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REVIEW

Role of the pioneer transcription factor GATA2 in health and disease

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Abstract

The transcription factor GATA2 is involved in human diseases ranging from hematopoietic disorders, to cancer, to infectious diseases. GATA2 is one of six GATA-family transcription factors that act as pioneering transcription factors which facilitate the opening of heterochromatin and the subsequent binding of other transcription factors to induce gene expression from previously inaccessible regions of the genome. Although GATA2 is essential for hematopoiesis and lymphangiogenesis, it is also expressed in other tissues such as the lung, prostate gland, gastrointestinal tract, central nervous system, placenta, fetal liver, and fetal heart. Gene or transcriptional abnormalities of GATA2 causes or predisposes patients to several diseases including the hematological cancers acute myeloid leukemia and acute lymphoblastic leukemia, the primary immunodeficiency MonoMAC syndrome, and to cancers of the lung, prostate, uterus, kidney, breast, gastric tract, and ovaries. Recent data has also linked GATA2 expression and mutations to responses to infectious diseases including SARS-CoV-2 and *Pneumocystis carinii* pneumonia, and to inflammatory disorders such as atherosclerosis. In this article we review the role of GATA2 in the etiology and progression of these various diseases.

Keywords GATA2 · Transcription · Cancer · Lung disease · Atherosclerosis · Inflammation · Hematopoietic disease

Abbreviations

AML	Acute myeloid leukemia
ALL	Acute lymphoblastic leukemia
AR	Androgen receptor
CGA	α-Subunit of glycoprotein hormone
EGF	Epidermal growth factor
EMT	Epithelial-mesenchymal transition
GATA2-AS1	GATA2 anti-sense 1
HPC	Hematopoietic progenitor cells
HSC	Hematopoietic stem cells
MonoMAC	Monocytopenia and mycobacterial infection
NLS	Nuclear localization signal
NRD	Negative regulatory domain
oxLDL	Oxidized low-density lipoprotein
PTEN	Phosphatase and tensin homolog
PAP	Pulmonary alveolar proteinosis
TAD	Trans-activation domain
TMPRSS2	Transmembrane protease/serine subfamily 2
ZnF	Zinc-finger domain

Introduction

GATA2 is one of six transcription factors (GATA1–GATA6) that bind to the DNA motif "GATA" through two zinc finger domains [1, 2]. Historically, mammalian GATA family members were grouped into two subfamilies: GATA1, 2 and 3 which were thought to be restricted to the hematopoietic compartment, and GATA4–GATA6 which were thought to be expressed in endodermal and cardiovascular tissues [3–5]. This view of GATA subfamilies is no longer considered correct, as many are expressed outside of their "canonical" locations. Indeed, GATA2 is expressed constitutively in several non-hematopoietic sites including the lymphatic endothelium, and is upregulated in myeloid cells responding to certain inflammatory and infectious stimuli. Within the hematopoietic system, GATA2 is crucial for the proliferation and maintenance of hematopoietic stem cells (HSC) and hematopoietic progenitor cells (HPC) [6]. While GATA2 is downregulated in HPCs that commit to the lymphoid

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lineage, expression is highest in early myeloid progenitors, in megakaryocyte and eosinophilic precursors, and is expressed by mast cells [7, 8]. Although GATA2 is most notably expressed in the hematopoietic compartment, it is also expressed in lymphatic endothelial cells, V2 interneurons within the central nervous system, and can be found expressed in multiple tissues during development including in the placenta, fetal liver, and fetal heart [9–15].

GATA transcription factors tend to work cooperatively with other transcription factors, allowing for the gene expression profile driven by a particular GATA protein to vary between cell types, with these differences dictated by the expression patterns of cooperating and competing transcription factors. These interactions can allow GATA2 to induce or suppress expression of the same gene depending on which GATA2-interacting partners are present [16]. GATA2 regulates genes both directly—by binding to promoters of target genes—and indirectly, by regulating the expression of other transcription factors. In this review, we described GATA2's regulation, post-translational modifications, and its role in the development and progression of several diseases.

GATA2 gene and structure

The *GATA2* gene is situated at 21.3 cM on the long arm of human chromosome 3, and was first cloned by Lee et al. as a 13,760 kb loci [17]. Three GATA2 transcripts have been identified, expressed from two different promoters. The first GATA2 promoter (specific/IS promoter) is found 5′ to the first exon, with expression from the IS promoter occurring in hematopoietic and neuronal cells [9, 18]. A second internal (general/IG) promoter is found between the first and second exons and is used in all tissues that express GATA2. The IS and IG promoters contain vastly different sets of predicted transcription factor binding sites [19, 20]. Combined with alternative splicing, these promoters allow for three different mRNAs to be produced, each differing in the 5′ UTR but sharing the same translation start site, protein coding region, and 3′ UTR (Fig. 1A–B). Alternative splicing of these mRNAs can produce the short GATA2 isoform, which lacks the first 14 residues of the second zinc finger, thus reducing its size from 480 to 466 amino acids (50.5 kDa to 49.0 kDa, Fig. 1B–C) [20, 21]. Unlike many putative protein isoforms, which may represent erroneous mRNA splicing events that do not result in an expressed protein, immunoblotting of HSCs has identified a doublet GATA2 band consistent in size with the long and short isoforms [22]. Interestingly, the lower-weight band in this doublet disappears once these cells have differentiated into mature monocytes and macrophages, indicating that the short isoform may be selectively expressed in certain cell types or at specific stages of hematopoiesis [23]. Whether this short isoform has a function different from that of the long isoform, and what regulates the formation of the short isoform, remains unknown. Note that in the hematopoiesis and hematological cancer fields, it is convention to number the GATA2 exons based on their inclusion and order in the IS promoter-derived transcript (Transcript 2, NM_032638). While this is the predominant mRNA isoform expressed in the hematopoietic compartment, the transcript produced from the IG promoter (Transcript 1, NM_001145661) is the predominant transcript outside of the hematopoietic compartment and includes two exons that form the 5′ UTR that are unnumbered in this convention. As such, care must be taken when interpreting the GATA2 literature as exon numbering can be inconsistent between studies, especially in studies outside of the hematopoietic compartment. For clarity, in this review, we have used the Transcript 2 nomenclature, numbering the as exons that are alternatively spliced to create different 5′ UTRs as exons 1A, 1B, and 1C, numbered based on their order in the genome (Fig. 1A). All references to SNPs and other mutations refer either to exons numbered in this manner, or where possible, refer to the specific amino acids or protein domains that are affected.

Transcriptional regulation of GATA2

As mentioned in the previous section, the *GATA2* gene is regulated by two promoters: IS and IG. The IS promoter, which produces transcript variant 2, is selectively utilized in hematopoietic and neuronal tissues. The IG promoter, which produces transcript variant 1, is active in all other tissues where GATA2 is expressed [20, 21, 24]. While the transcription factors which bind to the IS and IG promoters are not fully elucidated, the ENCODE database identified EGR1, GATA1, GATA2, GATA3, Myc, MAX, E2F1/F4/F6, ELF1, RAD21, and HDAC2/5 as factors which bind the IS promoter, while AP-1, STAT1, IRF-1, NF-kB, Myc, HDAC1, MAX, TCF12, and E2F4/F6 were found bound to the IG promoter (Fig. 1A) [25]. Experimental data have linked additional transcription factors to the regulation of GATA2, including ETS1 [26], BMP4 [27], NOTCH1 [28, 29], PU.1 [30], and EVI1 [31, 32]. Upstream of the IG and IS promoters is a − 110 kb intronic enhancer, and a second intronic enhancer can be found at the + 9.5 kb location [33, 34]. These enhancers have a significant role in the regulation of GATA2 expression, with GATA2 binding the − 110 kb enhancer in an autoregulatory fashion, along with SP1, and CTCF, while AP-1, STAT5a, GATA1, and GATA2 bind to the + 9.5 enhancer. There is a consensus sequence in + 9.5 enhancer where the hematopoietic heptad regulatory unit, comprised of GATA2, SCL, LYL1, LMO2, RUNX1, ERG, and FLI-1, which bind in this region to regulate GATA2 expression [35].

