The regulatory network controlling DCs differentiation - P248

Mauricio Pérez-Martínez[1 2] and Luis Mendoza[1 *]

[1] Instituto de Investigaciones Biomédicas, UNAM.
[2] Posgrado en Ciencias Biológicas, UNAM.
mauricio_pm@ciencias.unam.mx, lmendoza@biomedicas.unam.mx

INTRODUCTION: Dendritic cells (DCs) have an important role during the immune response. They are the link between the innate and adaptive immune systems. DCs develop from a common dendritic progenitor (CDP) in bone marrow (Fig. 1), and colonize hematopoietic, environmental contact, and immune priming sites in the organism. Transcriptionally, DCs express some factors involved in both ontogeny and immunological function: IRF8, IRF4, ID2, E2-2, BATF3, the STATs, and PU.1. Due to their ability to uptake an present antigens to T cells, it has been focussed on DCs potential therapeutic use.

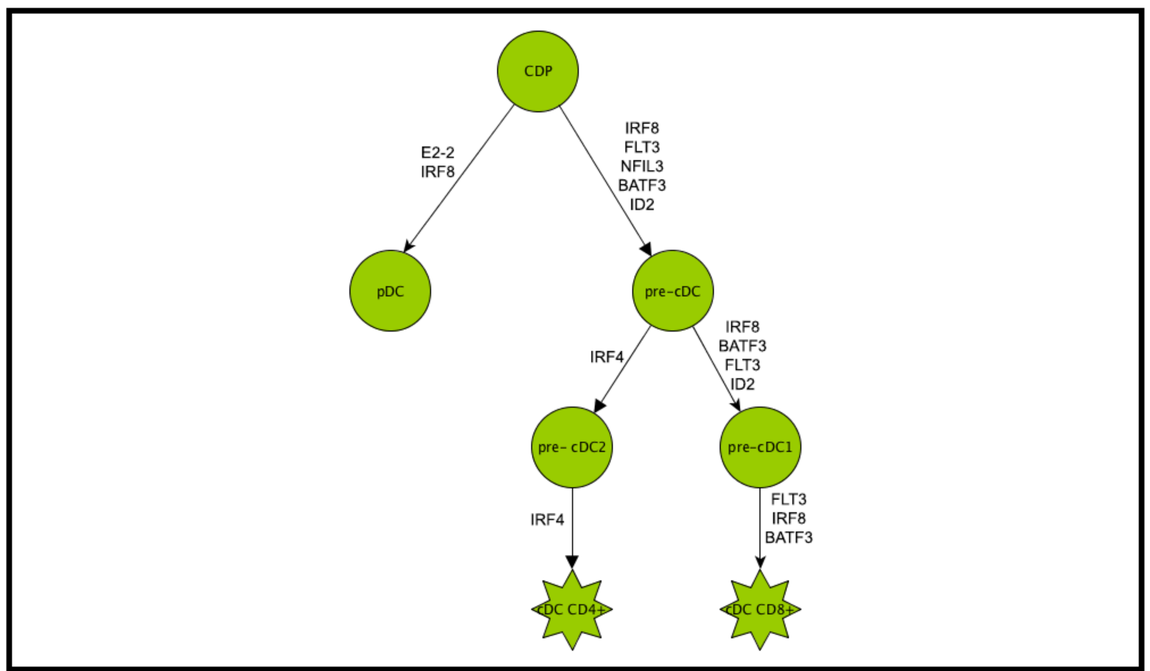

Fig. 1. *The DCs differentiation*. CDP = Common dendritic progenitor, pDC = plasmacytoid dendritic cell, pre-cDC = pre-classical dendritic cell. Tags beside lines represent the main molecules acting during cellular state transitions.

Boolean networks (BN) constitute a simplification in which every node may attain only one of two states: 0 (*OFF* or repressed), or 1 (*ON* or activated). BN describe, in an integrative-global view, complex biological phenomena involving multi-level-regulatory elements (genes, proteins, tissues or niches, organisms, etc.) interacting in a canonical or wild-type-way, or under perturbations (mutations, misregulation, etc.), and for which detailed kinetic information is lacking.

