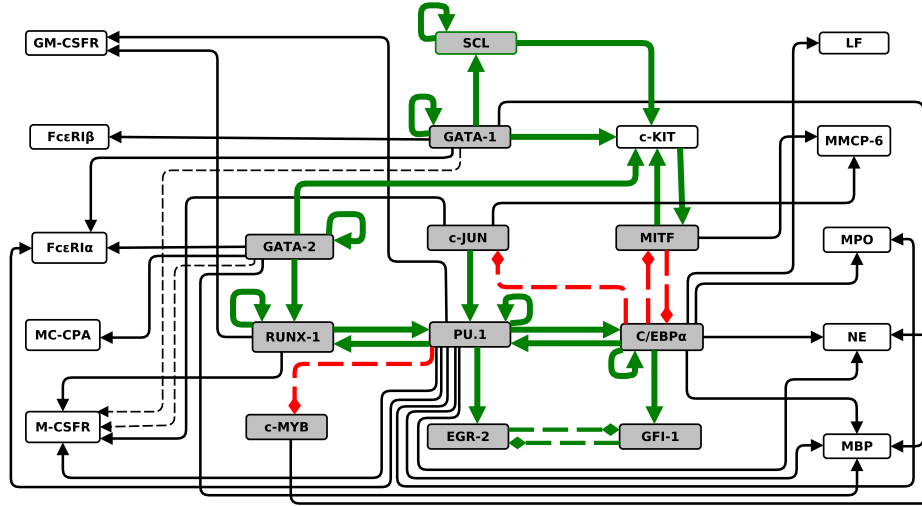
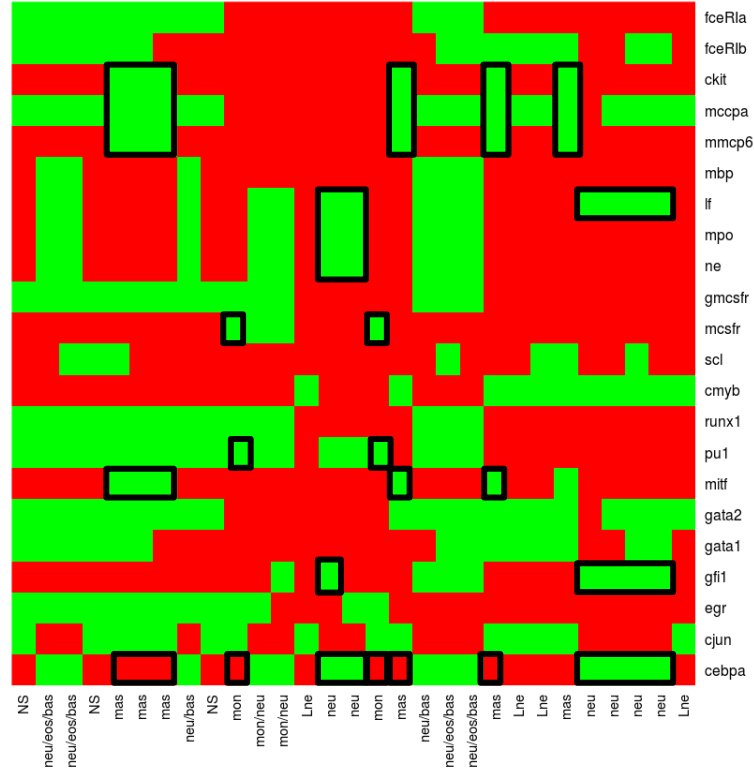


**Phenotypic stability and plasticity in
GMP-derived cells as determined by their
underlying regulatory network:
Supplementary Data**