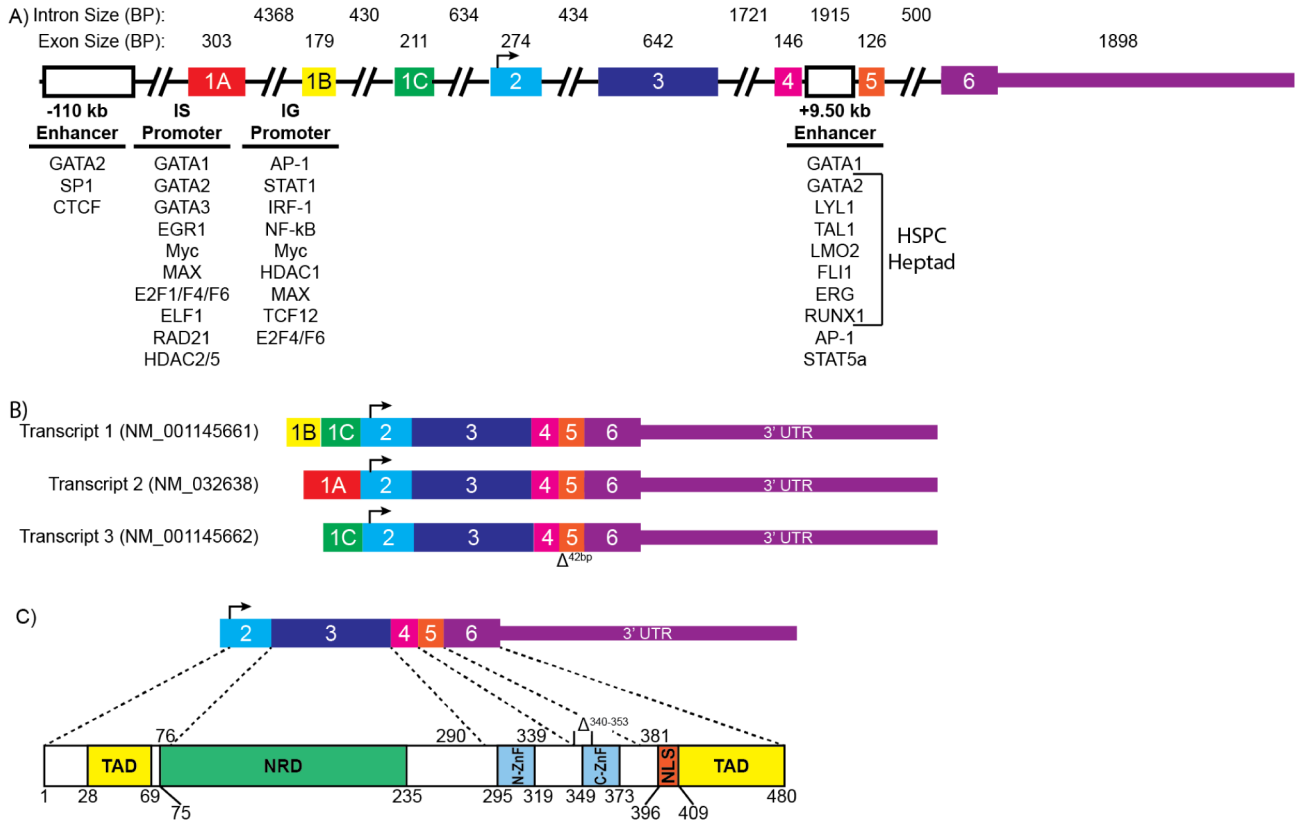

Fig. 1 Transcriptional regulation and structure of GATA2. **A** GATA2 is regulated from two separate promoters—IS (specific promoter) and IG (general promoter). The IS promoter is active in hematopoietic and neuronal tissue, while IG is active in most GATA2-expresing tissues. Exons are color-coded, numbered, and drawn to scale. Enhancers are shown as unfilled boxes. Introns are not illustrated, but their size in base pairs (bp) is indicated at the top of the panel. **B** Three mRNA transcripts are produced from the GATA2 gene via the IS and IG promoter and alternative splicing. All three mRNA transcripts can undergo additional alternative splicing at the junction of the first and second zinc finger, producing a 42 bp deletion. **C** Human GATA2 contains multiple functional domains, including a nuclear localization signal (NLS), two zinc-finger domains (N/C-ZnF), N- and C-terminal transactivation domains (TAD), and a negative regulatory domain (NRD). The short isoform of GATA2 lacks amino acids 340–353 of the C-ZnF. Domains are numbered by amino acid, starting at the N-terminus, and the coding of these domains within the GATA2 exon structure is indicated

The − 110 kb and + 9.5 kDa enhancers are required for human GATA2 expression during hematopoiesis [36–38]. An E box GATA element present in the + 9.5 kDa enhancer scaffolds a complex including GATA2 that maintains the + 9.5 site in an open chromatin state that is required for GATA2 expression [39]. A comparison of the human and xenopus GATA2 promoters identified conserved *ets* binding sites in the ~ 800 bp region upstream of the GATA2 transcription start site [19]. In zebrafish, the GATA2 promoter spans over 7 kb, with tissue-specific regulation driven by discrete regions of the promoter, although these sites are not conserved in mammals [40]. The mouse and human GATA2 promoters contain GATA-response elements (GATA-RE) at − 1.8 kb, − 2.8 kb, and − 3.9 kb, and both the IS and IG promoters are autoregulated by GATA2 via these GATA2-REs, [41, 42]. In addition to transcription factor binding sites, methylation within exons 3 and 4 may negatively regulate GATA2 expression, although this regulation has only been observed in patients which hypermethylated this region due to SNPs in the methylase DNMT3A [43].

GATA2 protein structure and its post-translational modification

GATA2 has a conserved DNA-binding domain made of two multifunctional zinc-finger domains (ZnF): N-ZnF/ZfN1 and C-ZnF/ZfN2 (Fig. 1C) [12]. The N-ZnF domain is encoded by exon 4, and C-ZnF by exon 5, with the short form of GATA2 lacking 14 amino acids from C-ZnF. Although no functional differences between the long and short GATA2 isoforms has been identified, the short isoform lacks part of C-ZnF domain and therefore may have modified DNA or protein binding characteristics [44]. Both the N-ZnF and C-ZnF domains regulate interactions with other transcription factors. For example, C-ZnF is required for GATA2 interactions with PU.1 [45] and FOG1 [46], while both the C-ZnF

and N-ZnF domains are required for interactions with PIASy [47], HDAC3 [48], RARα [5], c-MYB [4], PLZF [49], and PPARγ2 [50]. Not all inter-protein interactions occur via these zinc fingers—for example, a region proximal to the C-ZnF domain is required to interact with C/EBPA [51]. The exact size of the C-ZnF has not been resolved at high resolution, with deletion studies suggesting that it may extend from amino acid 349 through to the putative nuclear localization signal (NLS), while other studies and protein structure prediction identify a smaller zinc-finger domain that extends between amino acid 349 and 373 [52, 53]. Similarly, the localization of the NLS has not been mapped at high resolution, with Hsu et al. *mapping* it to the c-terminal half of GATA2 based on mutations identified in patients bearing GATA2 mutations [1, 54]. As NLS sequences are conserved across all six members of the GATA gene family, and are always found c-terminal to the second zinc finger, Hsu et al. were able to further refine the position of the GATA2 NLS to between the second zinc finger and the c-terminus, with deletion mapping by Visvader et al. refining this further to a region between amino acids 335 and 413 [2, 3, 55]. Consistent with these studies, using NLStradamus, we have identified a probable NLS between amino acids 396 and 409 (RNRKMSNKSKKSKKP), with this sequence being the only region in human GATA2 exhibiting the classical polybasic and lysine-rich structure of an NLS [4, 5, 16, 56, 57]. In addition to the zinc-finger and NLS domains, GATA2 has two transactivation domains (TAD), a negative regulatory domain (NRD), and regions that are important for GATA2 protein stability and degradation (Fig. 1C) [58, 59]. The function of these regions is not as well understood as the zinc finger domains; however, the NRD is homologous to the NRD of GATA3 which has transactivating activity [58, 60]. The N-terminal TAD is required for erythroid progenitor development, while the C-terminal TAD is required for megakaryocyte development [61]. GATA2 engages in concentration-dependent dimerization, with monomeric versus dimeric GATA2 interacting with unique DNA sites and transcription co-factors [62].

