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Systems Stem Cell Biology

Abstract:

Within the last decade, our modeling attempts in stem cell biology have considerably evolved. Starting from the cellular level, our models now comprise a broad spectrum of phenomena on different scales, ranging from the molecular to the tissue level. Such a scale-bridging description of biological processes does exactly match the intentions of the newly emerging field of systems biology with its central objective to understand biological complexity from molecular scales to ecosystems by a joint application of experimental and theoretical techniques. This work is an attempt to illustrate our systems biological perspective on tissue stem cell organization. Herein, I will describe the general principles of a new concept that understands stem cell organization as a dynamic, self-organizing process rather than as a pre-defined sequence of discrete developmental steps, as classically proposed.

The suitability of these principles to explain a broad variety of experimental results is illustrated for hematopoietic stem cells (HSC). For this system, the general stem cell concept has been translated into a stochastic model that comprises the processes of stem cell self-renewal and differentiation as well as lineage specification on the cellular level. Starting from this model, I will describe one possible way to extend the description towards the intra-cellular level. To do so, we considered a simple transcription factor network as the underlying mechanism controlling lineage specification decisions of HSC and analyzed its dynamical properties applying a system of ordinary differential equations. Finally, a clinical application of the proposed singlecell based model of HSC will shortly be outlined. This application again extends the description level of the model, now also incorporating systemic effects of therapeutic interventions. Based on the assumption that chronic myeloid leukemia can be modeled by a clonal competition process of normal and malignant cells, we analyzed the potential dynamic treatment effects of the tyrosine kinase inhibitor imatinib. Our results suggest a selective activity of *imatinib* on proliferating cells which implies the hypothesis that the therapeutic efficiency might benefit from a combination of *imatinib* with drugs promoting the cell cycle activation of primitive stem cells.