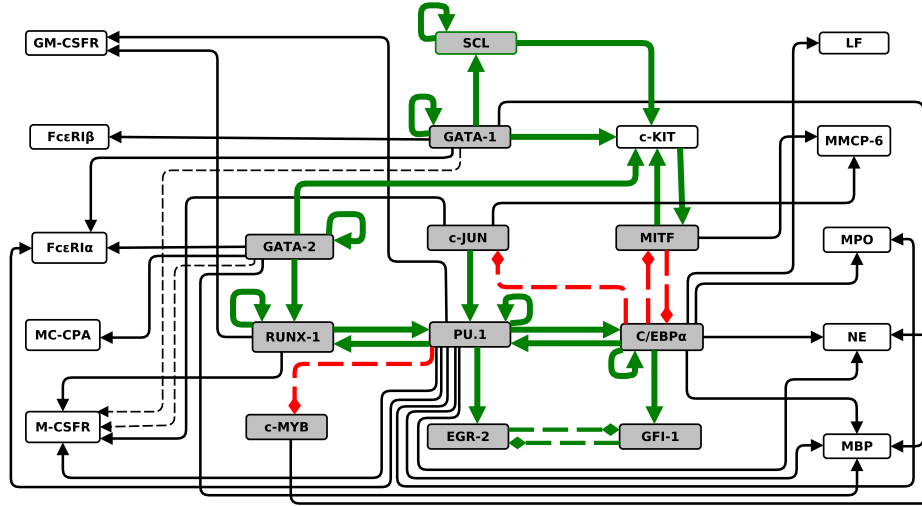
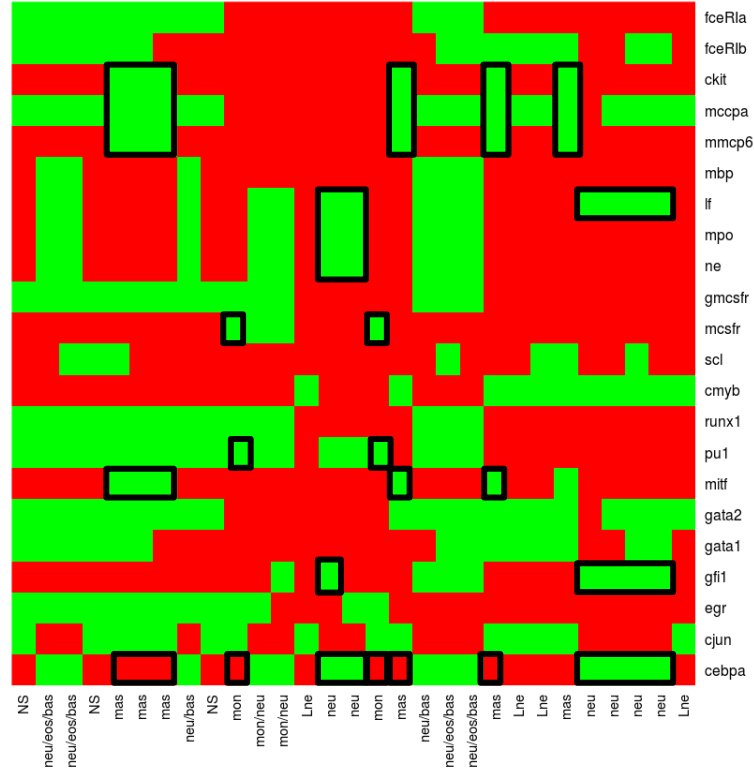


**Phenotypic stability and plasticity in
GMP-derived cells as determined by their
underlying regulatory network:
Supplementary Data**