While GATA2 expression levels represents the major mechanism of GATA2 regulation, GATA2's activity is also regulated by post-translational modifications. After translation, GATA2 is modified by acetylation, phosphorylation, and sumoylation, while uniquitination induces its rapid degradation [63, 64]. GATA2 has several evolutionarily conserved lysine-rich motifs where it is acetylated, with acetylation increasing both DNA-binding and transactivation activity. Mutation of any of these lysine residues reducing its transactivating activity [65]. GATA2 activity is also regulated by phosphorylation, with HPC proliferation requiring the constitutive phosphorylation of GATA2 [64]. This phosphorylation is regulated by a MAPK-dependent pathway that responds to developmental cytokines such as IL-3 [66, 67]. GATA2 is phosphorylated by the insulin dependent-PI3K/AKT pathway in preadipocytes and prevents GATA2 from translocating into the nucleus. The resulting loss of GATA2 nuclear activity allows preadipocyte to exit cell cycle and differentiate into adipocytes, and reduces the inflammatory activity of preadipocytes [68].

GATA2 expression varies during cell-cycle, peaking in S phase and declining through G1/S and M phase, with GATA2 protein levels largely regulated by phosphorylation-dependent changes in protein stability [69]. During cell cycle, GATA2 is phosphorylated and thus stabilized by Cdk2/cyclin A and Cdk4/cyclin D. Cdk2/cyclin A phosphorylates GATA2 during S-phase, which is required for protease-dependent degradation of GATA2 later in M phase. Control of GATA2 expression and degradation by its phosphorylation by the Cdk/cyclin systems regulates HSCs self-renewal and differentiation [69]. SUMO conjugation is another post-translational modification frequently found on GATA2. In endothelial cells, GATA2 is modified by SUMO2 addition mediated by the SUMO E3 ligase PIASy [47]. SUMOylated GATA2 acts as a transcriptional repressor by reducing Endothelin-1 expression in endothelial cells [47]. The half life of the GATA2 protein is short, typically around 30 min, although this can vary across cell types. GATA2 is turned over rapidly by the ubiquitin–proteasome pathway, in which poly-ubiquitination of GATA2 in the C- and N-terminal TADs triggers its degradation [63].

GATA2 as a pioneer transcription factor

Genome-wide location analysis demonstrated that the bulk of nuclear DNA is inaccessible due to being compacted into heterochromatin, meaning that most putative DNA-binding sites are inaccessible to transcription factors and other regulators [70]. Pioneer transcription factors have a special ability to bind these inaccessible DNA regions, in order to open the chromatin at these sites and make them accessible to other transcription factors [71, 72]. Pioneer transcription factors first gain access to compacted DNA by opening small regions of closed chromatin, allowing them to bind to their cognate DNA binding site. Once bound, pioneers then facilitate the binding of other transcription factors, co-factors, chromatin remodeling modifiers, and other modifying proteins (e.g. acetyltransferases) which facilitate the opening of the chromatin to an accessible state amenable to gene expression [72]. GATA2 is one of the first discovered pioneer transcriptions factors (Fig. 2). Once bound to heterochromatin, GATA2 recruits chromatin remodeling complexes such as the SWI/SNF complex and BRG1 [39, 73]. Once bound, these remodeling complexes modify histones and alter nucleosome positioning to open

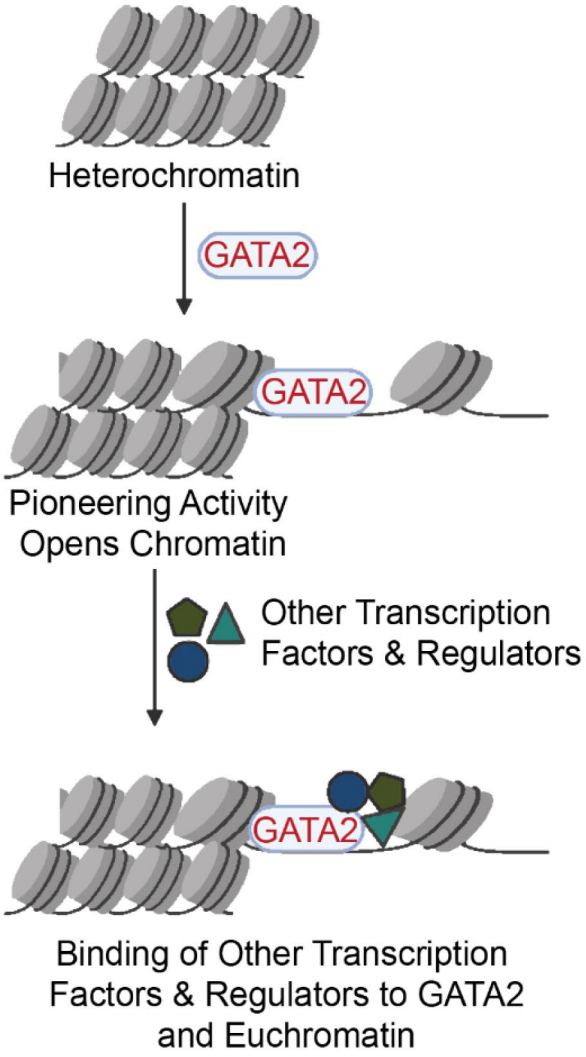

Fig. 2 Model of GATA2's pioneer function. Heterochromatin (closed chromatin, *top*) is usually inaccessible to transcription factors and is therefore not transcribed. GATA2 can bind to GATA2 binding sites within heterochromatin (*middle*), after which GATA2 recruits histone- and chromatin-modifiers which decompact the chromatin, forming accessible euchromatin. GATA2 can then facilitate the binding of additional transcription factors and regulators, leading to gene expression (*bottom*)

the chromatin structure and allow other transcription factors access to the DNA.

GATA2 can both activate or suppresses gene expression by facilitating the reorganization of the chromatin proximal to the GATA2 binding site [72]. For example, GATA2 opens the androgen receptor (AR) promoter by establishing an accessible local chromatin environment within the androgen receptor enhancer. Here, GATA2 recruits the histone acetyl transferase p300 that acetylates histone H3, producing H3K27 acetylation marks which open the chromatin structure to allow binding of other transcription factors which then enables AR expression [74]. While the mechanisms by which GATA2 opens chromatin are beginning to be uncovered, it is unclear how GATA2 inactivates genes through inducing heterochromatin formation, despite clear examples of GATA2-dependent heterochromatin formation. For example, using CUT-and-tag and ATAC-Seq, Jung et al. investigated the occupancy of GATA2 on GATA2-activated versus GATA2-suppressed genes [75]. GATA2 was found to occupy euchromatin at the GATA2-activated Far2, Gata1, Hdc, and Kit loci. In marked contrast, GATA2 was absent from the Ifi209, Tifab, Nlrp1a, and Trem1 loci, despite ATAC-seq demonstrating that GATA2 was required for the formation of heterochromatin at these loci. These data suggest that GATA2-mediated heterochromatin formation occurs via an indirect mechanism, but at this time, this mechanism has yet to be elucidated.

