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CRITICAL REVIEW

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GATA factor transcriptional activity: Insights from genome-wide binding profiles

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Abstract

The members of the GATA family of transcription factors have homologous zinc fingers and bind to similar sequence motifs. Recent advances in genome-wide technologies and the integration of bioinformatics data have led to a better understanding of how GATA factors regulate gene expression; GATA-factor-induced transcriptional and epigenetic changes have now been analyzed at unprecedented levels of detail. Here, we review the results of genome-wide studies of GATA factor occupancy in human and murine cell lines and primary cells (as determined by chromatin immunoprecipitation sequencing), and then discuss the molecular mechanisms underlying the mediation of transcriptional and epigenetic regulation by GATA factors.

KEYWORDS

ChIP-seq, GATA factors, gene regulation, genome-wide occupancy

1 | INTRODUCTION

The GATA family of transcription factors comprises six members (GATA1–GATA6) that are expressed in various cell types and are involved in numerous physiologic and pathologic processes. All GATA factors have two highly conserved central zinc-finger DNA-binding domains, which recognize a GATA sequence motif (Figure 1). The C-terminal and N-terminal regions are less well conserved, and the N-terminal region contains activation domains.

Here, we review the results of the main genome-wide studies of GATA factor chromatin occupancy. These studies have highlighted the GATA factors' pivotal role in the modulation of gene expression and in the biology and development of various cell types.

Abbreviations: AML, acute myeloid leukemia; BET, bromodomain and extraterminal domain; CHD, congenital heart disease; ChIP-seq, chromatin immunoprecipitation sequencing; HDACs, histone deacetylases; HSPCs, hematopoietic stem/progenitor cells; MDS, myelodysplastic syndrome; NuRD, the nucleosome remodeling and deacetylase; T-ALL, T cell acute lymphoid leukemia; Th, T helper.

Oriana Romano and Annarita Miccio contributed equally to this work.

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2 | GATA1

The transcription factor GATA1 is expressed mainly in the hematopoietic system and specifically in erythroid and megakaryocytic cells, mast cells, eosinophils, and basophils. GATA1 is expressed in both early megakaryocytic-erythroid progenitors and terminally differentiated megakaryocytic and erythroid precursors, where it drives the transcriptional programs associated with the commitment and differentiation of hematopoietic stem/progenitor cells (HSPCs) toward these lineages.[2,3] Furthermore, GATA1 is required for the development of mast cells, eosinophils, and basophils.[4–7]

GATA1 genome-wide occupancy has been studied in murine and human erythroid and megakaryocytic cell lines and primary cells (Table 1, Table S1). This factor mainly occupies intergenic and intragenic regions (particularly intron 1). Only a small proportion of GATA binding sites map to promoter regions—suggesting that GATA1 primarily

