

Competitive clonal hematopoiesis in mouse chimeras explained by a stochastic model of stem cell organization

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Abstract: Many current experimental results on stem cell behavior are challenging classical concepts and show the necessity of new conceptual approaches to understand tissue stem cell organization. Recently, we proposed a theoretical concept based on microenvironment dependent stem cell plasticity. The objective of our work is to subject this concept to an experimental test and to validate previous qualitative model predictions. Therefore, we set up a set of experiments, investigating clonal competition processes in DBA/2 – C57BL/6 mouse chimeras. After bone marrow transplantation, we observed a biphasic chimerism development with an initially increasing and a variable (mostly declining) long-term DBA/2 contribution. Furthermore, we found that chimerism can be perturbed transiently by cytokine and cytotoxic treatment. We show that these phenomena can quantitatively be reproduced in computational simulations based on the proposed concept. Our results strongly support the view that the hematopoietic stem cell system is controlled in a flexible, self-organized way, respecting microenvironmental growth restrictions. Minor differences in cellular properties can have major impact on the competitive potential of cells. Moreover, we conclude that it is necessary to consider the interplay of cell intrinsic properties and the local growth environment, to understand stem cell organization in general and clonal competition in particular.