In addition to modifying chromatin, GATA2 also interacts with other transcription factors to regulate and target their activity, and indeed, most of GATA2's transcriptional activity is though to occur via interactions with other transcription factors. For example, HSC survival and self-renewal is mediated by GATA2 interactions with GATA1, CEBPA, SPI1 (PU.1), and ZFPM1 (FOG1) [24], and indirect interactions with SPI1 (PU.1), FLI1, TAL1 (SCL), LMO2, LYL1, MEIS1, ERG, FLI-1, GFI1B, and RUNX1 [76–78]. Genome-wide analysis of HSC/HPCs demonstrated that GATA2 also forms heterodimeric transcriptional complexes with SCL/LMO2, LMO2, ERG, and FLI-1. Moreover, GATA2 binds to more than 1000 loci through cooperating with other transcription factors to form a core heptad regulatory unit in hematopoietic cells [79]. This heptad regulatory unit consist of GATA2, SCL, LYL1, LMO2, RUNX1, ERG, and FLI-1 and mainly targets microRNAs, lncRNAs, and lineage- and maturation-stage specific genes [79–82]. Interestingly, the GATA2 loci contains a lncRNA (GATA2-AS1) that is divergently transcribed with GATA2. GATA2-AS1 modifies the expression of over 1300 RNAs and contributes to the hypoxia response in endothelial cells [81].

This heptad controls cell fate during hematopoiesis through cooperative binding of heptad members within their promoters and regulatory regions. The exact mechanisms through which this complex web of interactions regulates hematopoietic cell fate are incompletely understood, but two mechanisms through which this heptad regulates hematopoietic fate determination have been identified. The balance of GATA2, RUNX1, and SCL expression controls several genes that are critical for determining the balance between HSC quiescence and proliferation, with increased GATA2 expression promoting HSC quiescence—likely in anticipation of the HSC committing to terminal differentiation [83]. This GATA2 upregulation was recently shown to promote commitment to the erythroid lineage via a subcircuit within the heptad. Recently discovered by Thoms et al., this subcircuit allows

HSCs to enter the erythroid developmental lineage through the GATA2-dependent upregulation of TAL1 and the concordant GATA2-independent downregulation of ERG. Amplifying this circuit through ectopic overexpression of GATA2 or knockdown of ERG promoted commitment to the erythrocyte lineage, while ectopic overexpression of ERG maintained progenitors in a self-renewing HSC-like state [84]. Given that this same lineage commitment also leads to the development of megakaryocytes, myeloid cells, and mast cells—and that these lineages share a similar dependency on GATA2 expression—it is likely that similar GATA2-directed heptad subcircuits are involved in the development of these cell types.

The GATA switch

A GATA switch, in which one GATA-family transcription factor displaces another GATA-family factor in a promoter, is an important element of cell fate determination during hematopoiesis. A GATA2/GATA1 switch controls the relative expression of these two transcription factors, with the altering balance between GATA1 and GATA2 defining lineage choice by regulating HSC renewal, differentiation of progenitors cells, and inducing terminal differentiation of erythrocytes, megakaryocytes, and mast cells [42, 85]. GATA2 and GATA1 engage in a dynamic reciprocal regulation of each others expression, which for example, can initiate HSC to erythrocyte development by reducing GATA2 levels and elevating GATA1 expression. The change of expression of GATA transcription factors is regulated by cis-acting GATA motifs, which in HSCs and HPCs are bound by GATA2, which is highly expressed in these cells. Later in hematopoiesis, GATA1 expression increases and displaces GATA2 from these cis-acting motifs, thus inducing terminal differentiation into erythrocytes and megakaryocytes [7, 8, 86]. The high levels of GATA2 in HPCs are mediated by a positive feedback loop in which GATA2 promotes its own expression through binding GATA motifs in its promoter and enhancer regions [42]. Once a progenitor cell commits to the erythrocytes or megakaryocytic lineage, GATA1 expression increases and forms a heterodimer with FOG-1. This GATA1/FOG1 heterodimer displaces GATA2 from the GATA2 gene promoter and enhancers, thus ceasing GATA2 expression and allowing for GATA1-mediated terminal differentiation [42, 85]. Conversely, during mast cell development GATA2 downregulates FOG-1 expression, allowing for mast cell development via a GATA2-mediated genetic program [87]. The GATA2/GATA1 switch also regulates expression of embryonic and fetal haemoglobins, with GATA2 expression driving expression of γ- and ε-globin, with increases in GATA1 expression suppressing expression of both GATA2 and ε-globin [88]. In addition, GATA2 expression prevents embryonic lethality due to GATA1 deficiency by allowing for embryonic and perinatal hematopoiesis. While this allows embryonic lethality to be bypassed, the requirement for GATA1 activity in adult hematopoiesis results in death shortly after birth [89].

Although the above studies indicate that GATA2 is expressed earlier than GATA1 during hematopoiesis, and GATA1 "switches" with GATA2 on target genes through a competition mechanism [90], a recent publication has challenged this GATA switch model. Using absolute quantification of mRNA and protein levels in HSCs and erythroid progenitors, Gillepsie et al. determined that while the pattern of GATA1 and GATA2 mRNA levels were consistent with the switch model, the protein levels of GATA1 and GATA2 were not. Unexpectedly, GATA1 protein was found at much higher abundance at early timepoints than its mRNA level would suggest, exceeding GATA2 protein levels at very early stages in differentiation. At later timepoints, GATA1 protein levels were up to 50 times higher than GATA2, even though the mRNAs for each protein was present at similar copy numbers. Moreover, GATA1 protein levels were consistent during erythropoiesis despite three to fourfold changes in its mRNA abundance, while GATA2 protein levels dropped below detection shortly after its mRNA levels began to decrease. As a consequence, at the time point where HSCs had committed to the erythrocyte lineage, little-to-no GATA2 protein was present in the cells while GATA1 protein levels remained high. This indicates that in some circumstances, the GATA2/GATA1 switch may be mediated simply by a loss of GATA2 protein rather than competition for promoter binding with GATA1 [91].

GATA2 in hematopoietic disease

GATA2 regulates the transition of embryonic endothelial cells into the first HSCs, and consequently, *GATA2* knockout causes embryonic lethality due to severe anemia [7]. In the bone marrow, GATA2 is expressed in HSCs, HPCs, erythroid precursors, eosinophilic and megakaryocytic progenitors, and in mast cells. In HSCs/HPCs, GATA2 is required for commitment to the myeloid lineage [92], with GATA2 expression decreasing once these precursor cells enter terminal differentiation, although some GATA2 expression is maintained in eosinophilic progenitors, and throughout the megakaryocytic and mast cell lineages [93]. GATA2 is present in the hematopoietic tissues of adult organisms [20, 94] where it continues to have an essential role in the maintenance of HSCs [6]. Knockdown of *GATA2* reduces the self-renewing capacity of HSCs [92, 95], with inactivation of even one *GATA2* allele causes insufficient HSC self-renewal without affecting the entry of HSCs into the myeloid differentiation pathway is unaffected [96, 97]. Not all *GATA2* mutations affect HSC

self-renewal, with some mutations resulting in monocytopenia and neutropenia due to failed differentiation following HSC commitment to the myeloid lineage [98]. Conversely, overexpression of GATA2 inhibits hematopoiesis by trapping HSCs in a self-renewal loop and by blocking myeloid and erythroid differentiation [83, 99]. GATA2 can also decrease the sensitivity of HSCs to apoptosis, through promoting the expression of the anti-apoptotic protein BCL2L1 [100].