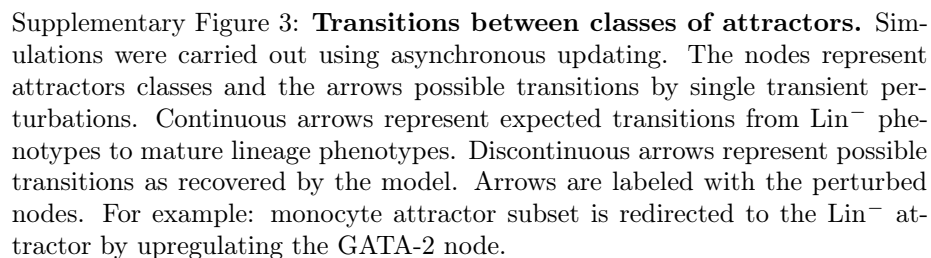
Carlos Ramírez and Luis Mendoza



Supplementary Figure 1: **Regulatory Network Model of direct interactions** inferred from experiments reported in the literature regarding the differentiation of GMP-derived cells. Continuous (discontinuous blunt) arrows represent positive (negative) interactions. Some interactions are shown as big colored arrows to highlight the regulatory circuit of transcription factors, in these case positive (negative) interactions are shown in green (red). Transcription factors are shown in gray.

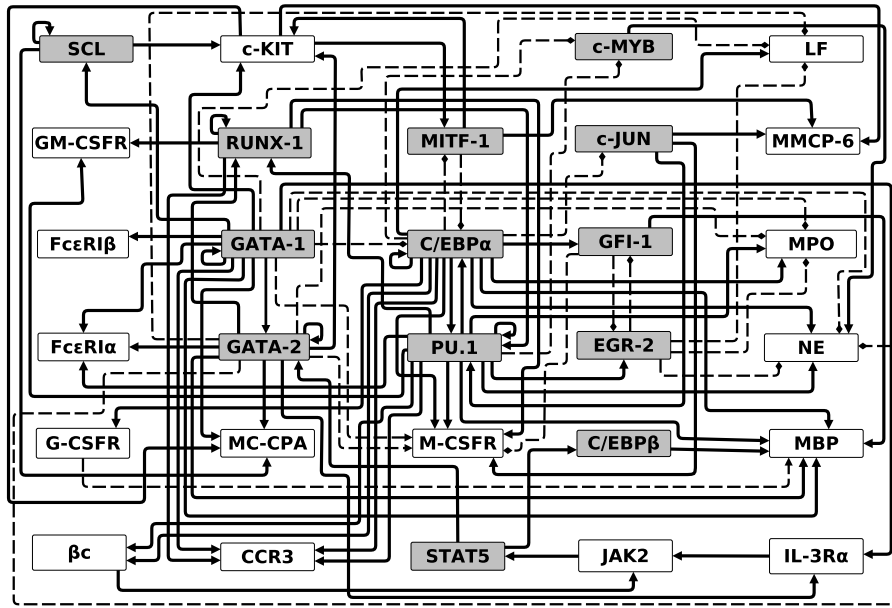


Supplementary Figure 2: **Attractors of the Boolean Regulatory Network of well grounded direct interactions** inferred from experiments reported in the literature. Green (red) boxes represent active (inactive) nodes. For attractors having one and only one GMP lineage pattern (defined in Supplementary Table 5), their molecular signatures are highlighted using black borders. Attractors with none of the GMP-derived cells lineage patterns (including lin⁻ pattern) are tagged as non-specified (NS).





Supplementary Figure 4: **Simulations on fixed environments.** Expression patterns refer to phenotypes as defined in Supplementary Table 5. Green (red) boxes represent presence (absence) of the lineage signature for each row. Combination of different constant values defines pro-Lineage fixed environment provided in the columns. For example, IL-3R α along with c-KIT are well known pro-Mast cells cytokines. In the transcription factor null environment (TFs NULL) the C/EBP α , PU.1, GATA-1, MITF-1 nodes were fixed to 1. Cytokines receptors (M-CSFR, G-CSFR, GM-CSFR, IL-3R α , c-KIT, Fc ϵ RI α , and Fc ϵ RI β) nodes are fixed to 1 or 0 in the Cy ALL or Cy NULL columns, respectively. These last three columns (marked as --) are not considered specific pro-Lineages environments. Color indicates whether the corresponding node was fixed to 1 (green) or 0 (red).



Supplementary Figure 5: **The Regulatory Network that controls the differentiation of GMP-derived cells.** Continuous (discontinuous blunt) arrows represent positive (negative) regulatory interactions. Transcription factors are shown as gray nodes.

Supplementary Table 1: Interactions of the Regulatory Network model. In this step of model construction we only included well grounded direct interactions. Key references supporting network logic rules. AND and OR logic operators are represented by & and | symbols respectively. Pointed or blunt arrows represent activation or inhibition outputs.