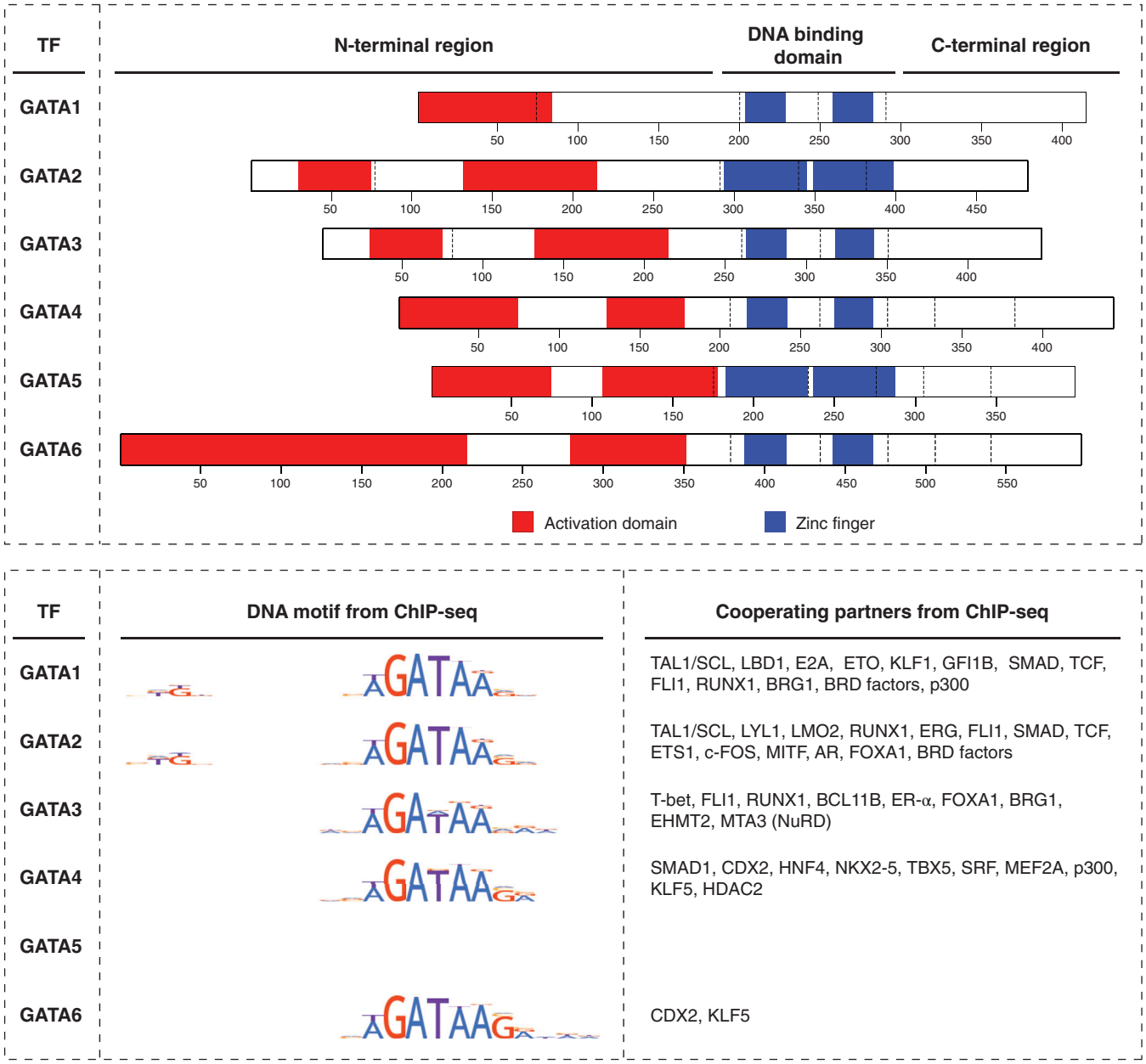

FIGURE 1 The structure of the GATA factors, their binding motifs, and the proteins that cooperate with them, as determined in genome-wide chromatin occupancy studies (upper panel). A schematic representation of the structure of the GATA factors, created with ProteinPaint (https://proteinpaint.stjude.org/). Activation domains are highlighted in red, and zinc finger domains are highlighted in blue. Dashed lines in the structure represent exon junctions (lower panel, left). Sequence motifs determined using genome-wide ChIP-seq data were obtained from the HOCOMOCO database (http://hocomoco11.autosome.ru/).[1] For GATA1 and GATA2, the E-Box motif recognized by TAL1 upstream of the GATA motif is shown (lower panel, right). Proteins cooperating with GATA factors, as determined in genome-wide chromatin occupancy studies. DNA motifs and cooperating partners are not reported for GATA5 because no ChIP-seq data are available

acts via long-range chromatin interactions.[8–16] Initially, it was shown that GATA1 binds to a WGATAR sequence motif. However, genome-wide studies of GATA1 chromatin occupancy have revised this original sequence motif and have highlighted the presence of single and dual (tandem or palindromic) GATA1 motifs and composite elements containing a sequence motif for collaborative transcription factors (for a review, see[17]).

GATA1 functions as either an activator or a repressor, depending on the gene context. Genome-wide studies suggested that the effect on gene expression is exerted not only by GATA1 but also by additional factors (other transcription factors, co-factors, and chromatin modifiers) that are recruited to a specific locus. In erythroid cells, GATA1 forms a complex with TAL1/SCL, LBD1, E2A, and LMO2. The complex then recognizes a GATA/E-box motif (a typical

TABLE 1 GATA1 ChIP-seq data sets

Organism	Cell type	# Data sets	# Samples	References
Homo sapiens	Hematopoietic progenitors	1	2	Huang et al. 2016
	Erythrocyte precursors	8	15	Canver et al. 2017; Pinello et al. 2014; Su et al. 2013; Kang et al. 2012; Xu et al. 2012; Trompouki et al. 2011; Hu et al. 2011
	Megakaryocytes	1	1	Tijssen et al. 2011
	Erythroleukemia cell lines	5	12	Huang et al. 2018; Trompouki et al. 2011; Pencovich et al. 2011; Fujiwara et al. 2009
	Colonrectal cancer cell lines	1	1	Yan et al. 2013
Mus musculus	Hematopoietic progenitors	4	4	Scialdone et al. 2016; Goode et al. 2016; Li et al. 2013; May et al. 2013
	Erythrocyte precursors	6	9	Hughes et al. 2014; Wontakal et al. 2012; Wu et al. 2011
	Erythroid cell lines	11	24	Stonestrom et al. 2015; Jain et al. 2015; May et al. 2013; Kadauke et al. 2012; Trompouki et al. 2011; Wu et al. 2011; Cheng et al. 2009; Yu et al. 2009
	Megakaryocytes	2	1	-
	Megakaryocytic cell lines	4	9	Chlon et al. 2015; Byrska-Bishop et al. 2015; Chlon et al. 2012; Doré et al. 2012

GATA1/TAL1 composite motif) and produces a general upregulation of gene expression. In this context, co-binding of TAL1/SCL and GATA1 occurs more frequently in activated genes than in repressed genes.[8,9,12,16,18–25] Furthermore, the looping factor LDB1 is involved in the GATA1-mediated activation of several erythroid-specific genes via long-range enhancer-promoter interactions (for a review, see Reference [26]). In contrast, a subcomplex of GATA1 and LDB1 lacking TAL1/SCL is present at repressed genes.[21] However, TAL1/SCL is still present at some repressed genes[8,18,27] where, in concert with GATA1, it might exert a repressive activity.[12] Indeed, several studies in both erythroid and non-erythroid cell types showed that TAL1/SCL can have a role in gene repression by recruiting co-repressors, such as SIN3A, ETO, and the polycomb repressive complex 2.[27–30] Moreover, the lack of TAL1/SCL accounts only for a small proportion of repressed genes.[23] In megakaryocytic cells, co-binding of GATA1 and TAL1/SCL is also associated with gene induction.[11,16]

GATA1 interacts and/or cooperates with several other transcription factors and cofactors (e.g., KLF1, GFI1B, FOG1, SMAD, TCF, ETS factors, and RUNX1).[9,11,13,16,18,31–36] Several studies have defined the genome-wide profile of many of these factors and highlighted their functional interaction with GATA1. It is known that GATA1 can interact with the erythroid transcription factor KLF1,[32] although the extent of colocalization is still subject to debate.[24,25,37,38] However, GATA1 and KLF1 were shown to bind conjointly to several erythroid enhancers and genes and thus cooperate in the gene induction process.[15,24,25,32,39–41] The transcriptional repressor GFI1B and GATA1 co-bind to some gene loci that are repressed upon erythroid development—suggesting that the two factors cooperate to repress gene expression in erythroid cells.[9,27] The transcriptional co-factor FOG1 is required for GATA1 activating or repressing activity at many loci in erythroid and megakaryocytic cells,[33–35,42] although genome-wide studies of FOG1 occupancy have not yet been performed. In erythroid cells, GATA1 co-occupies active enhancers together with the SMAD and TCF transcription factors activated during hematopoietic regeneration by stimulation of the BMP and Wnt signaling pathways, respectively.[36] In megakaryocytic cells, GATA1, ETS factors, and RUNX1 co-occupy regulatory regions and cooperate to upregulate megakaryocyte-specific gene expression.[11,13,16,18,31] Interestingly, the presence of ETS and RUNX1 binding sites constitutes the main difference between GATA1-bound active regulatory elements in megakaryocytic cells and those in erythroid cells.[13,16,18]