Several *GATA2* mutations have been identified that cause hematopoietic disorders. Mutations which decrease GATA2 expression, or which result in non-functional protein cause cytopenias including monocytopenia and mycobacterial infection (MonoMAC) syndrome and dendritic cell, monocyte, B and NK lymphoid deficiency syndrome (DCML). Similar mutations have been associated with inherited myelodysplastic syndrome [101]. Because of GATA2's central role in hematopoiesis, in addition to the primary hematopoietic deficiencies observed in patients with *GATA2* mutations, these patients are also prone to develop cytogenetic abnormalities and acute or chronic leukemias including acute myeloid leukemia (AML), chronic myeloid leukemia (CML), and rarely, acute lymphoblastic leukemia (Fig. 3)[102]. *GATA2* mutations can occur as both germline and stomatic mutations, with the latter typically arising as secondary mutations in response to an initiating oncogenic event. In addition, patients with mutations in *GATA2* are also prone to lymphedema, due to the requirement for GATA2 in the development of the lymphatic system [103]. While many *GATA2* mutations affecting the coding region are correlated with the severity of pediatric and adult AML, mutations can also be found in the non-coding enhancer regions that impart their oncogenic effect by altering GATA2 expression levels [52, 104].

Monocytopenia and mycobacterial infection (MonoMAC) and related syndrome

Germline mutations in *GATA2* cause a range of syndromes including MonoMAC, DCML, familial MDS/AML, and primary Emberger syndrome, while both germline and spontaneous mutations can lead to classic NK cell deficiency [54, 103, 105–109]. While these syndromes are all unified by sharing *GATA2* mutations as their root cause, the symptoms exhibited by these patients and the specific cell populations that are affected vary. How mutations in *GATA2* cause the different symptoms that define these syndromes is unknown, but the mutations driving MonoMAC syndrome are the best characterized. Patients with MonoMAC syndrome experience monocytopenia, NK- and B-lymphocytopenia, and severe infections with *M. avium* complex, and have an increased risk of developing myelodysplasia and AML [110]. Patients with MonoMAC syndrome have a 28% mortality rate and typically suffer from severe and recurrent nontuberculous mycobacterial infections, infections by opportunistic fungi, reoccurring human papilloma virus infections, and opportunistic bacterial infections [105, 111]. This syndrome is caused by *GATA2* germline mutations [54, 112], often occurring as a result of rare autosomal dominant mutations such as (E.G. c.1186C > T;p.R396W), resulting in loss of function in one allele of *GATA2* [54, 113]. These mutations can occur across the *GATA2* gene, with causal mutations reported in both TAD domains, the NRD domain, the NLS, and in both zinc finger domains (Fig. 1C) [114–125]. MonoMAC syndrome can also be caused by frameshift, nonsense, splice-site mutations, and deletion mutations, with these mutations typically inactivating one GATA2 allele [124, 125]. Historically, MonoMAC patients were often misdiagnosed as having some form of myelodysplastic syndrome, especially

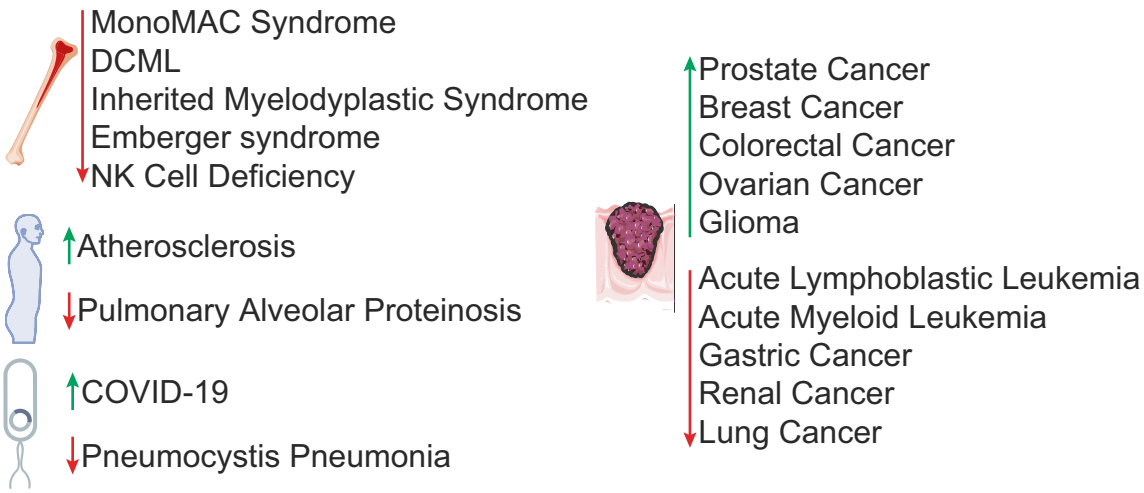

Fig. 3 Patterns of GATA2 expression in the onset of various GATA2-associated diseases. Green arrows indicate diseases promoted by elevated GATA2 expression, and red arrow indicates diseases promoted by lower levels of GATA2 expression or by inactivating mutations in GATA2

those with rarer *GATA2* mutations where the underlying germline mutation had not yet been identified. Recent work by Shen et al. has shown that next-generation sequencing can be used to effectively identify MonoMAC patients, even those with rare or unique mutations. For example, using this approach, a 65-year-old myelodysplastic syndrome patient who had a unique, heterozygous mutation in *GATA2* at exon 6:c.1126_1128del:p.K376del was identified [126]. MonoMAC syndrome develops with low *GATA2* mutational burden, emphasizing the sensitivity of hematopoiesis to *GATA2* mutations [54, 112]. Untreated, around 50% of the patients with MonoMAC syndrome will be diagnosed with myelodysplastic syndrome or AML [105, 111]. Allogenic HSC transplantation can be an effective solution to MonoMAC syndrome, by reconstituting the defective hematopoietic compartments with HSCs from an unaffected donor [111, 127]. HSC transplantation of MonoMAC syndrome has survival rate of 57% at 36 months, making transplantation a risky therapeutic approach [128].

Acute myeloid leukemia

AML is the most common form of acute leukemia in adults, accounting for around 80% of leukemia cases [129, 130]. AML is a heterogeneous disease caused by mutations in the genes that regulate hematopoietic cell proliferation and differentiation [131–133]. Abnormal proliferation and differentiation cause the accumulation of malignant and poorly differentiated myeloid cells within the bone marrow and peripheral blood, ultimately leading to AML. The main pathogenesis of AML is the excessive proliferation, lack of differentiation, and reduced apoptosis of myeloid stem cells, eventually leading to the replacement of normal myeloid precursors with malignant leukemia cells, thus preventing production of other hematopoietic cell types [134–136]. AML patients suffer from bone marrow failure, which in some patients is complicated by leukocytosis. If AML remains untreated, patients die due to infection or uncontrolled bleeding [130, 137]. GATA2 haploinsufficiency can be a cause of AML. GATA2 haploinsufficiency is most often caused by frameshift, nonsense and missense mutations which results in a non-functional GATA2 allele, and by mutations in GATA2's regulatory regions that result in uniallelic expression [102].

Both somatic and germline mutations in *GATA2* can lead to AML, with the former contributing to familial AML. Shiba et al. found that 5% of pediatric AML patients had somatic mutations in GATA2, 0.6% carried a germline GATA2 mutation, and these were often biallelic mutations with concordant mutations in CEBPA [138]. In some patients, chromosomal rearrangement in inv(3)/t(3;3) causes repositioning of the − 110 kb GATA2 enhancer, leading to *GATA2* gene silencing [139, 140]. Hahn et al. showed that a heterozygous c.1061C > T(p.Thr354Met) missense mutation predisposed members of three families to AML and identified a similar predisposing mutation [c.1063_1065delACA(p.Thr355del)] in a fourth family. These mutations all occurred in the C-ZnF of GATA2 [107]. Another study found heterozygous missense mutations in both the N-ZnF and C-ZnF domains within an AML patient cohort [141]. These mutations are thought to abrogate GATA2 activity through impairing DNA and transcriptional partner binding. Chemotherapy and allogeneic hematopoietic stem cell transplantation are most often the treatment for AML [141].