Updating logic rule	References
$C/EBP\alpha \rightarrow C/EBP\alpha$	[9]
$C/EBP\alpha \dashv c\text{-JUN}$	[66]
$C/EBP\alpha \rightarrow GFI\text{-}1$	[32, 37]
$C/EBP\alpha \rightarrow LF$	[25]
	[26]
$C/EBP\alpha \dashv MITF\text{-}1$	[63]
$C/EBP\alpha \& PU.1 \rightarrow MPO$	[14]
$(C/EBP\alpha c\text{-MYB}) \& PU.1 \rightarrow NE$	[55]
$C/EBP\alpha \& c\text{-JUN} \rightarrow PU.1$	[30, 7]
$c\text{-JUN} \rightarrow MMCP6$	[28]
$c\text{-JUN} \& PU.1 \rightarrow M\text{-CSFR}$	[4]
$c\text{-KIT} \rightarrow MITF\text{-}1$	[34]
$EGR\text{-}2 \dashv GFI\text{-}1$	[32]
$GATA\text{-}1 \rightarrow GATA\text{-}1$	[75]
$C/EBP\alpha \& (GATA\text{-}1 GATA\text{-}2) \& PU.1 \rightarrow MBP$	[11]
	[24]
$(GATA\text{-}1 GATA\text{-}2) \& PU.1 \rightarrow Fc\epsilon RI\alpha$	[51]
$GATA\text{-}1 GATA\text{-}2 \dashv M\text{-CSFR}$	[86]
$GATA\text{-}1 \& SCL \rightarrow c\text{-KIT}$	[74]
	[48]
$GATA\text{-}1 \& SCL \rightarrow SCL$	[57]
$GATA\text{-}1 \rightarrow Fc\epsilon RI\beta$	[40]
$GATA\text{-}2 \rightarrow GATA\text{-}2$	[16, 42]
	[54]
$GATA\text{-}2 \rightarrow c\text{-KIT}$	[41]
$GATA\text{-}2 \rightarrow MC\text{-CPA}$	[87]
$(GATA\text{-}2 \& PU.1) RUNX\text{-}1 \rightarrow RUNX1$	[53]
$! GFI\text{-}1 \& PU.1 \dashv EGR\text{-}2$	[32]
$MITF\text{-}1 \rightarrow c\text{-KIT}$	[77]

Supplementary Table 1 (Continued)

Network rules Key references supporting network logic rules.

Updating logic rule	References
MITF-1 \dashv C/EBP α	[63]
MITF-1 \rightarrow MMCP6	[46, 47]
PU.1 \dashv c-MYB	[5]
PU.1 \rightarrow EGR-2	[32]
PU.1 & RUNX-1 \rightarrow GM-CSFR	[21]
PU.1 & RUNX-1 \rightarrow M-CSFR	[21]
PU.1 \rightarrow PU.1	[60, 33]
RUNX-1 \rightarrow PU.1	[22]

Supplementary Table 2: Net rules of the Boolean Regulatory Network Model. Only well grounded interactions are included in this first model. The logic operators "AND", "OR" and "NOT" are represented by &, | and ! characters, respectively

Node	Updating logic rule	References
C/EBP α	C/EBP α & ! MITF-1	[9, 63]
c-JUN	! C/EBP α	[66]
EGR-2	! GFI-1 & PU.1	[32]
GFI-1	C/EBP α & ! EGR-2	[32]
GATA-1	GATA1	[75]
GATA-2	GATA-1 GATA-2	[58, 19, 45]
MITF-1	(! C/EBP α) c-KIT	[34, 63]
PU.1	PU.1 RUNX-1 (C/EBP α & c-JUN) & ! GFI-1	[30, 7, 60, 33, 22]
RUNX-1	(GATA-2 & PU.1) RUNX-1	[53]
c-MYB	! PU.1	[5]
SCL	SCL & GATA-1	[57]
M-CSFR	((PU.1 & RUNX-1) (PU.1 & c-JUN)) & ! (GATA-1 GATA-2)	[4, 21] [86]
GM-CSFR α	RUNX-1 & PU.1	[21]
NE	(C/EBP α c-MYB) & PU.1	[55]
MPO	C/EBP α & PU.1	[14]
LF	C/EBP α	[25, 32]
MBP	((C/EBP α & (GATA-1 GATA-2) & PU.1)	[11, 38]
MMCP6	MITF-1 & c-JUN	[28, 46, 47, 62]
MCCPA	GATA-2	[87]
c-KIT	(GATA-2 (SCL & GATA-1)) & MITF-1	[74, 41, 77, 77]

Supplementary Table 3: Proposed and indirect interactions added to the second version model. The operators "AND" (&) and "OR" (|) describes here the boolean behavior of the interaction. Arrows (blunted arrows) represents positive (negative) interactions.