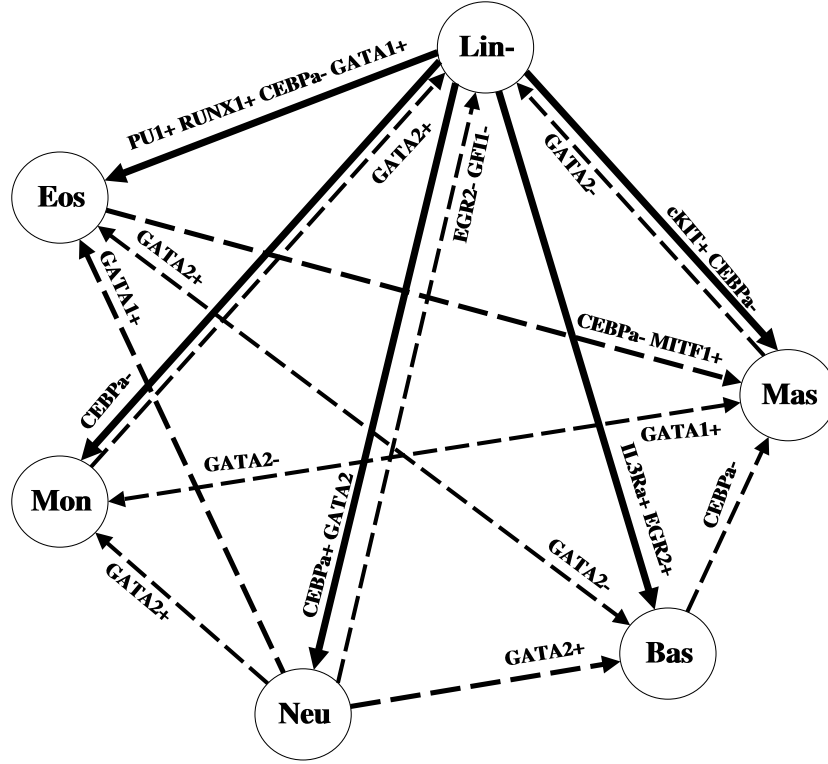
Carlos Ramírez and Luis Mendoza



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.



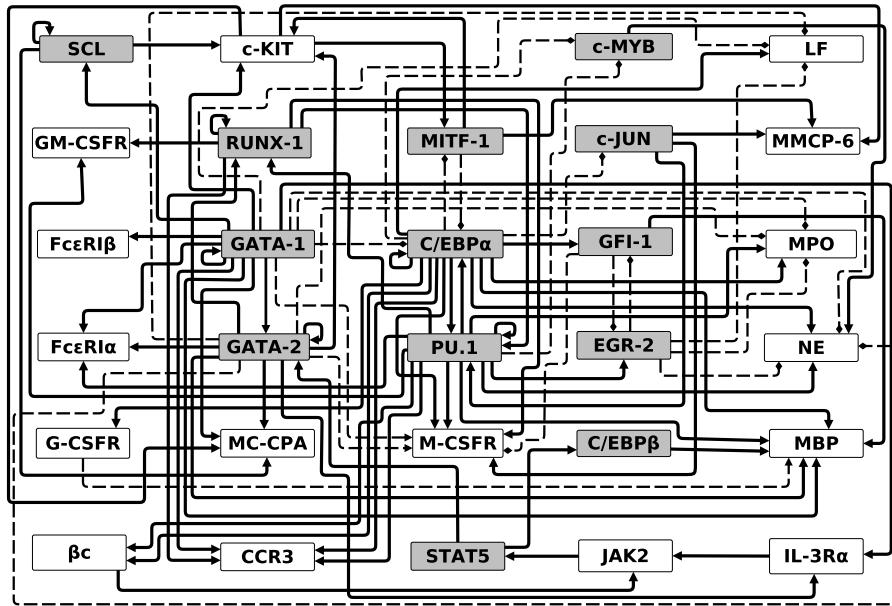
Supplementary Figure 2: **Attractors of the Boolean Regulatory Network of well grounded direct interactions** inferred from experiments reported in the literature. Green (red) boxes represent active (inactive) nodes. For attractors having one and only one GMP lineage pattern (defined in Supplementary 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 3: **Transitions between classes of attractors.** Simulations were carried out using asynchronous updating. The nodes represent attractors classes and the arrows possible transitions by single transient perturbations. Continuous arrows represent expected transitions from Lin^- phenotypes to mature lineage phenotypes. Discontinuous arrows represent possible transitions as recovered by the model. Arrows are labeled with the perturbed nodes. For example: monocyte attractor subset is redirected to the Lin^- attractor by upregulating the GATA-2 node.