Myelodysplastic syndrome (MDS)

Germline mutations of *GATA2* are one cause of myelodysplastic syndrome (MDS), an age-related hematopoietic malignancy characterized by abnormal blood cell maturation and a high frequency of leukemic transformation [142]. Patients with MDS suffer from chronic fatigue due to a lack of functional red blood cells, bleeding and bruising due to thrombocytopenia, and recurrent infections due to a lack of mature leukocytes. Although MDS and AML have similar clinical symptoms, they differ in the peripheral blood cell count and in the pathological presentation of patients' bone marrow. Patients with MDS are diagnosed with myelodysplasia (< 20% myeloblasts in the bone marrow) and cytopenia of one or more myeloid lineage in the peripheral blood. In comparison, AML patients have > 20% myeloblasts in their bone marrow [143, 144].

There is a significant difference in the presentation of primary MDS between children and adults. Pancytopenia and hypocellular bone marrow are present in children and adolescents [145], and monosomy 7 is the most frequent karyotype aberration in children whereas other aberrations are more common in adult MDS [146]. Wlodarski et al., in a cohort study, found that *GATA2* mutations are the most common germline defect that predispose to pediatric MDS, and that *GATA2* mutations occur at high prevalence in adolescents with monosomy 7. GATA2 deficiency is responsible for 7% of all primary MDS cases and is present in two third of adolescents with monosomy 7 [147]. In addition, Donadieu et al. determined that patients with GATA2 deficiencies have an elevated risk of developing MDS, with this risk increasing from 6% at 10 years of age to 80% at 40 years of age [124].

Acute lymphoblastic leukemia

Acute lymphoblastic leukemia (ALL) is the malignant transformation and uncontrolled proliferation of lymphoid progenitor cells. As with AML, this results in the replacement of normal hematopoietic progenitors by malignant cells,

which in ALL results in an increase in the number of circulating leukemic cells and infiltration of these cells to the central nervous system and testes. Both children and adults can develop ALL, with the highest incidence observed in children under 4 years of age [148]. Although the majority of ALL develops in healthy persons, genetic susceptibility and common allelic variants can predispose patients to ALL [149]. Abnormal, constitutive activation of transcription factors is one of the main drivers of ALL [150, 151]. There are two primary types of ALL: B-cell acute lymphoblastic leukemia (B-ALL) and T-cell acute lymphoblastic leukemia (T-ALL). GATA2 is a very rare driver of ALL, likely because GATA2 is not normally expressed by lymphoid progenitor cells [1, 152]. Even so, Wang et al. identified GATA2 expression in 20.5% of pediatric B-ALL patients. This expression of GATA2 was found across a range of B-ALL subtypes, and there was no single mechanism that accounted for GATA2 expression in these patients. Interestingly, however, GATA2 expression was associated with KMT2A-USP2 fusion in a subset of patients, while a single patient was identified with a somatic focal deletion of a regulatory region downstream of GATA2, indicating that both cis- and trans-activation of GATA2 can contribute to B-ALL [153]. This aberrant expression of GATA2 in these patients produced B-ALL cells that exhibited myeloid-like gene expression patterns, including activation of genes that induce myeloid proliferation, thus contributing to leukemogenesis [153].

GATA2 in non-hematological cancers

Normally, GATA2's expression is restricted to the hematopoietic compartment, lymphatic endothelial cells, the central nervous system, and fetal development of the placenta, liver, and heart [9–13]. In adults, aberrant expression outside of these compartments can led to various cancers including prostate, breast, lung, endometrial, urothelial, and renal cancer (Fig. 3).

Prostate cancer

Prostate cancer is one of the most common cancers of men. Many prostate cancers are confined to the prostate gland and grow slowly, but aggressive forms can be highly metastatic. The transition from a slowly growing non-invasive cancer to rapidly-growing invasive metastatic disease is often driven by a transition from AR-dependent to AR-independent tumor growth, with GATA2 contributing to both forms of disease [154]. Overexpression of GATA2 increases cellular proliferation, tumorigenicity, cellular motility, and invasiveness, and can contribute to resistance to standard prostate cancer therapies [154]. Inhibition of GATA2 reduced prostate cancer proliferation [155], with GATA2 driving prostate cancer progression in both AR-dependent and AR-independent disease [156]. The transition of prostate cancer from AR-dependent to AR-independent growth is accompanied by an increase in invasiveness and metastatic potential, with a GATA2-driven regulatory network driving proliferation in both the AR-dependent and -independent stages of disease [74, 157]. Moreover, GATA2 expression may contribute to progression to the more lethal AR-independent state [158]. GATA2 drives prostate cancer metastasis, with higher GATA2 expression correlating to greater metastatic potential, higher invasiveness, and increased cell motility in primary tumor samples [158–160]. Conversely, silencing GATA2 in LNCap cells (an AR-dependent human prostate adenocarcinoma) decreased expression of multiple genes required for migration, invasion, and proliferation, and was accompanied by decreases in cell migration and tissue invasion, and increased adhesion [159].

GATA2 drives AR-dependent prostate cancer progression via three mechanisms. Firstly, GATA2 binds to the regulatory region upstream of the AR promoter, thus increasing AR expression. If required, GATA2 also acts as a pioneer transcription factor at this site to open the chromatin to other transcription factors [161]. Secondly, GATA2 acts as a pioneer transcription factor that generates an accessible local chromatin environment in the AR enhancers to further promote AR expression. Thirdly, GATA2 increases the expression of multiple AR-regulated genes by recruiting the co-regulatory complex subunit MED1 to form and maintain a regulatory chromatin loop between AR-bound distal enhancers and the promoters of AR target genes [74]. In addition to upregulating AR-dependent genes, GATA2 also promotes prostate cancer through mediating AR-independent expression of IGF2, PAK4, FOXM1, GLNT7, and ARRDC3 [158]. GATA2 can be upregulated by the EGFR/ERK/Elk-1 signaling axis, with GATA2 expression decreased by inhibition of EGFR signaling using EGFR or ERK inhibitors [159]. Upregulation of GATA2 contributes to chemotherapy resistance by regulating genes that are associated with resistance to chemotherapy, and GATA2 knockdown-sensitized prostate cancer cells to chemotherapy by increasing sensitivity to apoptosis [158]. Inhibition of Elk-1 expression or inhibition of the EGFR/ERK pathway may be a target for limiting GATA2 tumor-inducing activity, and inhibition of this pathway may be a potential therapeutic target for prostate cancer [162].

Breast cancer

Breast cancer is one of the most common cancers of women and affects some men. Expression of GATA2 by breast carcinoma cells promotes metastasis by stimulating their proliferation and migration [163]. This increase in proliferation occurs via a GATA2-driven enhancement of PI3K/AKT signaling, through regulation of the inhibitory protein

phosphatase and tensin homolog (PTEN). There is a negative correlation between GATA2 expression and expression PTEN in breast cancer cells, which has several effects on breast cancer growth and metastasis. Firstly, GATA2 directly inhibits PTEN expression by acting as a transcriptional repressor at the PTEN promoter [163]. This reduction in PTEN expression alleviates PTEN's suppression of the PI3K/AKT signaling pathway, with the resulting elevated AKT activity inhibiting cancer cell apoptosis and enhancing cell survival [163]. Activated AKT also increases GATA2 expression, producing a positive feedback loop which further inhibits PTEN expression and enhances AKT activity [163]. Secondly, GATA2 inhibits AR-dependent expression of PTEN by preventing the nuclear translocation of dihydrotestosterone-ligated AR [164, 165]. GATA2 likely has additional effects on breast cancer development, with the results of Ercelylan et al. demonstrating that GATA2 is one of 59 core genes that forms a regulatory network that may be a target for breast cancer therapies [166]. Germline mutations in *GATA2* are not commonly considered to be risk factors for breast cancer; however, in a screen of *GATA2* mutations of patients with familial aggregations of hematological malignancies, a single patient with AML and breast cancer was found with a p.Arg396Gln mutation in *GATA2*, suggesting that some germline *GATA2* mutations may increase a patients risk of developing breast cancer [167]. As with prostate cancer, GATA2 may be a viable target for future breast cancer therapies.

