Quantitative lineage specification: mathematical modeling and biological implications

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Introduction Numerous observations in different experimental contexts agree upon a low level co-expression of potentially antagonistic genes regulating differentiation in early progenitor cells. This co-existence, commonly referred to as priming [1], is disappearing in the course of differentiation when certain lineage restricted genes are up-regulated while others are down-regulated. Although this phenomenology is widely accepted, it is unclear how these specific gene expression dynamics are generated and how they are controlled by cell-cell and cell-environment interactions.
Materials and methods Based on the phenomenological description, we propose a model of interacting components, representing e.g. lineage specific transcription factors, to account for the underlying intracellular dynamics. In the framework of two antagonistic external signaling environments cells can change between a repressive and a progressive control regime, promoting a switch from stable co-expression to the dominance of one factor over the others. These assumptions of a context dependent intracellular differentiation control have been embedded into our previously proposed model of tissue stem cell organization [2,3] which explains self-renewal as the result of a within-tissue plasticity of cellular properties.
Results Under the simplified assumption of only two different signaling environments we are able to quantitatively characterize the major developmental processes of tissue stem cells, namely self-renewal and lineage specification on the cellular level. We present simulation results that are in very good accordance with experimental findings on the lineage specification of single cells as well as of cell populations. Moreover, the single-cell based structure of the model allows the tracing of individual cell fates. A quantitative analysis of the emerging cellular genealogical trees can potentially reveal selection mechanisms of the underlying differentiation process.
Conclusion We propose a general conceptual framework to explain tissue stem cell organization as a self-organizing process. This replaces the view of tissue stem cells as being entities with a preprogrammed development by a concept that inherently accounts for the capabilities of flexible and regulated tissue self-organization based on cell-cell and cell-microenvironment interactions. The model provides a novel, quantitative understanding of lineage specification based on the idea of a self-organized competition process between different lineage specific factors.

Literature

[1] Cross MA, Enver T. The lineage commitment of haemopoietic progenitor cells. Curr Opin Genet Dev. 1997; 7(5):609-13.
[2] Loeffler M, Roeder I. Tissue stem cells: definition, plasticity, heterogeneity, self-organization and models--a conceptual approach. Cells Tissues Organs. 2002; 171(1):8-26.
[3] Roeder I, Loeffler M. A novel dynamic model of hematopoietic stem cell organization based on the concept of within-tissue plasticity. Exp Hematol. 2002; 30(8):853-861.