GATA1 also forms complexes with chromatin remodeling and modifying factors (the nucleosome remodeling and deacetylase [NuRD] complex, BRG1, and BRD factors),[12,43–46] histone-modifying enzymes (CBP/p300, Dot1l, and histone deacetylases [HDACs])[47–49] and polycomb-group members (Suz12, a subunit of the PRC2 complex).[9] In erythroid cells and megakaryocytes, NuRD mediates both activation and repression of GATA1 target genes,[42] whereas BRG1 (the ATPase subunit of the

SWI/SNF chromatin remodeling complex) shifts nucleosomes away from the GATA1 binding sites and thus facilitates TAL1/SCL binding and transcriptional activation upon erythroid differentiation.[12] In erythroid cells, the bromodomain and extraterminal domain (BET) family members BRD2, BRD3, and BRD4 facilitate GATA1-mediated transcriptional activation but are not essential for repression.[45,46] GATA1 associates with CBP/p300 acetyltransferases, HDACs, and the histone H3 lysine 79 methyltransferase Dot1l.[47–49] On the genome-wide scale, active histone modifications (e.g., H4K16 and H3K27ac, mediated by CBP/p300, and H3K4me1, 2, and 3) and the elongation mark H3K79me2 (produced by Dot1l) are enriched in GATA1-occupied regions in erythroid cells,[8,10,12,24,25,50] while H3K27me3 (mediated by the PRC2 complex) is present at lower levels at GATA1-occupied regions.[8,24] In particular, in erythroid cells, GATA1 binds to both active promoters ($H3K4me3^+$ and $H3K27ac^+$) and bivalent promoters ($H3K4me3^+$ and $H3K27me3^+$), and binds more to active, highly acetylated enhancers than to poorly acetylated enhancers.[50] The histone modifications distinguish active genes from inactive genes but do not distinguish genes activated from genes repressed by GATA1 upon erythroid differentiation—suggesting that chromatin states are established at the lineage commitment stage in early progenitors (lineage priming).[8,23] However, H3K27me3 has been found at some repressed genes in erythroid and megakaryocytic cells, which suggests that PRC2 is involved in the epigenetic silencing of a subset of GATA1-repressed genes.[8,9,13,24] In erythroid cells, this subset of genes shows low TAL1/SCL occupancy,[8] is involved in non-erythroid cell fate, and is strongly silenced. However, genes that are downregulated but still expressed in erythroid cells have low H3K27me3 levels and are involved in housekeeping processes.[24]

GATA1 drives major transcriptional changes during erythroid differentiation. GATA1-targeted genes differentially expressed upon erythroid differentiation have multiple GATA binding sites, which are located closer to the transcription start site[8,9,51] than for non-differentially expressed genes. Interestingly, these differences are more pronounced for upregulated genes than for downregulated genes.[8] Upregulated GATA1-targeted genes are involved in heme biosynthesis and erythrocyte differentiation, whereas downregulated GATA1-targeted genes are involved in RNA processing, translation, ribosome biogenesis, autophagy, cell proliferation, early hematopoiesis, and myeloid/immune system development.[24] Interestingly, GATA1 represses the myeloid/lymphoid master regulator PU.1 and PU.1-regulated genes[15] and silences mast-cell specific genes.[52]

Similarly, during megakaryocytic differentiation, GATA1 activates cell-specific genes and silences genes associated with the immature, proliferative state and alternative lineages.[13,16] For example, GATA1 likely represses mast-cell specific genes via FOG1 and NuRD,[52] as observed in erythroid cells.

Given its prominent role in erythroid and megakaryocytic cells, in humans GATA1 mutations cause dyserythropoietic anemia and/or thrombocytopenia, X-linked thrombocytopenia and thalassemia, and congenial erythropoietic porphyria.[53–56] Compared with wild-type GATA1, mutants unable to bind to FOG1 either have different DNA binding preferences (leading to aberrant gene expression)[14] or showed a reduced binding to regions where an association with FOG1 is required.[57] Other GATA1 mutants are associated with poor recruitment of the TAL1/LMO2 complex.[57] Mutations leading to the exclusive production of a short GATA1 protein isoform lacking the N-terminus (GATA1s) are associated with myeloproliferative disorders[58] and acute megakaryocytic leukemia in children with Down syndrome[59,60] or with impaired erythropoiesis.[61] Mutations that lead to the expression of the GATA1s isoform are also observed in some patients with Diamond-Blackfan anemia—a bone marrow failure syndrome characterized by macrocytic anemia.[62] Genome-wide studies have shown that GATA1s binding is impaired at erythroid target genes but not at megakaryocytic target genes.[63,64]

3 | GATA2

GATA2 is expressed in multipotent HSPCs, erythroid/megakaryocytic committed progenitors/precursors, eosinophils, and mast cells. This factor is essential for maintaining hematopoietic progenitors but is also required for the terminal differentiation of eosinophils and mast cells.[65–67] In humans, mutations in GATA2 are associated with immunodeficiencies, myeloproliferative disorders, and myeloid leukemia. These mutations either lead to haploinsufficiency or to the generation of GATA2 mutants with impaired transcriptional activity, dominant negative activity, or increased transactivation activity.[53,55] Heterozygous GATA2 mutations that reduce or abrogate GATA2 transcriptional activity resulted in four human syndromes often associated with myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML): (a) monocytopenia/*Mycobacterium avium* complex; (b) dendritic cell, monocyte, B and natural killer lymphoid deficiency; (c) Emberger's syndrome; and (d) familial MDS/AML. The first three disorders cause alterations in the immune system (i.e., low monocyte, B cell, NK cell, and dendritic cell counts) and thus indicate that GATA2 also has an important role in the development of the immune system.[53–56,68,69] Activating GATA2 mutations have been identified in chronic myeloid leukemia and were also associated with an enhanced inhibitory effect on

PU.1—a transcription factor essential for myeloid cell differentiation.[53–56,68,69]

GATA2 is also expressed in a variety of non-hematopoietic tissues (mesenchymal stem cells, endothelium, central nervous system, urogenital organs, lung, prostate, and endometrium) and cancers (lung and prostate cancers).[56,70]

