
Drugs modulating stochastic gene expression affect the erythroid differentiation process

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Abstract

It has been established that isogenic cells display an heterogeneous phenotype in an homogeneous environment. The main source of this variability arises in eukaryotic cells from the transcriptional process^{1,2} through stochastic gene expression (SGE).

To understand how a metazoan cell takes the decision to differentiate, we study the role of SGE during the erythroid differentiation process. Our hypothesis is that SGE could positively participate in decision making for each cell³. We obtained experimental evidence that is fully compatible with such a view (Richard *et al.*, submitted), but the conclusive demonstration for a causative role for SGE would require to be able to experimentally manipulate the amount of SGE.

To do so in our cellular system, we tested 10 drugs known to modify expression noise in a LTR driven reporter gene in human lymphocytes⁴ on a chicken erythroid progenitor cell line harboring a fluorescent reporter gene⁵. We obtained evidence that two drugs, Artemisinin and Indomethacin, significantly decreased SGE in these cells. In order to get a better understanding of their molecular action, we fitted a two-state model of gene expression. This led to the conclusion that the two drugs acted via different mechanisms.

We then asked whether or not such a drug-induced modulation of SGE could affect the differentiation process. We observed that indeed both drugs were able to significantly reduce

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the amount of differentiated cells. This provided the first evidence that the modulation of SGE can result in impairment of the differentiation process.

We then analyzed what might be the cellular basis for such an effect. After fitting a dynamical model of erythroid cell differentiation on control untreated cells, we used it to estimate which parameters were modified by Artemisinin treatment. We observed that most of the parameters of the differentiation process were affected, including the death rate of differentiated cells, as well as the rate of differentiation from the committed cell compartment toward the differentiated cells compartment.

We recently showed that cell-to-cell variability (as assessed by a measure of entropy at the single cell level) was significantly increased during the differentiation process, before returning to much lower values at the end of the process (Richard et al. submitted). We are now in the process of analyzing how such cell-to-cell variability is affected by drugs treatment.

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