Updating logic rule	References
$\beta c \& (\text{GM-CSFR} \text{IL-3R}\alpha) \rightarrow \text{JAK2}$	[18]
$\text{C/EBP}\alpha \rightarrow \text{CCR3}$	Proposed in this work
$\text{C/EBP}\alpha \dashv \text{c-MYB}$	[70]
$\text{C/EBP}\alpha \& \text{PU.1} \rightarrow \beta c$	[2]
	[78]
$\text{C/EBP}\alpha \& \text{PU.1} \rightarrow \text{G-CSFR}$	[65]
	[69]
$\text{GATA-1} \& \text{PU.1} \& \text{RUNX-1} \rightarrow \text{CCR3}$	[29]
$\text{c-KIT} \rightarrow \text{MMCP6}$	[62]
$\text{MITF-1} \& \text{c-KIT} \rightarrow \text{MMCPA}$	Proposed in this work
$\text{EGR-2} \dashv \text{LF}$	[32]
$\text{EGR-2} \dashv \text{MPO}$	Proposed in this work
$\text{EGR-2} \dashv \text{NE}$	Proposed in this work
$\text{GATA-1} \rightarrow \text{GATA-2}$	[58]
	[19]
	[45]
$\text{GATA-1} \text{GATA-2} \rightarrow \text{IL-3R}\alpha$	[44]
$\text{GATA-1} \text{GATA-2} \dashv \text{NE}$	Proposed in this work
$\text{GATA-1} \text{GATA-2} \dashv \text{MPO}$	Proposed in this work
$\text{GATA-1} \text{GATA-2} \dashv \text{LF}$	Proposed in this work
$\text{G-CSFR} \& \text{GFI-1} \dashv \text{MBP}$	[38]
$\text{JAK2} \rightarrow \text{STAT5}$	[56]
	[3]
$\text{STAT5} \rightarrow \text{C/EBP}\beta$	[80]
$\text{STAT5} \rightarrow \text{GATA-2}$	[35]

Supplementary Table 4: Net rules of the Boolean Regulatory Network Model (second version). The logic operators "AND", "OR" and "NOT" are represented by &, | and ! characters, respectively. Expressions in green show indirect or proposed interactions mentioned in Supplementary table 3.

Node	Updating logic rule	References
C/EBP α	C/EBP α & ! MITF-1	[9, 63]
C/EBP β	STAT5	[80]
c-JUN	! C/EBP α	[66]
EGR-2	! GFI-1 & PU.1	[32]
GFI-1	C/EBP α & ! EGR-2	[32]
GATA-1	GATA1	[75]
GATA-2	GATA-1 GATA-2 STAT5	[58, 19, 45, 35]
MITF-1	(! C/EBP α) c-KIT	[34, 63]
PU.1	PU.1 RUNX-1 (C/EBP α & c-JUN) & ! GFI-1	[30, 7, 60, 33, 22]
RUNX-1	(GATA-2 & PU.1) RUNX-1	[53]
c-MYB	! (PU.1 C/EBP α)	[5, 70]
SCL	SCL & GATA-1	[57]
IL-3R α	GATA-1 GATA-2	[44]
STAT5	JAK2	[56]
JAK2	(IL-3R α GM-CSFR α) & β c	[18]
β c	C/EBP α & PU.1	[2]
M-CSFR	((PU.1 & RUNX-1) (PU.1 & c-JUN)) & ! (GATA-1 GATA-2)	[4, 21] [86]
GM-CSFR α	RUNX-1 & PU.1	[21]
G-CSFR	C/EBP α & PU.1	[65]
NE	(C/EBP α c-MYB) & PU.1 & ! EGR-2 & ! (GATA-1 GATA-2)	[55]
MPO	C/EBP α & PU.1 & ! EGR-2 & ! (GATA-1 GATA-2)	[14]
LF	C/EBP α & ! EGR-2 & ! (GATA-1 GATA-2)	[25, 32]
MBP	((C/EBP α C/EBP β) & (GATA-1 GATA-2) & PU.1) & ! (GFI-1 & G-CSFR)	[11, 38]
MMCP6	MITF-1 & c-KIT & c-JUN	[28, 46, 47, 62]
MCCPA	GATA-2 & MITF-1 & c-KIT	[87]
c-KIT	(GATA-2 (SCL & GATA-1)) & MITF-1	[74, 41, 77, 77]