GATA2 genome-wide occupancy has been studied in murine and human cell lines and primary cells, including multipotent progenitors, and erythroid, megakaryocytic and mast cells (Table 2, Table S2). Like GATA1, GATA2 binds mostly to intragenic and intergenic regions.[11,13,71,72] Genome-wide GATA2 chromatin immunoprecipitation sequencing (ChIP-seq) studies identified the expected GATA motif at GATA2-bound regions.[13,71–75] However, compared to GATA1, GATA2-bound sequences contain novel GATA-related motifs and GATA2 motif usage changes in different cell types.[74]

GATA2 has mainly been described as a positive regulator of gene expression. Critical GATA2 partners include TAL1/SCL, LYL1, LMO2, RUNX1, the ETS factors, and FOG1.[71,76–79] Genome-wide studies have shown that GATA2 cooperates with some of these factors to regulate gene expression. In HSPCs, GATA2 forms a regulatory complex with TAL1/SCL, LYL1, LMO2, RUNX1, and the ETS factors ERG and FLI1. This complex binds to the regulatory regions (i.e., active H3K27ac$^+$ enhancers) of genes involved in HSPC biology.[71–73] In HSPCs, GATA2 marks a subset of bivalent H3K27me3$^+$ H3K4me3$^+$ regulatory regions that are bound by GATA1 upon erythroid differentiation and tend to be located close to erythroid-specific genes—suggesting that GATA2 is at least partially involved in lineage priming.[16,41,51,71,72] Lastly, upon activation of the BMP and Wnt signaling pathways in HSPCs, SMAD and TCF co-occupy GATA2-bound enhancers associated with actively transcribed genes and enhance transcriptional activation by GATA2.[36]

In megakaryocytes, GATA2-occupied regions are generally enriched in the activating H3K4me3 mark, although

TABLE 2 GATA2 ChIP-seq data sets

Organism	Cell type	# Data sets	# Samples	References
Homo sapiens	Hematopoietic progenitors	2	2	Beck et al. 2013; Trompouki et al. 2011
	Erythrocyte precursors	2	3	Huang et al. 2016; Shearstone et al. 2016
	Megakaryocytes	1	1	Tijssen et al. 2011
	Erythroleukemia cell lines	6	10	Mazumdar et al. 2015; Trompouki et al. 2011; Fujiwara et al. 2009
	Endometrial stromal cells	1	1	Mika et al. 2018
	Trophoblast progenitors	1	3	–
	Endothelial cell lines	3	7	Wang et al. 2019; Linnemann et al. 2011
	Prostate cancer cell lines	4	15	Chaytor et al. 2019; Zhao et al. 2016; Wu et al. 2014
	AML cell lines	6	9	Yi et al. 2019; Loke et al. 2017; Sotoca et al. 2016; Katsumura et al. 2016; Mandoli et al. 2016
	Reprogrammed fibroblasts	1	4	Gomes et al. 2018
	Neuroblastoma cell lines	1	1	–
	Colonrectal cancer cell lines	1	1	Yan et al. 2013
Mus musculus	Hemangioblasts	1	1	Goode et al. 2016
	Hematopoietic progenitors	7	6	Hamey et al. 2017; Goode et al. 2016; Billing et al. 2016; May et al. 2013; Li et al. 2011; Wilson et al. 2010
	Erythroid cell lines	6	12	May et al. 2013; Trompouki et al. 2011; Wu et al. 2011
	Myeloid cell lines	2	2	Schütte et al. 2016
	Megakaryocytic cell lines	1	1	Doré et al. 2012
	Mast cells	2	2	Calero-Nieto et al. 2014; Moignard et al. 2013
	Trophoblast progenitors	1	1	Home et al. 2017
	Uterus	1	1	Rubel et al. 2016
	Fibroblast cell lines	1	2	Tolkachov et al. 2018
	Sarcoma cell lines	1	2	Tolkachov et al. 2018

some of these regions map to H3K27me3 domains.[13] GATA2 together with GATA1, TAL1/SCL, RUNX1, and the ETS factor FLI1 binds primarily to active promoters, and upregulates megakaryocyte-specific gene expression.[11] The ETS1 factor is a key determinant of GATA2 site selection in megakaryocytes, and is associated with GATA2-mediated target activation.[13] In HSPCs, megakaryocyte-associated *cis*-regulatory elements are bound by GATA2 and HSPC-expressed transcription factors (LYL1, TAL1/SCL, FLI1, ERG, RUNX1, and LMO2), indicating that transcriptional priming of megakaryocyte-specific genes occurs in HSPCs.[16] Furthermore, GATA2 is thought to have an extensive role in late megakaryopoiesis as a transcriptional repressor of genes expressed in HSPCs and alternative lineages.[16] Lastly, in mast cells, GATA2 activates cell-specific genes[80] in concert with the mast cell-specific transcription factors c-FOS and MITF.[75,81]

Genome-wide ChIP-seq studies of GATA2 occupancy have been performed in leukemic and prostate cancer cells. In AML, p38/ERK signaling causes GATA2 phosphorylation that leads to increased GATA2 chromatin occupancy, and GATA2-mediated induction of selected target genes (including IL1B and CXCL2); this activates a positive-feedback mechanism that promotes AML cell proliferation.[82] In prostate cancers, GATA2 is often overexpressed and is associated with tissue invasion, metastasis, and thus a poor prognosis.[83] In an androgen-dependent prostate cancer cell line, GATA2 colocalizes with the androgen receptor (AR, a ligand-activated transcription factor) and its co-factor FOXA1, and positively regulates the AR transcriptional program.[84,85] Like FOXA1, GATA2 acts as a pioneer transcription factor for AR.[84] GATA2 binds to AR target gene enhancers prior to hormone stimulation. GATA2 then recruits p300 to induce an accessible chromatin environment and the Mediator subunit MED1 to facilitate chromatin loop formation between AR enhancers and the target promoter.[84] Moreover, GATA2 directly promotes the expression of the AR before and after androgen stimulation.[84] In cell lines derived from an aggressive, castrate-resistant (antiandrogen-resistant) prostate cancer, GATA2 is a critical regulator of the transcriptional activity of a constitutively active AR variant; an interaction with BET proteins facilitates GATA2 chromatin occupancy and promotes the expression of cell-cycle-related genes targeted by GATA2 and regulated by the AR variant—thus favoring cell proliferation and disease progression.[86]

