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Towards an understanding of lineage specification in hematopoietic stem cells: A mathematical model for the interaction of transcription factors GATA-1 and PU.1

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Abstract

In addition to their self-renewal capabilities, hematopoietic stem cells guarantee the continuous supply of fully differentiated, functional cells of various types in the peripheral blood. The process which controls differentiation into the different lineages of the hematopoietic system (erythroid, myeloid, lymphoid) is referred to as lineage specification. It requires a potentially multi-step decision sequence which determines the fate of the cells and their successors. It is generally accepted that lineage specification is regulated by a complex system of interacting transcription factors. However, the underlying principles controlling this regulation are currently unknown.

Here, we propose a simple quantitative model describing the interaction of two transcription factors. This model is motivated by experimental observations on the transcription factors GATA-1 and PU.1, both known to act as key regulators and potential antagonists in the erythroid vs. myeloid differentiation processes of hematopoietic progenitor cells. We demonstrate the ability of the model to account for the observed switching behavior of a transition from a state of low expression of both factors (undifferentiated state) to the dominance of one factor (differentiated state). Depending on the parameter choice, the model predicts two different possibilities to explain the experimentally suggested, stem cell characterizing *priming* state of low level co-expression. Whereas increasing transcription rates are sufficient to induce differentiation in one scenario, an additional system perturbation (by stochastic fluctuations or directed impulses) of transcription factor levels is required in the other case.

Keywords: Lineage specification; Hematopoietic stem cell; Transcription factor network; PU.1; GATA-1

1. Introduction

The hematopoietic system consists of a variety of functionally different cell types, including mature cells such as erythrocytes, granulocytes, platelets, or lymphocytes, as well as several different precursor cells (i.e., premature cell stages) and hematopoietic stem cells (HSC) (Lord, 1997; Orkin, 2000). Most mature cell types have limited life spans ranging from a few hours to several months, which implies the existence of a source capable of replenishing these differentiated cells throughout the life span of an individual. This supply is realized by the population of HSC, which is maintained and even regenerated after injury or depletion throughout the whole life of the organism. This self-renewal property is a major characteristic defining HSC (Loeffler and Roeder, 2002; Lord, 1997; Potten and Loeffler, 1990). A second major characteristic of HSC is their ability to contribute to the production of cells of all hematopoietic lineages, thus ensuring the supply of functionally differentiated cells meeting the needs of the organism. The process controlling the development of undifferentiated stem or progenitor cells into one specific functional direction (i.e., one specific hematopoietic lineage) is called *lineage specification*. It is generally accepted that the process of lineage specification

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is governed by the interplay of many different transcription factors (Akashi, 2005; Cantor and Orkin, 2002; Cross et al., 1994; Orkin, 1995, 2000; Tenen, 2003). Experimental results suggest that a number of relevant transcription factors are expressed simultaneously in HSC, although at a low level (Akashi et al., 2003; Hu et al., 1997). Some authors refer to this state of a low level co-expression as *priming* behavior (Akashi, 2005; Cross and Enver, 1997; Enver and Greaves, 1998). During differentiation the balanced co-expression of these potentially antagonistic transcription factors is assumed to be broken at some point (or even multiple points). Thereafter, the system is supposed to be characterized by an up-regulated level of some transcription factors, specific for a particular lineage, while other transcription factors are down-regulated. These observations suggest a transcription factor network, capable of switch-like behavior by changing from unspecific co-expression to different states of specific expression. However, the general underlying principles of the regulatory mechanisms are currently unknown. Particularly, it is unclear whether the assumption of a dynamically balanced low level co-expression state is justified or whether *priming* should rather be interpreted as the result of an inactive transcription factor network overlaid by stochastic fluctuations of transcription factor expression.

In this paper we propose a simple mathematical model describing different interaction scenarios of two transcription factors. Biologically, this simple two component network model is motivated by experimental observations on the transcription factors GATA-1 and PU.1, known to be involved in the process of lineage specification of HSC (Du et al., 2002; Oikawa et al., 1999; Rekhtman et al., 1999; Rosmarin et al., 2005; Tenen, 2003; Voso et al., 1994). The zinc finger factor GATA-1 is reported to be required for the differentiation and maturation of erythroid/megakaryocytic cells, while the Ets-family transcription factor PU.1 supports the development of myeloid and lymphoid cells (reviewed by Cantor and Orkin, 2002; Tenen, 2003). For both, GATA-1 and PU.1, it has been demonstrated that they are able to stimulate their own transcription through an auto-catalytic process (Chen et al., 1995; Nishimura et al., 2000; Okuno et al., 2005; Tsai et al., 1991). Additionally, there are physical interactions between GATA-1 and PU.1 which induce a mutual inhibition and, therefore, favor one lineage choice at the expense of the other (erythroid/megakaryocyte vs. myeloid) (Du et al., 2002; Nerlov et al., 2000; Rekhtman et al., 1999, 2003; Voso et al., 1994; Yamada et al., 1998; Zhang et al., 1999, 2000). In particular, two different mechanisms for the mutual inhibition of these two transcription factors have been suggested by experimental observations: on one hand, GATA-1 binds to the $\beta 3/\beta 4$ region of PU.1 (complex 1) and displaces the PU.1 co-activator c-Jun from its binding site, thereby, inhibiting the transcription initiation of PU.1 (Zhang et al., 1999). On the other hand, the inhibition of GATA-1 transcription is mediated by the binding of the N-terminal region of PU.1 to the C-finger region of GATA-1 (complex 2), thus blocking the binding of GATA-1 to its promoter (Zhang et al., 2000). That means, although both inhibition mechanisms are interfered through the formation of PU.1/GATA-1 heterodimers, the two complexes are structurally different. Whereas complex 1 (inhibition of PU.1 transcription by GATA-1) is known to bind to DNA, thus occupying a PU.1 promoter site, DNA-binding of complex 2 (inhibition of GATA-1 transcription by PU.1) has not been reported so far.

The mechanisms of antagonistic interdependence together with positive auto-catalytic regulation provide a framework for the theoretical investigation of different scenarios of transcription factor interaction and their implications for the explanation of lineage specification control. Applying a mathematical model, which formalizes the described interactions, it is now possible to analyze different combinations of transcription factor activation and inhibition on a qualitative and quantitative level. The proposed model relies on principles suggested for the description of general genetic switches (e.g. Becskei et al., 2001; Cinquin and Demongeot, 2002, 2005; Gardner et al., 2000).

In this paper it is our objective to examine the following questions within the framework of this model structure:

- Are the experimentally described interactions of the two transcription factors sufficient to generate a switching behavior between a stable co-expression of two factors and the dominance of one of these factors?
- What are the conditions inducing such a qualitative change in the system behavior?
- Is there evidence for a functional role of the (experimentally suggested) *priming* status?

To answer these question the following strategy is applied. Firstly, the model equations are derived on the basis of the described biological mechanisms of transcription factor interaction for GATA-1 and PU.1 (Section 2). Secondly, this model is analyzed with respect to the existence of steady state solutions and their dependence on the model parameters. According to our objective, to understand the mechanisms leading to switches between different stable system states, we focus our analysis particularly on the determination of bifurcation conditions, considering different scenarios of transcription factor interaction (Section 3). Finally, the obtained results are discussed in relation to the ongoing debate about lineage specification control in the hematopoietic system, specifically with respect to potential explanations of the experimentally suggested low level co-expression of transcription factors (*priming*) in undifferentiated progenitors and stem cells (Section 4).

2. Model description

Although our analysis is motivated by experimental observations of specific transcription factor interactions