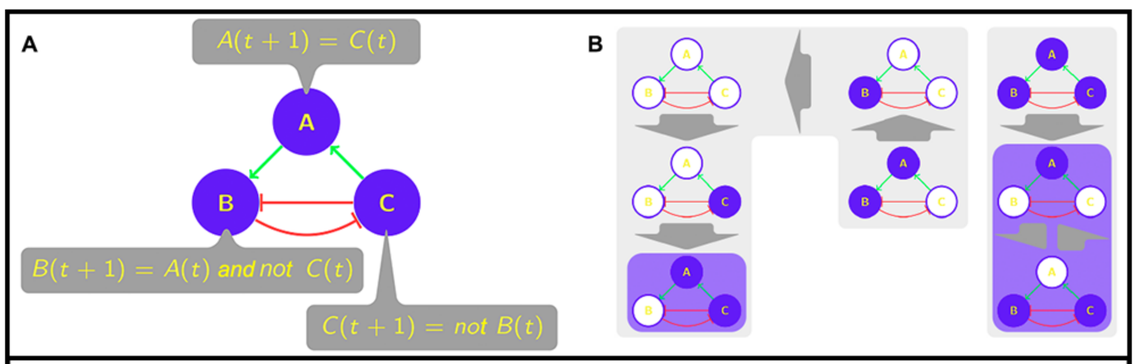

Fig. 2. *Boolean network*. A. Nodes (A, B, C) and the interactions (activations: green, repressions: red) among them. B. Network dynamic simulation.

In this work, the regulatory network controlling DCs differentiation in mice from experimental data was inferred, and modeled as BN. The wild-type process, and under-mutation effects is described.

METODH:

1. Exhaustive literature review to infer the regulatory network controlling cDCs CD8+ differentiation process.

2. Model the regulatory network as a BN.

3. Obtain the wild-type BN attractors and under single loss- and gain-of-function mutants.

4. Description of the differentiation process.

RESULTS: We propose a regulatory network containing 21 nodes and 61 interactions among them (Fig. 3).

Model simulations as BN recuperate the experimentally reported cellular states expression patterns : CDP, pre-cDC, pre-cDC1, and cDC CD8+ (Table 1 and Fig. 4).