4 | THE GATA2-TO-GATA1 SWITCH

During erythropoiesis, the *GATA2* locus is shut down, while GATA1 levels increase; this phenomenon is known as the "GATA switch." The handover from GATA2 to GATA1 is essential for the expansion, survival, and terminal differentiation of erythroid cells via the up- or downregulation of several genes.[87–89] Genome-wide studies have shown that the GATA switch during erythroid differentiation occurs at many regulatory regions during the erythroid differentiation of murine erythroid cell lines[23] and human primary multipotent progenitor and committed erythroid precursors.[51] A time-course analysis in erythroid cells differentiating from a multipotent mouse progenitor cell line suggested that GATA2 is retained during recruitment of GATA1 in the early erythroid commitment stage.[74]

ChIP-seq analyses have shown that genes associated with GATA2-bound regulatory regions in HSPCs that fail to recruit GATA1 in erythroid cells tend to be downregulated.[51,74] In contrast, de novo binding of GATA1 is more often associated with genes that are upregulated in primary erythroid cells.[51,74] In the mouse, regulatory elements that undergo the GATA switch are located close to genes that tend to be upregulated.[74] Upon human erythroid differentiation, the GATA switch occurs at enhancers that are mostly either constitutively active or active only in differentiated erythroblasts, whereas only a small fraction of the enhancers lost upon erythroid differentiation undergo the GATA switch.[51]

In contrast to erythroid differentiation, GATA-2 expression is not rapidly downregulated during megakaryocyte maturation. However, evidence of a GATA2-to-GATA1 switch was reported in megakaryocytes, where it was associated with transcriptional activation or repression and GATA2 and GATA1 acted oppositely on target genes.[13,16]

5 | GATA3

GATA3 is expressed in lymphoid cells, mammary gland, central nervous system, skin, inner ear, kidney, and adrenal and parathyroid glands.[56,70,90–95] Indeed, GATA3 expression is fundamental for the development of these organs, and its dysregulation is involved in diseases such as T cell acute lymphoid leukemia (T-ALL), breast cancer, neuroblastoma, and hypoparathyroidism, sensorineural deafness, and renal disease syndrome.[96–100]

GATA3 has an essential role during T cell development.[90,91] In order to investigate the role of GATA3-mediated transcriptional regulation in this process, several groups have performed ChIP-seq for GATA3 at different stages of murine[101–105] and human T cell development[106,107] (Table 3, Table S3). The level of GATA3 expression varies with the developmental stage: higher levels of GATA3 were detected in double-negative thymocytes and T helper 2 (Th2) cells, while lower levels were present in double-positive thymocytes and Th1 cells.[101] The number of GATA3 binding sites ranged from a few hundred to several thousand, and was correlated with GATA3

TABLE 3 GATA3 ChIP-seq data sets

Organism	Cell type	# Data sets	# Samples	References
Homo sapiens	T cells	3	6	Van de Walle et al. 2016; Kanhere et al. 2012
	T-ALL cell lines	5	6	Saint-André et al. 2016; Hnisz et al. 2016; Sanda et al. 2012
	Trophoblast progenitors	1	3	–
	Breast cancer cell lines	14	73	Cornelissen et al. 2019; Nair et al. 2019; Hoffman et al. 2018; Yang et al. 2017; Takaku et al. 2016; Si et al. 2015; Liu et al. 2014; Adomas et al. 2014; Theodorou et al. 2013; Gertz et al. 2013; Kong et al. 2011
	Breast cancer primary tumors	1	3	Severson et al. 2018
	Neuroblastoma cell lines	5	10	Durbin et al. 2018; Boeva et al. 2017; Oldridge et al. 2015
	Lung adenocarcinoma cell lines	1	1	–
Mus musculus	Innate lymphoid cells	2	6	Miyamoto et al. 2019; Zhong et al. 2016
	T cells	7	25	Hosokawa et al. 2018; Fang et al. 2018; Zhong et al. 2016; Nakatsukasa et al. 2015; Zhang et al. 2012; Wei et al. 2011; Horiuchi et al. 2011
	Embryonic stem cells	1	1	Rhee et al. 2017
	Trophoblast stem cells	2	2	Rhee et al. 2017; Home et al. 2017

expression levels.[101,102] The analysis of GATA3 ChIP-seq profiles at different stages of T cell development showed that GATA3 genome-wide occupancy is cell-specific: distinct sets of GATA3-bound genes were identified at each stage in T cell development, whereas only a few binding sites were conserved among the various T cell types; these findings suggest that in each cell context, distinct co-factors may have critical roles in the differential binding of GATA3.[101] By the way of example, the genomic distribution of GATA3 binding profiles differs in human Th1 versus Th2 cells, and GATA3 distribution in Th1 cells is mediated by T-bet (the Th1 master regulator).[107]

GATA3 can act as transcriptional activator or repressor, and its binding sites have been found to be enriched at open chromatin regions (predominantly distal enhancers but also promoters).[101–103,106,107] The GATA3 binding sites mainly correspond to distal regulatory elements with active (H3K4me1 and H3K4me2) and repressive (H3K27me3) histone marks that strongly correlated with target gene activation and repression, respectively.[101,103,107] In some loci, GATA3 occupancy precedes the full activation of regulatory elements—suggesting a possible role as pioneer transcription factor.[103]

Motif analyses have shown that WGATAA is the predominant enriched motif at the center of GATA3 binding sites.[101–103,106,107] Moreover, ETS and RUNX motifs were found to be neighboring secondary motifs at GATA3 binding sites.[101–103,106] Furthermore, ChIP-seq analyses of the ETS factor FLI1 in Th2 cells and RUNX1 in T-ALL cell lines showed that both factors colocalize with GATA3.[101,108] These findings suggest that GATA3 cooperates with FLI1 and RUNX1 to regulate the transcription of its target genes. GATA3 also interacts directly with BCL11B, a zinc finger transcription factor that is essential for T cell development.[105] BCL11B binds to a subset of GATA3 binding sites and controls both GATA3-mediated gene activation and repression—indicating that this transcription factor has an important role in the fine-tuning of GATA3 transcriptional activity.[105]

