Stochastic model for IL-4 expression dynamics

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***Short Abstract* — The alleles of the Interleukin-4 (IL-4) gene are expressed in a highly stochastic manner in T cells. We studied the kinetics of IL-4 induction at different stages of T-memory cell development, linking stochastic modeling to single cell expression data. To explain the observed fluctuations in IL-4 protein, we had to introduce a multi-step process of gene induction, with the opening of chromatin structure and the assembly of the transcription initiation complex as sequential random events. Under reasonable assumptions on the kinetic parameters, the model is able to explain the experimental data and predicts: (1) IL-4 expression is preceded by slow, transient chromatin opening; (2) chromatin accessibility increases as T-memory cells mature; (3) mRNA is transcribed in infrequent bursts during a limited time window of transcription factor availability.**

***Keywords* — Th2 differentiation, IL-4 stochastic expression, chromatin remodeling, transcriptional pulses, intrinsic noise.**

I. Purpose

UPON antigen stimulation, T helper lymphocytes (Th) trigger the adaptive immune response by expression and secretion of specific cytokine patterns. Interleukin-4 (IL-4) leads Th signaling against extracellular pathogens, and promotes Th2 differentiation [1]. The probabilistic nature of IL-4 gene activation and the high interallelic variability of its expression are in marked contrast to earlier results in bacteria and yeast, where noise in gene expression seems mainly intercellular [2]. This difference points out the complex interplay between chromatin structure and transcription factors in higher eukaryotes. A progressive structural modification on the IL-4 locus has been linked to the development of Th phenotype [3]. These changes in chromatin structure influence the DNA accessibility for transcription factors. In this study we address the impact of slow time scales in both mechanisms on the IL-4 variability.

II. Results

A. *Statistical analysis*

A GFP reporter was inserted into one IL-4 allele, to monitor the expression from each allele separately [4]. Statistically, IL-4 activation and expression levels show high interallelic variability and are not maintained in successive stimulations. We conclude that the probabilistic regulation of IL-4 gene starts at the allele level.

B. *IL-4 expression stochastic model*

We model the IL-4 expression dynamics from a single allele as a multi-step process, in which each event happens at random. Besides transcription (III) and translation (IV), chromatin remodeling of the IL-4 locus (I) and recruitment of the transcription initiation complex (II) are included. Moreover, we add a downstream step for the fast protein secretion through specific vesicles (V).

C. *Predictions*

Bimodality arises from a slow step in chromatin remodeling which acts as a switch between closed and open states. The opening is restricted to a limited window of opportunity defined by T cell receptor signaling. High variability among IL-4 expressing cells is caused by burst-like mRNA production. The short (~9min) and infrequent (~1/h) assembly of the initiation complex ends in a transcriptional pulse (~100 mRNA) because of high POLII recruitment efficiency. In contrast to activation, the deactivation of the gene is a rapid, deterministic process due to loss of transcription factors (~minutes), followed by slow closing of the gene (~days). During Th2 differentiation the increase of IL-4 activation originates from a faster gene opening, due to higher accessibility of the IL-4 locus. Several model predictions have been observed experimentally in related systems.

III. Conclusion

Strength and timing of IL-4 activation are crucial for several physiological tasks and mirror the progressive differentiation of Th2 cells. We distinguish the effects of different slow mechanisms at the DNA level, as chromatin remodeling and initiation complex assembly, on the stochastic characteristics of IL-4 expression. To make quantitative predictions, it was necessary to match experimental measurements with mathematical analysis.

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