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 supported direct interactions. AND and OR logic operators are represented by "&" and "|", 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]
$\neg GFI\text{-}1 \& PU.1 \dashv EGR\text{-}2$	[32]
$MITF\text{-}1 \rightarrow c\text{-KIT}$	[77]
$MITF\text{-}1 \dashv C/EBP\alpha$	[63]
$MITF\text{-}1 \rightarrow MMCP6$	[46, 47]
$PU.1 \dashv c\text{-MYB}$	[5]
$PU.1 \rightarrow EGR\text{-}2$	[32]
$PU.1 \& RUNX\text{-}1 \rightarrow GM\text{-CSFR}$	[21]
$PU.1 \& RUNX\text{-}1 \rightarrow M\text{-CSFR}$	[21]
$PU.1 \rightarrow PU.1$	[60, 33]
$RUNX\text{-}1 \rightarrow PU.1$	[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 "!", 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. Arrows and blunted arrows represent positive and negative interactions, respectively.

Updating logic rule	References
$\beta c \ \& \ (\text{GM-CSFR} \mid \text{IL-3R}\alpha) \rightarrow \text{JAK2}$	[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]
$\text{GATA-1} \mid \text{GATA-2} \rightarrow \text{IL-3R}\alpha$	[44]
$\text{GATA-1} \mid \text{GATA-2} \dashv \text{NE}$	Proposed in this work
$\text{GATA-1} \mid \text{GATA-2} \dashv \text{MPO}$	Proposed in this work
$\text{GATA-1} \mid \text{GATA-2} \dashv \text{LF}$	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]
Fc ϵ RI β	GATA-1	[40]
Fc ϵ RI α	(GATA-1 GATA-2) & PU.1	[51]
CCR3	C/EBP α & GATA-1 & PU.1 & RUNX-1	[29, 31]

Supplementary Table 5: Definition of the attractor subsets. Lin-
eage 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 MM-
CPA, 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 tertiary 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	Defect 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]
SC ^{-L}	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]
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]

References

- [1] Arinobu Y *et al.*, (2005) Developmental checkpoints of the basophil/mast cell lineages in adult murine hematopoiesis. *PNAS*, 102, 18105-10.
- [2] Baltus B *et al.*, (1998) An AP-1 site in the promoter of the human IL-5R alpha gene is necessary for promoter activity in eosinophilic HL60 cells. *FEBS letters*, 434, 251-4.
- [3] Barahmand-Pour F *et al.*, (1998) Jak2-Stat5 interactions analyzed in yeast. *The Journal of biological chemistry*, 273, 12567-75.
- [4] Heath V *et al.*, (1999) c-Jun is a JNK-independent coactivator of the PU.1 transcription factor. *The Journal of biological chemistry*, 274, 4939-46.
- [5] Bellon T *et al.*, (1997) Granulocytic differentiation of normal hematopoietic precursor cells induced by transcription factor PU.1 correlates with negative regulation of the c-myc promoter. *Blood*, 90, 1828-39.
- [6] Burda P *et al.*, (2009) PU.1 Activation Relieves GATA-1-Mediated Repression of Cebpa and Cbfb during Leukemia Differentiation *Molecular Cancer Research*, 7, 1693-47.
- [7] Cai 2008 *et al.*, (2008) C/EBP β :AP-1 leucine zipper heterodimers bind novel DNA elements, activate the PU.1 promoter and direct monocyte lineage commitment more potently than C/EBP β homodimers or AP-1 *Oncogene*, 27, 2772-2779.
- [8] Chen H *et al.*, (1995) Neutrophils and monocytes express high levels of PU.1 (Spi-1) but not Spi-B. *Blood*, 85, 2918-28.
- [9] Christy R *et al.*, (1991) CCAAT / enhancer binding protein gene promoter : Binding of nuclear factors during differentiation of 3T3-L1 preadipocytes *PNAS*, 88, 2593-2597.
- [10] Dahl R *et al.*, (2003) Regulation of macrophage and neutrophil cell fates by the PU.1:C/EBP α ratio and granulocyte colony-stimulating factor. *Nature Immunology*, 4, 1029-1036.
- [11] Du J *et al.*, (2002) Novel combinatorial interactions of GATA-1, PU.1, and C/EBP ϵ isoforms regulate transcription of the gene encoding eosinophil granule major basic protein. *The journal of biological chemical chemistry*, 277, 43481-94.
- [12] Dyer K *et al.*, (2007) Eosinophils from Lineage-Ablated dblGATA Bone Marrow Progenitors: The dblGATA Enhancer in the Promoter of GATA-1 Is Not Essential for Differentiation Ex Vivo. *The Journal of Immunology*, 179, 1693-1699.
- [13] Eferl R *et al.*, (1999) Functions of c-Jun in liver and heart development. *The Journal of cell biology* , 145, 1049-61.
- [14] Ford A *et al.*, (1996) Regulation of the myeloperoxidase enhancer binding proteins Pu1, C-EBP alpha, -beta, and -delta during granulocyte-lineage specification. *PNAS*, 93, 10838-43.
- [15] Fukuchi Y *et al.*, (2008) Activation of CCAAT/Enhancer-Binding Protein or PU.1 in Hematopoietic Stem Cells Leads to Their Reduced Self-Renewal and Proliferation *Stem Cells*, 26, 3172-3181.
- [16] Grass J *et al.*, (2003) GATA-1-dependent transcriptional repression of GATA-2 via disruption of positive autoregulation and domain-wide chromatin remodeling. *PNAS*, 100, 8811-6.
- [17] Grimbaldeston M *et al.*, (2005) Mast cell-deficient W-sash c-kit mutant KitW-sh/W-sh mice as a model for investigating mast cell biology in vivo. *Am. J. Pathol.*, 167, 835-848.
- [18] Hercus T *et al.*, (2012) The GM-CSF receptor family: mechanism of activation and implications for disease. *Growth Factors*, 30, 63-75.