GATA3 transcriptionally regulates key stages of T-lineage differentiation—particularly T cell commitment and Th2 cell specification. During T cell commitment (after the initial strong Notch signal that induces T-lineage specification), GATA3 controls the progression of T-lineage differentiation at various levels. Firstly, GATA3 directly regulates the expression of several critical T-lineage specific genes, including T-cell receptor components and several transcription factors.[101,103,106] Secondly, it prevents differentiation toward other lineages by repressing genes associated with NK and B cell development.[106] Thirdly, it modulates the expression of Notch target genes, leading to the overall reduction in Notch signaling required for the progression of T-lineage differentiation.[106] In Th2 cells, GATA3 acts as a master transcription factor. The IL4/STAT6 pathway is

essential for Th2 cell differentiation, and increases GATA3 expression via the direct binding of STAT6 to the GATA3 locus.[101] Genome-wide analyses of GATA3-binding profiles in Th2 cells identified thousands of binding sites in both mouse and human; the sites target key immune regulatory genes, receptor and Th2 cytokine genes that are upregulated by GATA3.[101,102,107] Concomitantly, GATA3 downregulates the expression of Th1 cell-specific genes in Th2 cells, which prevents differentiation toward the Th1 lineage.[101]

The role of GATA3 in neoplastic diseases has been extensively studied in the setting of human breast cancer (Tables 3 and S3). GATA-3 is a key developmental factor for the mammary gland, where it specifies the luminal epithelial cells' fate.[92] In normal human mammary epithelial cells, GATA3 directly targets genes associated with differentiation and reduced proliferation.[109] In cases of breast cancer, GATA3 has prognostic value: high GATA3 expression is correlated with a good prognosis,[92,110] while low GATA3 expression is associated with a larger tumor size, higher tumor grade, and an increased risk of recurrence and metastasis.[111] Moreover, GATA3 is mutated in more than 10% of human breast cancer tumors.[112–114] The role of GATA3 mutations in breast cancer is currently under investigation, as GATA3 appears to act as a tumor suppressor or as an oncogene depending on the mutation and the tumor subtype.[110]

GATA3 mutations often result in the formation of truncated proteins.[110] In a luminal breast cancer cell line, ChIP-seq studies revealed that truncated GATA3 mutants are unable bind to DNA through canonical GATA motifs but are tethered to the chromatin by interacting with other transcription factors (such as FOXA1).[115] This partially alters GATA3 genome-wide distribution, relative to the wild-type protein.[109,115] Moreover, truncated GATA3 mutants are more stable than the wild-type protein.[116] As a consequence, stronger GATA3 binding after stimulation with estradiol[116] resulted in greater transduction of hormone and growth factor signals in mutant cells than in normal mammary epithelial cells.[109]

Several groups have performed ChIP-seq analyses of GATA3 occupancy in luminal breast cancer cell lines with a heterozygous GATA3 mutation causing the formation of a truncated protein. The studies used antibodies that bind to both the wild-type GATA3 and the truncated mutant. It was found that GATA3 colocalizes with the estrogen receptor α (ER-α, a ligand-activated transcription factor) and its cofactor FOXA1 at enhancer regions.[117–119] In particular, GATA3 facilitated ER-α binding to genomic regions lacking active histone marks (H3K4me1 and H3K27Ac) and mediated chromatin interactions after estradiol induction—thus acting as a pioneer transcription factor.[120] Moreover, by recruiting BRG1, GATA3 can remodel local nucleosome occupancy and thus open up the chromatin structure.[121] In luminal breast cancer cell lines, however, GATA3 also acts as a transcriptional repressor by recruiting the EHMT2 histone lysine methyltransferase and the NuRD complex, and inducing the inhibitory GATA3/EHMT2/NuRD complex to bind to the promoter regions of genes related to cell migration and invasion.[122] Indeed, GATA3 overexpression in an invasive breast cancer cell line (derived from an aggressive triple-negative/basal-like breast cancer subtype) induced epithelial differentiation (by targeting genes related to the mesenchymal-to-epithelial transition) and maintained epithelial identity.[121]

The results of these studies in breast cancer cell lines indicate that together with ER-α, GATA3 has a critical role in both the promotion of tumor growth and the suppression of breast cancer metastasis. The circumstances under which GATA3 has a positive or negative impact in breast cancer biology have yet to be determined.

6 | GATA4

GATA4 and the related GATA5 and GATA6 factors are involved in the development and differentiation of endoderm- and mesoderm-derived tissues, such as the stomach, intestine, pancreas, liver, lung, and heart.[123–127] GATA4 genome-wide occupancy has been studied during development and in adult tissues, with a view to understanding how this factor regulates the fate of many cell types (Tables 4 and S4).

ChIP-seq profiles of GATA4 in different cell types have shown that this factor recognizes the canonical WGATAR motif, binds to genomic regions that are marked by H3K4me3, H3K4me1, and H3K27ac and are depleted for H3K27me3, and is mainly located in both intragenic regions (primarily in the first intron) and intergenic regions; only a small subset of the binding sites target promoters.[128–134] Comparisons of GATA4 genome-wide occupancy in different tissues and at different stages of development have revealed that the transcription factor is tissue- and stage-specific.[128,130,132,135] These findings therefore suggest that specific factors influence GATA4's binding preferences.

Furthermore, the ChIP-seq profiles for GATA4 in endoderm and mesoderm derived from human embryonic stem cells differ, with only a small subset of binding sites shared by the two lineages.[135] In mesoderm, GATA4 preferentially bind to mesodermal gene promoters and super-enhancers; in endoderm, the binding sites are located in endoderm gene enhancer regions.[135] GATA4 binding is associated with targeted loss of DNA methylation when embryonic stem cells differentiate into endoderm and mesoderm.[135] A concomitant increase in DNA methylation occurs at GATA4

