

How does the hematopoietic erythroid-myeloid switch live up to its commitment?

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ABSTRACT

The erythroid - myeloid lineage decision in the hematopoietic stem cell system is governed by the mutually antagonistic pair of transcription factors PU.1 and GATA-1 which is thought to function as a bistable switch [1, 2]. However, prior to a choice of fate, they are expressed at low levels. Such priming behavior [3] could allow for rapid implementation of particular genetic programs. For the hematopoietic stem cell system several lineage branch points with key transcription factors and external signals have been identified [4, 5, 6], with one example being that of PU.1/GATA-1 [7, 8]. In addition to being autoregulatory, the transcription factors PU.1 and GATA-1 also regulate each other in a mutually antagonistic way [9], such that either of them are expressed exclusively in a fully committed state [8]. The PU.1–GATA-1 system, has encouraged the development of computational models which describe the dynamics of the transcriptional network [1, 2].

However, these models, while successful at describing the key features of the network, require high co-operativity in bindings between the transcription factors and the genes for bistability to occur. However, recent experiments show that the mutual regulation of PU.1 and GATA-1, is through the binding of heterodimers, and not due to higher order multimers [9]. We have devised a simple model of this network based upon mechanisms inferred from biochemical experiments [9]. The model incorporates an additional hypothesis which generates the required bistability. We postulate the existence of an additional gene X, that, when appropriately connected to PU.1 and GATA-1, makes the system bistable. The expression level of X also determines the priming properties of the network. Priming is thus implemented by a connector gene X, whose expression in turn depends upon the master regulators and an external signal, the latter which can be used to control X independently.

The PU.1–GATA-1 system is also coupled to the mutually antagonistic pair C/EBP α and FOG-1, which are responsible for the eosinophil lineage. The nature of the regulation, due to feedback loops, between these two pairs of genes, leads to the following consequence.

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The C/EBP α –FOG-1 pair first inherits the state of its master genes, PU.1–GATA-1 and, then further reinforces the decision, by feeding back positively. This leads to an irreversible commitment, which implies that once an external signal has induced the system into one of its alternative stable states, on subsequent removal of the signal, the system remains in the same state – the commitment is final. Understanding how this irreversible decision arises can provide insights into how, in general, lineage commitment can be reprogrammed. A study of the dynamics of commitment properties, in conjunction with experiments could serve as a common platform to investigate different branches of the hematopoietic stem cell system and in other types of developmental systems.

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