- [19] Hirasawa R *et al.*, (2002) Essential and Instructive Roles of GATA Factors in Eosinophil Development *Journal of Experimental Medicine*, 195, 1379-1386.
- [20] Hock M *et al.*, (2003) Intrinsic requirement for zinc finger transcription factor Gfi-1 in neutrophil differentiation. *Immunity*, 18, 109-20.
- [21] Hu Z *et al.*, (2011) RUNX1 regulates corepressor interactions of PU.1. *Blood* , 117, 6498-508.
- [22] Huang G *et al.*, (2008) PU.1 is a major downstream target of AML1 (RUNX1) in adult mouse hematopoiesis. *Nature Genetics*, 40, 51-60.
- [23] Iwasaki H *et al.*, (2005) Identification of eosinophil lineage-committed progenitors in the murine bone marrow. *The Journal of experimental medicine*, 201, 1891-7.
- [24] Iwasaki H *et al.*, (2006) The order of expression of transcription factors directs hierarchical specification of hematopoietic lineages. *Genes & development*, 20, 3010-21.
- [25] Khanna A *et al.*, (2000) Sp1 and C/EBP are necessary to activate the lactoferrin gene promoter during myeloid differentiation. *Blood*, 95, 3734-41.
- [26] Khanna A *et al.*, (2003) Chromatin immunoprecipitation (ChIP) studies indicate a role for CCAAT enhancer binding proteins alpha and epsilon (C / EBP Î¸ and C / EBP Î) and CDP / cut in myeloid maturation-induced lactoferrin gene expression Chromatin immunoprecipitation (ChIP) *Blood*, 101, 3460-68.
- [27] Kim D *et al.*, (1999) Different effect of various mutant MITF encoded by mi, Mior, or Miwh allele on phenotype of murine mast cells. *Blood*, 93, 4179-86.
- [28] Kim D *et al.*, (2004) Requirement of c-jun transcription factor on the mouse mast cell protease-6 expression in the mast cells. *Archives of biochemistry and biophysics*, 431, 71-78.
- [29] Kim B *et al.*, (2010) The crucial role of GATA-1 in CCR3 gene transcription: modulated balance by multiple GATA elements in the CCR3 regulatory region. *Journal of immunology*, 185, 6866-75.
- [30] Kummalue T *et al.*, (2003) Cross-talk between regulators of myeloid development: C/EBPalpha binds and activates the promoter of the PU.1 gene. *Journal of leukocyte biology*, 74, 464-70.
- [31] Kong S *et al.*, (2016) Roles of RUNX1 and PU.1 in CCR3 Transcription. *Immune network*, 16, 176-82.
- [32] Laslo P *et al.*, (2006) Multilineage transcriptional priming and determination of alternate hematopoietic cell fates *Cell*, 126, 755-6.
- [33] Leddin M *et al.*, (2011) Two distinct auto-regulatory loops operate at the PU.1 locus in B cells and myeloid cells. *Blood*, 117, 2827-38.
- [34] Lee Y *et al.*, (2011) KIT signaling regulates MITF expression through miRNAs in normal and malignant mast cell proliferation. *Blood*, 117, 3629-40.
- [35] Li Y *et al.*, (2015) The STAT5-GATA2 pathway is critical in basophil and mast cell differentiation and maintenance *J Immunol*, 194, 4328-4338.
- [36] Lieu Y *et al.*, (2009) Conditional c-myb knockout in adult hematopoietic stem cells leads to loss of self-renewal due to impaired proliferation and accelerated differentiation. *PNAS*, 106, 21689-21694.
- [37] Lidonnici M *et al.*, (2010) Expression of the transcriptional repressor Gfi-1 is regulated by C/EBPalpha and is involved in its proliferation and colony formation-inhibitory effects in p210BCR/ABL-expressing cells. *Cancer Research*, 70, 7949-59.