TABLE 4 GATA4 ChIP-seq data sets

Organism	Cell type	# Data sets	# Samples	References
Homo sapiens	ES cells	1	1	Tsankov et al. 2015
	Mesendoderm	1	1	Tsankov et al. 2015
	Endoderm	2	8	Tsankov et al. 2015
	Mesoderm	1	8	Tsankov et al. 2015
	Foregut	1	2	–
	Pancreatic progenitors	1	2	–
	Fibroblast cell lines	2	4	Donaghey et al. 2018
	Cardiomyocytes	1	7	Ang et al. 2016
	Lung cancer cell lines	1	1	–
	Gastric cancer cell lines	1	3	Chia et al. 2015
	Colonrectal cancer cell lines	1	1	Yan et al. 2013
Mus musculus	ES cells	1	2	Oda et al. 2013
	Mesoderm	1	2	Oda et al. 2013
	Instestinal epithelial cells	1	1	Aronson et al. 2014
	Cardiac muscle cells	1	1	He et al. 2011
	Heart	3	12	He et al. 2014; van den Boogaard et al. 2012
	Liver	1	1	Zheng et al. 2013
	Reprogrammed fibroblasts	2	6	Shu et al. 2015
	Skeletal muscle myoblasts	1	1	–

binding sites in the alternative lineage, preventing later GATA4 binding that might activate inappropriate downstream genes.[129]

GATA4 can up- or downregulate transcription, depending on the cellular context. In adult mouse liver, GATA4 has a prominent role as transcriptional activator of genes involved in liver function (including lipid metabolism, glucose metabolism, and cytochrome p450-mediated metabolism); however, it also represses a subset of target genes that need to be expressed in immature hepatocytes but must be turned off in mature liver cells.[130] In the mouse small intestine, GATA4 activates genes that promote a jejunal identity (including those associated with transcription and digestion/absorption processes) while repressing genes related to cell death, signal transduction, cytoskeleton, and lipid metabolism, preventing an ileal identity.[131] In mouse cardiomyocytes, GATA4 promotes the expression of genes linked to heart development and function and represses those related to development of the vasculature.[128,132]

Genome-wide studies have highlighted several partners that cooperate with GATA4 in the transcriptional regulation of several lineages. In mesoderm, GATA4 and the signal transducer and transcriptional modulator SMAD1 co-bind to super-enhancers.[135] In mouse small intestine, GATA4 binding sites are co-occupied by the transcription factors CDX2 and HNF4, both of which are known to regulate gene expression programs in the intestine.[131] In mouse cardiomyocytes, a subset of GATA4 binding sites are occupied by other key cardiac transcription factors, including NKX2-5, TBX5, SRF, and MEF2A.[128,132,134] Moreover, fetal-specific GATA4 binding sites are enriched in the motif recognized by TEAD1 (a transcriptional regulator required for heart development), while adult-specific regions are enriched in the motif recognized by EGR1 (a transcription factor involved in various pathologic cardiovascular processes).[128,132] Lastly, in some cell types, p300 is recruited by GATA4 mainly at enhancer regions close to activated genes, where it increases H3K27ac levels; conversely, GATA4 binding sites close to repressed target genes showed lower p300 occupancy rates and lower H3K27ac levels.[128,131,132]

Given the importance of GATA4's actions during development, the mutation or overexpression of this factor leads to disease. Gastric cancer is associated with elevated levels of GATA4, GATA6, and KLF5.[136] In gastric cancer cell lines, ChIP-seq studies have highlighted a high degree of overlap between GATA4 and GATA6 binding sites, some of which are also occupied by KLF5.[133] Each of these transcription factors binds to regulatory regions of its own gene and also to those of genes encoding other transcription factors; this establishes a self- and cross-regulatory circuit that

controls the expression of genes involved in cell movement, cell death, proliferation, and development, and that is strongly activated in gastric cancer.[133]

GATA4 has an important role in cardiac hypertrophy, in which sources of pathologic cardiac stress (such as pressure overload) alter cardiomyocyte growth and gene expression. Cardiac stress induces a significant change in GATA4 occupancy, relative to physiological conditions.[132] GATA4 is recruited at a number fetal-specific regulatory regions (reactivating a fetal gene program) or targets new genomic sites not bound in normal heart development (thus acting as pioneer factor at closed chromatin regions).[132] These stress-related GATA4 binding sites map to genes that are upregulated in a context of cardiac hypertrophy and are enriched in the binding motif for of NFAT—a calcium-responsive transcription factor family that is essential for heart development and that is involved in the heart's response to pathologic stimuli.[132]

Human mutations in GATA4 are associated with congenital heart disease (CHD).[137] Cardiomyocytes with a heterozygous GATA4-G296S missense mutation display impairments in contractility, calcium handling, and metabolic activity, and the mutated GATA4 failed to interaction with TBX5 in vitro.[126] The G296S mutation induces the redistribution of GATA4 to different genomic sites and disrupts the recruitment of TBX5—particularly to super-enhancers of important cardiac genes.[134] This results in the downregulation of target cardiac genes, which display lower GATA4 and TBX5 binding. Moreover, the G296S mutant causes the aberrant activation of the expression program for alternative lineages. Endothelial genes normally repressed by GATA4 are upregulated in mutated cardiomyocytes due to a reduced binding of GATA4; in turn, this results in a loss of HDAC2 recruitment, and the genes' promoters fail to adopt a closed chromatin conformation.[134]

7 | GATA5

GATA5 is expressed in the heart, liver, pancreas, ovary, lungs, gastrointestinal tract, and genitourinary system. This factor has a role in cardiovascular development, intestinal epithelial cell differentiation, and development of the female genitourinary system.[138–142] In humans, GATA5 mutations are associated with heart conditions (i.e., CHD and familial atrial fibrillation).[56] GATA5 gene promoter silencing by methylation in gastrointestinal, bladder, and lung cancers is associated with lower expression levels of the candidate target genes—suggesting a role for GATA5 in gene activation.[143]

Indeed, GATA5 has been described as a transcriptional activator of cardiac, intestinal, and hepatic genes.[144–148] GATA5 interacts with the hepatocyte nuclear factor HNF1α, the cardiac T-box transcription factor Tbx20, and p300 to synergistically activate gene promoters.[145,146,148–150] To date, no genome-wide studies of GATA5 occupancy have been performed.

