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

Roeder I, Kamminga LM, Braesel K, Dontje B, De Haan G, Loeffler M.

Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Leipzig, Germany; Center for High Performance Computing, University of Technology Dresden, Dresden, Germany.

Many current experimental results show the necessity of new conceptual approaches to understand hematopoietic stem cell organization. Recently, we proposed a novel theoretical concept and a corresponding quantitative model based on microenvironment dependent stem cell plasticity. The objective of our present work is to subject this model to an experimental test for the situation of chimeric hematopoiesis. Investigating clonal competition processes in DBA/2 - C57BL/6 mouse chimeras, we observed biphasic chimerism development with initially increasing but long-term declining DBA/2 contribution. These experimental results were used to select the parameters of the mathematical model. To validate the model beyond this specific situation, we fixed the obtained parameter configuration to simulate further experimental settings, comprising variations of transplanted DBA/2 - C57BL/6 proportions, secondary transplantations, and perturbation of stabilized chimeras by cytokine and cytotoxic treatment. We show that the proposed model is able to consistently describe the situation of chimeric hematopoiesis. Our results strongly support the view that the relative growth advantage of strain specific stem cells is not a fixed cellular property, but is sensitively dependent on the actual state of the entire system. We conclude that hematopoietic stem cell organization should be understood as a flexible, self-organized rather than a fixed, pre-programmed process.