- [38] Liu Q *et al.*, (2012) Gfi-1 inhibits the expression of eosinophil major basic protein (MBP) during G-CSF-induced neutrophilic differentiation. *International journal of hematology*, 95, 640-7.
- [39] Ma O *et al.*, (2014) Granulopoiesis Requires Increased C/EBP β Compared to Monopoiesis, Correlated with Elevated Cebpa in Immature G-CSF Receptor versus M-CSF Receptor Expressing Cells. *PloS one*, 9, e95784.
- [40] Maeda K *et al.*, (2003) Regulation of Cell Type-Specific Mouse Fc RI -Chain Gene Expression by GATA-1 Via Four GATA Motifs in the Promoter. *The Journal of Immunology*, 170, 334-40.
- [41] Maeda K *et al.*, (2010) GATA2 and Sp1 positively regulate the c-kit promoter in mast cells. *The Journal of Immunology*, 185, 4252-60.
- [42] Martowicz M *et al.*, (2005) Dynamic GATA factor interplay at a multicomponent regulatory region of the GATA-2 locus. *The Journal of biological chemistry*, 280, 1724-32.
- [43] McCormack M *et al.*, (1997) Expression of activated mutants of the human interleukin-3/interleukin-5/granulocyte-macrophage colony-stimulating factor receptor common beta subunit in primary hematopoietic cells induces factor-independent proliferation and differentiation. *Blood*, 90, 1471-81.
- [44] Miyajima I *et al.*, (1995) The murine interleukin-3 receptor alpha subunit gene: chromosomal localization, genomic structure, and promoter function. *Blood*, 85, 1246-53.
- [45] Moignard V *et al.*, (2013) Characterization of transcriptional networks in blood stem and progenitor cells using high-throughput single-cell gene expression analysis. *Nature cell biology*, 15, 363-72.
- [46] Morii E *et al.*, (1996) Regulation of mouse mast cell protease 6 gene expression by transcription factor encoded by the mi locus. *Blood*, 88, 2488-94.
- [47] Morii E *et al.*, (2002) Interaction and cooperation of mi transcription factor (MITF) and myc-associated zinc-finger protein-related factor (MAZR) for transcription of mouse mast cell protease 6 gene. *The Journal of biological chemistry*, 277, 8566-71.
- [48] Munugalavadla V *et al.*, (2005) Repression of c-kit and its downstream substrates by GATA-1 inhibits cell proliferation during erythroid maturation. *Molecular and cellular biology*, 25, 6747-6759.
- [49] Mukai K *et al.*, (2012) Critical role of P1-Runx1 in mouse basophil development. *Blood*, 120, 76-85.
- [50] Nishinakamura R *et al.*, (1995) Mice deficient for the IL-3/GM-CSF/IL-5 beta c receptor exhibit lung pathology and impaired immune response, while beta IL3 receptor-deficient mice are normal. *Immunity*, 2, 211-22.
- [51] Nishiyama C *et al.*, (2002) Regulation of Human FcepsilonRIalpha-Chain Gene Expression by Multiple Transcription Factors *The Journal of Immunology*, 168, 4546-4552.
- [52] Nishiyama C *et al.*, (2005) GATA-1 is required for expression of FcepsilonRI on mast cells: analysis of mast cells derived from GATA-1 knockdown mouse bone marrow. *International immunology*, 17, 847-56.
- [53] Nottingham W *et al.*, (2007) Runx1-mediated hematopoietic stem-cell emergence is controlled by a Gata/Ets/SCL-regulated enhancer. *Blood*, 110, 4188-97.
- [54] Nozawa D *et al.*, (2009) GATA2-dependent and region-specific regulation of Gata2 transcription in the mouse midbrain. *Genes to cells*, 14, 569-82.
- [55] Oelgeschlager M *et al.*, (2004) C/EBP, c-Myb, and PU.1 cooperate to regulate the neutrophil elastase promoter. *C Molecular and cellular biology*, 16, 4717-25.