Gastric cancer

Gastric cancer is one of the most prevalent cancers worldwide, with most gastric cancers starting within the stomach's inner lining and developing into epithelial dysplasia and gastric adenomas. Unlike breast and prostate cancer, it is the loss of GATA2 expression that creates a favorable environment for the growth and survival of gastric tumors. This is largely due to the upregulation of GATA6 expression that follows the loss of GATA2 [168]. Hypermethylation of the GATA2 promoter silences GATA2 expression in gastric cancer cells, with the loss of GATA2 allowing for GATA2/GATA6 switch that constitutes one of the first steps that leads to gastric cancer. Normally, GATA2 suppresses transcription of *GATA6* by stabilizing polycomb repressive complex 2 on the *GATA6* promoter [168]. Depletion of GATA2 removes this suppression, allowing for GATA6 expression. While the signals that initiate the hypermethylation of the GATA2 promoter in gastric cells are unknown, it has been shown that this process is independent of *Helicobacter pylori* infection [168]. Once gastric cancer has formed, re-expression of GATA2 is associated with chemoresistance. Sublethal chemotherapy induces GATA2 expression, thereby increasing the GATA2-dependent upregulation of the α-subunit of glycoprotein hormone (CGA). Upregulated CGA binds to and activates EGFR, thereby promoting survival of gastric cancer cells [169]. Through this mechanism, CGA/EGFR/GATA2 act as a positive feedback loop that induce resistance to chemotherapy in established gastric cancers [169]. While GATA2 is not likely a viable therapeutic target for gastric cancer, detection of epigenetic silencing of GATA2 may serve as a biomarker for precancerous or early-stage disease.

Colorectal cancer

Colorectal cancer is one of the most lethal cancers globally. Elevated GATA2 expression is associated with poor survival of colorectal patients, especially in those with concomitant mutations in KRAS [170]. Moreover, the single nucleotide polymorphism rs2335052 ($A^{164}P$) in GATA2 significantly correlates with increased risk of colorectal cancer recurrence [171]. Overexpression of GATA2 promotes the progression of colorectal cancer by upregulating genes for proliferation, invasion, epithelial-mesenchymal transition (EMT), and stemness [172]. Located next to the *GATA2* gene is a region coding for GATA2 antisense RNA 1 (GATA2-AS1), which when expressed, promotes GATA2 expression in colorectal cancer cells. Here, GATA2 directly induces GATA2-AS1 expression by binding to its promoter, with GATA2-AS1 then recruiting DEAD-box helicase 3 X-linked to the 3′UTR of GATA2 where it stabilizes the GATA2 mRNA, thus enhancing GATA2 expression [172].

Other cancers

GATA2 expression is significantly decreased in renal tumor tissue compared to normal tissue, where decreased GATA2 expression correlates with renal tumor development and aggressiveness [173]. GATA2 can also indirectly contribute to tumor growth by aiding in the formation of an immunosuppressive environment. In glioblastoma, overexpression of GATA2 induced expression of PD-L1 and PD-L2 in glioma cells. These then inhibit T cell production of IFNγ, thus worsening the immunological control of glioma [174]. Aberrant expression of GATA2 is not always deleterious in the context of cancer. For example, higher GATA2 expression in ovarian cancer is correlated with better patient survival [175].

GATA2 in lung disease

In humans, GATA2 has been found to be expressed in alveolar cells, bronchial epithelium, and endothelial cells of the lung, while in rats GATA2 expression has been reported in bronchial epithelial cells, alveolar macrophages, and resident lung monocytes [176]. This expression pattern may be unique to rats, as the alveolar macrophages of mice express minimal levels of GATA2 unless CISH—a negative regulator of

GM-CSF signaling—is deleted [177]. At this time there are no published studies analyzing GATA2 expression in human alveolar macrophages or their monocytic progenitors, but unpublished data from our lab shows that human monocytes do not express GATA2 at a level detectable by flow cytometry (data not shown). Patients with germline *GATA2* mutations experience frequent lung infections, driven in-part by the loss of myeloid immune cells, resulting in susceptibility to a range of viral, fungal, and mycobacterial infections [105]. These recurrent infections can lead to lung remodeling and a loss of elasticity due to depletion of elastin [178, 179]. Therefore, identification of GATA2 deficiency is important to prevent the recurrent infection and concordant lung damage that can occurs in these patients (Fig. 3) [178].

Lung cancer

Lung cancer is one of the leading causes of death worldwide. Repressed GATA2 expression is associated with human lung cancer development with a similar phenotype observed in mouse models [180]. Repression of GATA2 in humans occurs through GATA2 promoter CpG hypermethylation that develops early in transformation, with similar epigenic silencing observed in mouse models [180]. Zhang et al. found that GATA2-AS1 also represses GATA2 expression in lung cancer cells, thus promoting cancer cell growth [181]. Comprehensive analysis of lung cancers found lower expression of GATA2 in lung adenocarcinoma, squamous cell carcinoma, and large cell lung carcinoma. However, no significant relationship between GATA2 expression and patient survival was found [182]. Overexpression of GATA2 inhibits A549 and H460 lung cancer cell line proliferation, invasion, migration, and EMT through upregulation of long non-coding RNA LINC00891. GATA2 directly binds to the promoter of LINC00891 to induce its expression, with LINC00891 inhibiting malignant behaviors by supressing the RhoA pathway required for invasion and migration [183]. While suppression of GATA2 generally promotes lung cancer formation, this is not always the case. Kumar et al. found that deletion of GATA2 decreased KRAS-mutated non-small cell lung cancer cell viability and increased apoptosis [184], with in vivo delivery of a GATA2 siRNA suppressing proliferation and inducing apoptosis in a mouse model of lung cancer [185]. Thus, whether GATA2 expression is pro- or anti-tumorigenic in lung cancer likely depends on the gene expression profile and presence or absence of other tumorigenic mutations within the cancerous cell.

Pulmonary alveolar proteinosis

Pulmonary alveolar proteinosis (PAP) is a rare lung disorder characterized by the abnormal accumulation of alveolar surfactant in the alveoli of the lung and dysfunction of alveolar macrophages, which together lead to hypoxemic respiratory failure and even death [186]. Pulmonary surfactant is a mixture of phospholipids and proteins which coat the alveoli, reducing their surface tension at the air-cell interface, thereby promoting alveoli inflation and gas exchange [187]. However, abnormal accumulation of surfactant can block lung airways and impair the transfer of oxygen to the blood. Most cases of PAP are caused by autoantibodies against GM-CSF, but the subset of PAP patients who lack these autoantibodies often have mutations in *GATA2* [188]. For example, Matias et al. identified an otherwise benign variant of GATA2 (rs1573858) in a 43-year-old PAP patient who was anti-GM-CSF antibody negative [189]. Pilarski et al. identified a frameshift mutation (exon 5 C.1020_1029dup: p.R344GfsX43) in the *GATA2* gene of a PAP patient who had severe interstitial lung fibrosis [190]. In autoantibody-mediated PAP, much of the lung pathology is due to a loss of GM-CSF signaling in alveolar macrophages. This results in the formation of abnormal alveolar macrophages with a poor ability to phagocytose and process surfactant, thus allowing for surfactant to accumulate [191]. How *GATA2* mutations contribute to PAP is unclear. One possibility is that there may be depletion of alveolar macrophages due to decreasing levels of the circulating monocytes which give rise to alveolar macrophages in adults [192]. Alternatively, an inability to upregulate GATA2 in response to inflammatory stimuli may prevent alveolar macrophages from responding properly to the accumulation of surfactant. While not reported in humans, mouse macrophage cell lines upregulate GATA2 in response to LPS and IL-1β [193], while in rats, infection by *Pneumocystis carinii* induces GATA2 expression in the lung, with *GATA2* knockdown impairing pathogen phagocytosis by alveolar macrophages [176, 194, 195]. A similar loss of GATA2-enhanced phagocytosis may impair the phagocytic function of alveolar macrophages in PAP patients, reducing their ability to catabolize excess surfactant [191]. GATA2 may further modulate macrophage activity and differentiation by modulating the expression of the M-CSF receptor, which is required for macrophage differentiation and survival [196]. Therefore, GATA2 deficiency may induce PAP by either reducing alveolar macrophages number or altering alveolar macrophage function. For patients with GATA2-mediated PAP, treatment with whole lung lavages to reduce surfactant and HSC transplantation improved their symptoms [197].