8 | GATA6

GATA6 has a major role in the development of the heart, vascular system, stomach, intestine, colon, liver, pancreas, lungs, and adrenal glands.[151–158] Mutations in GATA6 have been linked to CHD and pancreatic agenesis.[56] The genome-wide studies of GATA6 occupancy were mainly performed in murine and human endoderm-derived tissues (Tables 5 and S5). GATA6 acts both as a transcriptional activator and repressor, and binds to promoters, intragenic regions, and distal intergenic regions through the canonical GATA motif.[133,135,159–164]

A genome-wide binding profiling during the endoderm differentiation of human pluripotent stem cells demonstrated that GATA6 directly regulates the expression of several transcription factors (including GATA4) required for the establishment and maintenance of the endoderm fate.[163] As also described for GATA4, GATA6 binding is associated with a targeted loss of DNA methylation during early embryonic development.[135]

Like GATA4, GATA6 is amplified in the setting of gastric cancer[136]; ChIP-seq profiles in gastric cancer cell lines have highlighted a high degree of overlap between GATA4- and GATA6-occupied regions.[133] In this context, GATA6 and GATA4 activate genes involved in cell movement, death, and survival and that are associated with tumor development.[133,160]

In human intestinal cells, GATA6 binds to active regulatory elements together with CDX2, a master regulator of the intestinal epithelium.[159] In colorectal tumors, GATA6 sustains cancer stem cell renewal through the repression of genes encoding negative regulators of the Wnt pathway. In particular, GATA6 exerts its repressive activity by blocking the binding of the activating β-catenin/TCF4 complex to the genes' regulatory elements.[161]

In the mouse pancreas, GATA6 is required for the complete differentiation and then maintenance of acinar cells. GATA6 upregulates genes coding for acinar master transcription factors and digestive enzymes, and genes involved in protein synthesis and secretion, while repressing genes expressed in alternative endodermal lineages.[162] In human pancreatic ductal adenocarcinoma cell lines, GATA6 promotes the expression of epithelial genes and concomitantly inhibits the mesenchymal program.[164] This transcriptional activity suggests that GATA6 exerts a tumor-suppressor-like activity in pancreatic cancer by enforcing acinar cell differentiation and inhibiting the epithelial-to-mesenchymal

TABLE 5 GATA6 ChIP-seq data sets

ORGANISM	Cell type	# Data sets	# Samples	References
Homo sapiens	ES cells	1	1	Tsankov et al. 2015
	Mesendoderm	1	1	Tsankov et al. 2015
	Endoderm	4	12	Fisher et al. 2017; Tsankov et al. 2015
	Mesoderm	1	2	Tsankov et al. 2015
	Foregut	1	4	–
	Pancreatic progenitors	1	4	–
	Pancreatic cancer cell lines	1	1	Martinelli et al. 2017
	Gastric cancer cell lines	2	5	Chia et al. 2015; Sulahian et al. 2014
	Colonrectal cancer cell lines	3	6	Whissell et al. 2014; Yan et al. 2013; Verzi et al. 2010
Mus musculus	ES cells	1	2	Wamaitha et al. 2015
	Extraembryonic endoderm	1	2	Wamaitha et al. 2015
	Primary keratinocytes	1	2	Donati et al. 2017
	Pancreas	1	4	Martinelli et al. 2016
	Reprogrammed fibroblasts	1	2	Shu et al. 2015

transition.[164] In fact, high GATA6 levels are associated with well-differentiated tumors and better patient outcomes, while the loss of GATA6 is associated with impaired differentiation and shorter overall patient survival.[165]

9 | SUMMARY AND OUTLOOK

GATA factors are expressed and have fundamental roles in the development of many cell types and organs, as demonstrated by the wide range of diseases and pathologic phenotypes associated with GATA factor mutations or dysregulated GATA expression. This highly diversified expression pattern is strictly regulated by cell-specific *cis*-regulatory elements that enable the expression of each GATA factor at the appropriate time and in the appropriate place within the organism.

Even though the different GATA factors have a highly conserved DNA binding domain[56] and recognize highly similar GATA motifs (Figure 1), a number of studies have demonstrated that the various GATA factors can only partially replace each other in functional terms and recapitulate the specific transcriptional programs in the related cellular context[166–171]; this suggests that differences in the GATA factor regulatory activity is due to elements other than the DNA binding domains and the core DNA motif. However, several studies suggested that residues within (and also residues close to) the zinc-finger domains can explain the GATA factor-specific binding preferences.[172–174] For example, it has been suggested that residues in the less conserved C-terminal region (adjacent to the second zinc finger) have a role in determining DNA binding by hematopoietic- versus endoderm-specific GATA factors.[175] Future ChIP-seq studies will clarify the respective roles of these residues in mediating differences in chromatin binding. Furthermore, the cell-specific expression of interacting partners can influence GATA factor-specific binding preferences. In fact, GATA factors cooperate with recurrent partners in different cell types but interact also with cell-type-specific proteins (Figure 1) that can modulate their DNA binding activity in distinct cellular contexts.

The comparison of different studies of GATA factor occupancy is complicated by a number of study- and/or laboratory-specific variables: (a) the cell type (human vs. murine, and primary cells vs. cell lines), (b) the factor expression (endogenous vs. inducible expression, or overexpression), (c) the details of the ChIP-seq protocol (e.g., the antibody, the epitope-tagging approach, and the sequencing depth), and (d) the bioinformatics and statistical analyses and criteria. However, several concepts and mechanisms underlying transcriptional regulation by GATA factors have been confirmed in different cellular and animal models, and by several laboratories.

Overall, GATA factors share many regulatory properties. For example, GATA factor binding sites are mainly located in distal regulatory regions. Most GATA factors appear to exert both activating and repressing activities, although it is not fully understood why target genes are activated or repressed. During the development and differentiation of several cell types, GATA factors activate cell-specific genes and repress genes involved in the generation of alternative lineages. Physical interactions and/or cooperation with other transcription factors, co-factors, and chromatin modifiers

can often distinguish the GATA factor activating and repressing activities. In addition, the GATA switch is a well-documented mechanism for changing the transcriptional program during hematopoietic differentiation. Similar GATA switches might occur in other cell types,[176] and are likely to be investigated in future research.

Lastly, we expect the use of optimized and novel techniques (e.g., transcriptomic and epigenomic technologies requiring low numbers of cells, e.g., single cell technologies) to provide a better definition of GATA factor occupancy in relevant primary cells from normal and pathologic samples. In turn, this knowledge should enable researchers to better characterize the mechanisms underlying GATA-factor-mediated transcriptional regulation in health and in disease.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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