- [56] Ogata N *et al.*, (1997) The activation of the JAK2/STAT5 pathway is commonly involved in signaling through the human IL-5 receptor. *International archives of allergy and immunology*, 114, 24-7.
- [57] Ogilvy S *et al.*, (2007) The SCL +40 enhancer targets the midbrain together with primitive and definitive hematopoiesis and is regulated by SCL and GATA proteins. *Molecular and cellular biology*, 27, 7206-19.
- [58] Ohmori S *et al.*, (2012) Regulation of GATA factor expression is distinct between erythroid and mast cell lineages. *Molecular and cellular biology*, 32, 4742-55.
- [59] Ohneda K *et al.*, (2002) A minigene containing four discrete cis elements recapitulates GATA-1 gene expression in vivo. *Genes to cells*, 7, 1243-54.
- [60] Okuno Y *et al.*, (2005) Potential Autoregulation of Transcription Factor PU . 1 by an Upstream Regulatory Element *Molecular Cell Biology*, 25, 2832-2845.
- [61] Olson M *et al.*, (1995) PU. 1 is not essential for early myeloid gene expression but is required for terminal myeloid differentiation. *Immunity*, 3, 703-14.
- [62] Piao X *et al.*, (1996) A point mutation in the catalytic domain of c-kit induces growth factor independence, tumorigenicity, and differentiation of mast cells *Blood*, 87, 3117-23.
- [63] Qi X *et al.*, (2013) Antagonistic regulation by the transcription factors C/EBP β and MITF specifies basophil and mast cell fates. *Immunity*, 39, 97-110.
- [64] Qiu Z *et al.*, (2009) GATA transcription factors regulate the expression of the human eosinophil-derived neurotoxin (RNase 2) gene. *The Journal of biological chemistry*, 284, 13099-109.
- [65] Radomska H *et al.*, (1998) CCAAT/enhancer binding protein alpha is a regulatory switch sufficient for induction of granulocytic development from bipotential myeloid progenitors. *Molecular and cellular biology*, 18, 4301-14.
- [66] Rangatia J *et al.*, (2002) Downregulation of c-Jun Expression by Transcription Factor C / EBP alpha Is Critical for Granulocytic Lineage Commitment *Molecular and cellular biology*, 22, 8681-8694.
- [67] Robb L *et al.*, (1995) Absence of yolk sac hematopoiesis from mice with a targeted disruption of the scl gene. *PNAS*, 92, 7075-7079.
- [68] Scott E *et al.*, (1994) Requirement of transcription factor PU.1 in the development of multiple hematopoietic lineages *Science*, 265, 1573-1577.
- [69] Smith L *et al.*, (1996) PU.1 (Spi-1) and C/EBP alpha regulate the granulocyte colony-stimulating factor receptor promoter in myeloid cells. *Blood*, 88, 1234-47.
- [70] Soliera A *et al.*, (2008) Transcriptional repression of c-Myb and GATA-2 is involved in the biologic effects of C/EBPalpha in p210BCR/ABL-expressing cells. *Blood*, 112, 1942-50.
- [71] Takahiko H *et al.*, (1995) Interleukin-3 (IL-3) Poor-Responsive inbred mouse strains carry the identical deletion of a branch in the IL-3 Receptor α Subunit Gene *Blood*, 85, 2331-2336.
- [72] Timchenko N *et al.*, (1995) Autoregulation of the human C/EBP alpha gene by stimulation of upstream stimulatory factor binding. *Molecular and cellular biology*, 15, 1192-202.
- [73] Tijssen M *et al.*, (2010) Genome-wide analysis of simultaneous GATA1/2, RUNX1, FLI1, and SCL binding in megakaryocytes identifies hematopoietic regulators. *Developmental cell*, 20, 597-609.
- [74] Tripic T *et al.*, (2009) SCL and associated proteins distinguish active from repressive GATA transcription factor complexes. *Blood*, 113, 2191-201.