Supplementary Table 4 (Continued)

Supplementary Table 4: Net rules of the Boolean Regulatory Network Model (second version). The logic operators "AND", "OR" and "NOT" are represented by &, | and ! characters, respectively.

Node	Updating logic rule	References
FcεRIβ	GATA-1	[40]
FcεRIα	(GATA-1 GATA-2) & PU.1	[51]
CCR3	C/EBPα & GATA-1 & PU.1 & RUNX-1	[29, 31]

Supplementary Table 5: Definition of the attractor subsets. Lineage negative (Lin^-) attractors do not express any of the following markers expressed in mature cells: MPO, LF, NE, IL-5R α , MBP, MCSFR, Fc ϵ RI α MMCPA, MMCP6, and MITF).

Subset	Phenotype definition	References
Neutrophil (Neu)	(MPO $^+$ LF $^+$ NE $^+$ C/EBP α^+ GFI-1 $^+$) or (LF $^+$ C/EBP α^+ GFI-1 $^+$)	[8] [10] [39]
Eosinophil (Eos)	GATA-1 $^+$ GATA-2 $^+$ C/EBP α^+ CCR3 $^+$ Fc γ RI α^+	[23]
Monocyte (Mon)	MCSFR $^+$ PU.1 $^+$ EGR2 $^+$	[8] [10] [39]
Mast (Mas)	MITF-1 $^+$ C/EBP α^- MMCP6 $^+$ c-KIT $^+$ MMCPA $^+$	[1]
Basophils (Bas)	C/EBP α^+ MITF $^-$ GATA-2 $^+$ RUNX-1 $^+$ CCR3 $^-$ IL-3R α^+	[1] [24] [49]

Supplementary Table 6: *In Silico* model and experimental null mutants reported in literature. Left column shows the mutated node (gene) affected in the simulation (experiment). Agreement (disagreement) with experimental findings are highlighted in green (red).

	In Silico Mutant	Experimental mutant
C/EBP α	Only monocytes and mast cells are produced	No granulocyte formation but monocyte cells can be found [85]
c-JUN	Monocytes are lost	Erythoblast massive apoptosis [13]
EGR-2	Basophils attractors are lost	Monocytes are present but at low levels [32]
GFI-1	Neutrophil and basophil classes are not found	No secondary or terciary granule protein production in neutrophils [20]
GATA-1	Eosinophil pattern attractors are lost	Contradictory results. Eosinophils are lost [19]. Mature eosinophils are found, but at low levels [12]
GATA-2	Basophil attractors are lost	Mast cells are lost [76]
MITF-1	Mast cell patterns are lost	Low mast cell production [27]
PU.1	Monocytes and eosinophils steady states are lost	Deffect in granulocyte and monocyte formation [68, 61]
RUNX-1	Monocyte, eosinophils, and basophil steady states are lost	Decrease basophil levels [49]
c-MYB	All lineage attractors are still found	Neutrophil and monocyte production is enhanced [36]
SCL	All lineage attractors are still found	Early hematopoiesis is impaired [67]
c-KIT	Mast cell attractors are lost	Mast cell deficiency [17]
IL-3R α	All lineages attractors are found	Normal hematopoiesis [71]
βc	All lineages attractors are found	Normal hematopoiesis [50]

Supplementary Table 7: *In Silico* model and experimental gain of function mutants reported in literature. Color code is similar to Supplementary Table 6.

	In Silico Mutant	Experimental mutant
c-JUN	All lineages are found	Aberrant excessive monocyte production [83]
GATA-2	Neutrophils and monocytes are lost	Disrupted myelo-monocytic production and eosinophilia [88]

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