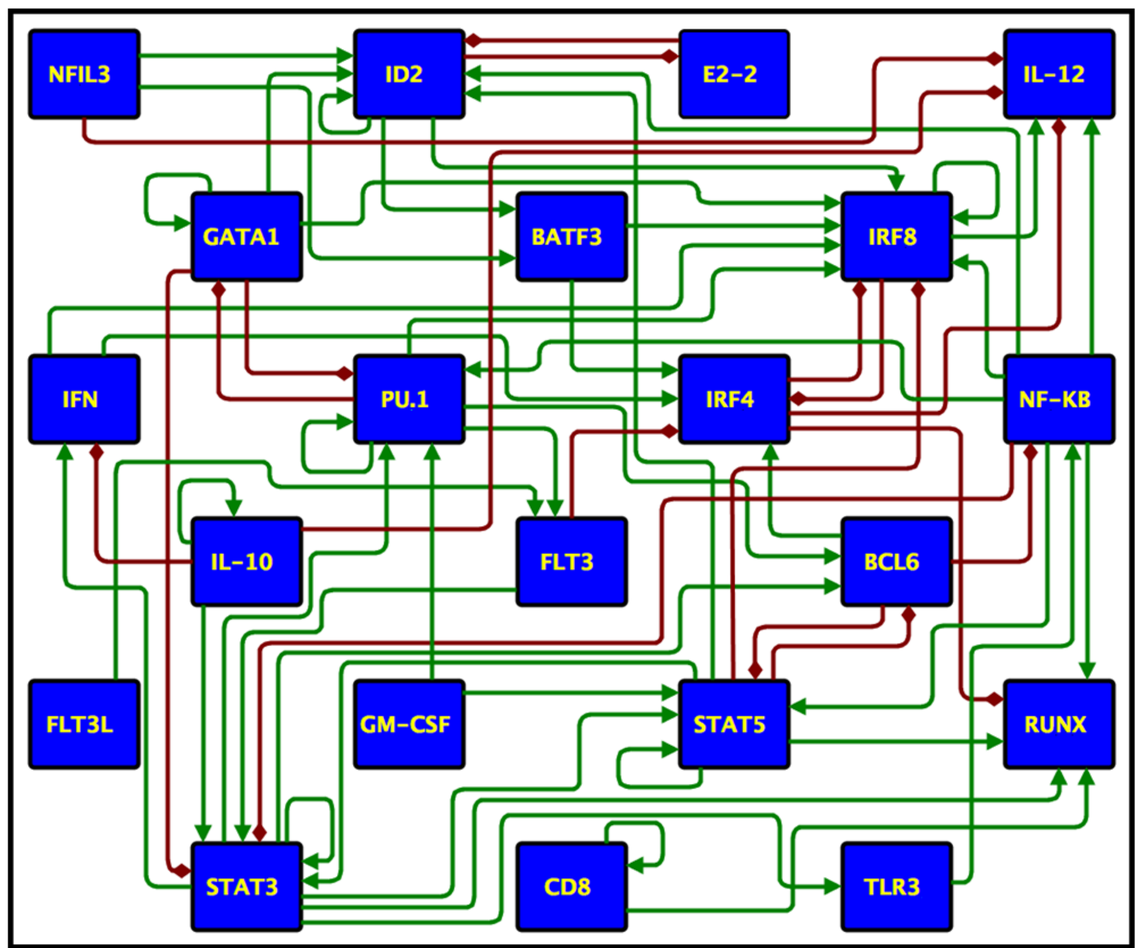

Fig. 3. *The regulatory network controlling DCs differentiation*. Nodes (blue squares) represent molecules. Green and red lines represent positive (activation) or negative (repression) regulations respectively. Arrows indicate the sense of each regulation.

CELLULAR STATE	EXPERIMENTALLY OBSERVED PATTERN EXPRESSION
CDP	IR8+, FLT3+, BATF3+, NFIL3+, IRF4+, PU.1+, STAT5+, ID2+, STAT3+
pre-cDC	IR8+, FLT3+, BATF3+, BCL6+, NFIL3+, IRF4+, PU.1+, STAT5+, ID2+
pre-cDC1	IR8+, FLT3+, BATF3+, BCL6+, PU.1+, STAT5+, ID2+
cDC CD8+	IR8+, FLT3+, BATF3+, BCL6+, IL-12+, CD8+, TLR3+, PU.1+, STAT5+, NF-κB+

Table. 1. *Experimentally oberved pattern expression during DCs differentiation.* CDP = Common dendritic progenitor, pre-cDC = pre-classical dendritic cell.

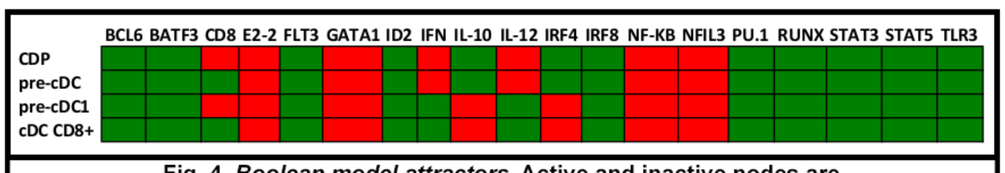

Fig. 4. *Boolean model attractors*. Active and inactive nodes are depicted as green and red boxes, respectively. CDP = Common dendritic progenitor, pre-cDC = pre-classical dendritic cell.

Perturbation analyzes, viewed as single loss- and gain-of-function mutants showed concordance with some experimental observatios (Table 2).

MUTANT MODEL	EFFEC	REFERENCES
IRF8 loss	cDC CD4-like attractor	Murphy *et al.*, 2016
FLT3L loss	No effect	Karsunky *et al.*, 2003
NFIL3 gain	No IL-12	Kashiwada *et al*. 2011
PU.1 loss	Unspecific attractors	Carotta *et al.*, 2010
BCL6 loss	IRF4 repression	Ohtsuka *et al.*, 2011
STAT5 loss	IRF4 repression	
ID2 loss	pDC-like attractor	Ghosh *et al.*, 2010

Table. 2. *Mutant models with experimental correspondence effects.*

DISCUSSION: The model recuperates the cellular states CDP, pre-cDC, pre-cDC1 and cDC CD8+, and includes the main regulators experimentally reported during cDCs differentiation process. However, in order to obtain expression patterns experimentally observed, the ID2 activation by NFIL3 is proposed in the model (Fig.3). Single mutant models show some proprieties about DCs differentiation program. For example, they support the IRF8 and ID2 roles notion on cell fate to cDCs or pDC, respectively (Table 2). The model also supports the proposal about rename cDC CD8+ as IRF8+ cDCs or BATF3-dependent cDCs.

PERSPECTIVES: Further model improvements must be conducted to infer the regulatory networks behind the pDC and Lanherhans cells (LCs) differentiation and integrate molecular concentration variations in a continuous system modeling.

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