- [75] Tsai S *et al.*, (1991) Functional analysis and in vivo footprinting implicate the erythroid transcription factor GATA-1 as a positive regulator of its own promoter *Genes and Development*, 5, 919-931.
- [76] Tsai F *et al.*, (1997) Transcription factor GATA-2 is required for proliferation/survival of early hematopoietic cells and mast cell formation, but not for erythroid and myeloid terminal differentiation. *Blood*, 89, 3636-43.
- [77] Tsujimura T *et al.*, (1996) Involvement of transcription factor encoded by the *mi* locus in the expression of c-kit receptor tyrosine kinase in cultured mast cells of mice. *Blood*, 88, 1225-33.
- [78] van Dijk T *et al.*, (1999) A composite C/EBP binding site is essential for the activity of the promoter of the IL-3/IL-5/granulocyte-macrophage colony-stimulating factor receptor beta c gene. *Journal of immunology*, 163, 2674-80.
- [79] Wilson N *et al.*, (2010) Gfi1 expression is controlled by five distinct regulatory regions spread over 100 kilobases, with Scl/Tal1, Gata2, PU.1, Erg, Meis1, and Runx1 acting as upstream regulators in early hematopoietic cells. *Molecular and cellular biology*, 30, 3853-63.
- [80] Xu G *et al.*, (2003) STAT5-induced Id4 transcription involves recruitment of HDAC1 and deacetylation of C/EBP β *The EMBO Journal*, 22, 893-904.
- [81] Yamaguchi Y *et al.*, (1998) Mechanisms of transcription in eosinophils: GATA-1, but not GATA-2, transactivates the promoter of the eosinophil granule major basic protein gene *Blood*, 91, 3447-58.
- [82] Yamaguchi Y *et al.*, (2014) C/EBP β and GATA-1 synergistically regulate activity of the eosinophil granule major basic protein promoter: implication for C/EBP β activity in eosinophil gene expression *Blood*, 94, 1429-1439.
- [83] Yang Z *et al.*, (2009) Increased c-Jun Expression and Reduced GATA2 Expression Promote Aberrant Monocytic Differentiation Induced by Activating *Mol Cell Biol*, 29, 4376-4393.
- [84] Yeaman C *et al.*, (2007) C/EBP α binds and activates the PU.1 distal enhancer to induce monocyte lineage commitment. *Blood*, 110, 3136-42.
- [85] Zhang D *et al.*, (1997) Absence of granulocyte colony-stimulating factor signaling and neutrophil development in CCAAT enhancer binding protein α -deficient mice. *PNAS*, 94, 569-74.
- [86] Zhang P *et al.*, (1999) Negative cross-talk between hematopoietic regulators: GATA proteins repress PU.1. *PNAS*, 96, 8705-10.
- [87] Zon L *et al.*, (1991) GATA-binding transcription factors in mast cells regulate the promoter of the mast cell carboxypeptidase A gene. *The Journal of biological chemistry*, 266, 22948-53.
- [88] Zhang S *et al.*, (2002) Gain-of-function mutation of GATA-2 in acute myeloid transformation of chronic myeloid leukemia. *PNAS*, 105, 2076-81.