissue architecture favoring symmetric divisions. We consider a stochastic model of two-hit mutant generation, and we obtain optimal type of divisions and optimal fraction of stem cells that delays carcinogenesis. We also compare the rate of double-mutant production in a hierarchical model with the conventional homogeneous model has been studied in [5-8]. In order to obtain analytical insights, we consider a stochastic process and we present the results for the so-called "tunneling rates" - the rates at which the stem cell system of a given size produces double-hit mutants (assuming that one-hit mutants drift at relatively low levels). This analytical model gives us predictions that are in excellent agreement with the results of the numerical simulations.

[1]Inistitute for Genomics and Bioinformatics, University of California Irvine. E-mail: shahriyl@uci.edu

[2]Department of Mathematics, University of California Irvine. E-mail: komarova@uci.edu

II. Conclusion

We find that symmetrically dividing stem cells are producing significantly lower amount of two-hit mutants compared to asymmetrically-dividing stem cells. This is especially important in the context of tumor-suppressor gene inactivation, which is one of the more common patterns of carcinogenesis. This provides an evolutionary framework for reasoning about stem cell division patterns. Mammalian stem cells have been reported to employ both symmetric and asymmetric divisions to regulate their numbers and tissue homeostasis [9, 10]. A switch from a symmetric mode of divisions to the asymmetric model has also been reported to take place in development [11, 12]. The fact that the rate of two-hit mutant production is the lowest for symmetric dividing cells provides an alternative hypothesis for the observation that in mammalian tissues, symmetric patterns of stem cell division seem to be common.

References

[1] Klein AM, Simons BD (2011) Universal patterns of stem cell fate in cycling adult tissues. Devel opment 138: 3103–3111.

[2] Simons BD, Clevers H (2011) Strategies for homeostatic stem cell self-renewal in adult tissues. Cell 145: 851–862.

[3] Klein AM, Nakagawa T, Ichikawa R, Yoshida S, Simons BD (2010) Mouse germ line stem cells undergo rapid and stochastic turnover. Cell Stem Cell 7: 214–224.

[4] Doupé DP, Klein AM, Simons BD, Jones PH (2010) The ordered architecture of murine ear epidermis is maintained by progenitor cells with random fate. Developmental cell 18: 317–323.

[5] Nowak MA, Komarova NL, Sengupta A, Jallepalli PV, Shih IM, et al. (2002) The role of chromosomal instability in tumor initiation. Proceedings of the National Academy of Sciences 99: 16226–16231.

[6] Komarova NL, Sengupta A, Nowak MA (2003) Mutation-selection networks of cancer initiation: tumor suppressor genes and chromosomal instability. Journal of theoretical biology 223: 433–450.

[7] Iwasa Y, Michor F, Nowak MA (2004) Stochastic tunnels in evolutionary dynamics. Genetics 166: 1571–1579.

[8] Weissman DB, Desai MM, Fisher DS, Feldman MW (2009) The rate at which asexual populations cross fitness valleys. Theoretical population biology 75: 286–300.

[9] Noctor SC, Martínez-Cerdeño V, Ivic L, Kriegstein AR (2004) Cortical neurons arise in symmetric and asymmetric division zones and migrate through specific phases. Nature neuroscience 7: 136–144.

[10] Morrison SJ, Spradling AC (2008) Stem cells and niches: mechanisms that promote stem cell maintenance throughout life. Cell 132: 598–611.

[11] Egger B, Gold KS, Brand AH (2011) Regulating the balance between symmetric and asymmetric stem cell division in the developing brain. Fly 5: 237–241.

[12] Egger B, Gold KS, Brand AH (2010) Notch regulates the switch from 731 symmetric to asymmetric neural stem cell division in the drosophila optic lobe. Development 137: 2981–2987.