Pneumocystis pneumonia

While not observed in humans, GATA2 has been shown to be an important mediator of macrophage function during

fungal pneumocystis pneumonia. *Pneumocystis jirovecii* is a yeast-like fungal pathogen which causes severe pneumonia in immunocompromised patients [198, 199]. *P. jirovecii* selectively infects humans and asymptomatically colonizes the lungs of up to 80% of the human population [200]. In rats, GATA2 mRNA is present at detectable levels in lung homogenates under basal conditions and its expression decreases upon infection with *P. carinii* – the rat-infecting species of the *Pneumocystis* genus [176]. Alveolar macrophages of *P. carinii* infected rats exhibit poor phagocytosis of the fungal invader [201]. A similar phenotype is observed in HIV-patients infected with *P. jirovecii*, with this loss of phagocytic function attributed to the decreased expression of the phagocytic mannose receptor by alveolar macrophages [202]. siRNA depletion of GATA2 in the rat lung restored the phagocytic capacity of alveolar macrophages to near-normal levels, and improved clearance of *P. carinii* [194]. While this was interpreted as evidence that GATA2 expressed by alveolar macrophages mediates the suppression of phagocytosis, later microarray analyses of highly purified alveolar macrophages from *P. carinii* infected rats failed to detect GATA2 expression in either control or infected animals [203]. Moreover, in rats this suppression of alveolar macrophage phagocytosis can be transferred to cultured macrophages via cell/fungus-free bronchoalveolar lavage fluid [204]. Combined, these results indicate that a soluble factor produced normally repressed by GATA2 and expressed by a non-macrophage cell type—not a cell-intrinsic defect of macrophages—mediates this suppression of phagocytosis during pneumocystis pneumonia.

SARS-CoV-2

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection causes Corona Virus Disease 19 (COVID-19). Pneumonia and Acute Respiratory Distress Syndrome are severe outcomes of COVID-19 that are predominantly caused by dysregulated and uncontrolled inflammation. Much of this inflammation is driven by a cytokine storm, with this cytokine storm being one of the main drivers of COVID-19 mortality [205]. Among the cytokines released during the cytokine storm, high levels of IL-1β have been found in severe and critical patients compared to patients with mild or moderate disease [206]. This elevated IL-1β induces expression of transmembrane protease/serine subfamily 2 (TMPRSS2) in lung epithelial cells [207], which can then enhance SARS-CoV-2 entry into host cells by cleaving and activating the viral spike protein (S) following its binding to host angiotensin I Converting Enzyme 2. This cleavage of the S protein by TMPRSS2 is required to induce membrane fusion and viral entry, with increased TMPRSS2 expression enhancing viral entry [208]. GATA2 promotes SARS-CoV-2 virus infection by inducing TMPRSS2 transcription [207]. This is mediated by binding of GATA2 to the -13kb DNA enhancer region of the *TMPRSS2* gene, thus promoting TNPRSS2 expression [209]. GATA2 also contributes to the cytokine storm by inducing the expression of several pro-inflammatory cytokines including IL-1β and CXCL2 [210]. Indeed, Islam et al. found 177 differentially expressed genes in lung epithelial cells responding to SARS-CoV-2 infection, with a quintet of transcription factors—GATA2, FOXC1, YY1, FOXL1, and NFKB1—forming a central hub that regulated the differential expression of these genes [211]. To date, these studies have been limited to analyses of infected lung epithelial cells, but given the broad trophism of SARS-CoV-2, it is likely that GATA2 has additional roles in other SARS-CoV-2 infected cell types.

GATA2 in the cardiovascular system

Atherosclerosis

Atherosclerosis is the thickening or hardening of arteries caused by a buildup of plaque beneath the inner lining of an artery. These plaques are unstable structures comprised of fats, cholesterol, and necrotic cell debris. Several single nucleotide polymorphisms in *GATA2* are associated with the development of atherosclerosis and coronary artery disease, although the mechanism leading to this susceptibility remains unclear [212]. We identified higher GATA2 expression in macrophages collected from early human aortic plaque, and demonstrated that oxidized low-density lipoprotein (oxLDL)—a major driver of atherosclerosis [213–216]—induced significant GATA2 expression in cultured macrophages [217]. During atherosclerosis, several distinct macrophage populations arise via polarization of monocyte-derived macrophages which infiltrate the plaque [218]. This includes polarization toward inflammatory (M1 and Mox), pro-resolving (M2), lipid-metabolizing (TREM2), and heme-metabolizing (Mhem) populations [218–222]. Interestingly, the early-lesion macrophages we identified lacked markers of polarization toward any of these phenotypes, and instead were characterized primarily by their high expression of GATA2. In vitro, GATA2 overexpression increased cholesterol efflux from macrophages, suggesting that GATA2 may be induced in response to the cellular stress caused by cholesterol accumulation [223]. However, GATA2 overexpression also decreased the expression of several receptors and signaling molecules required for the removal of apoptotic cells and pathogens, and of genes required for the degradation and processing of materials engulfed by the macrophages [217]. These combined defects lead to poor uptake and processing of apoptotic cells, likely contributing to the accumulation of necrotic debris in the developing plaque [224–227]. Importantly, knockdown of GATA2 reversed many of these defects, even in the presence

of high concentrations of oxLDL [217]. This suggests that GATA2 expression in early-stage plaque may be a maladaptive response to the stress of cholesterol accumulation, with GATA2 expression improving the ability of macrophages to remove intracellular cholesterol, but in doing so, generates a population of macrophages which are unable to engage in the anti-atherogenic removal of dead and dying cells.

Endothelial cell function and repair

Thrombosis occurs in a large portion of patients with germline inherited GATA2 variants, with up to 25% of these patients experiencing one or more strokes, venous thromboembolism, or other thrombotic events [228–230]. Using chromatin immunoprecipitation, Purgatoro et al. determined that GATA2 binds to the promoter of endothelial nitric oxide synthase (eNOS) and is required for the expression of eNOS. Consequentially, it was found that both basal nitric oxide production and nitric oxide production following platelet activation were reduced in cells isolated from a patient with MonoMAC syndrome [231]. Nitric oxide promotes endothelial cell migration and, through enhancing migration, drives both angiogenesis and the closure of wounded endothelium [232, 233]. Consistently with this role of nitric oxide, reduced angiogenesis was observed in endothelial cells derived from this MonoMAC patient, with restoration of both nitric oxide production and angiogenesis observed when eNOS expression was increased by treatment with atorvastatin.

Conclusions

GATA2 has a central role in multiple diseases including inherited hematological disorders, a broad range of cancers, and in responses to infectious and inflammatory stimuli. While the role of GATA2 in hematological disorders and cancer is well understood, research into its role in infectious and inflammatory diseases has only begun. Further exploration of GATA2 will improve our understanding of these diseases, and of how GATA2 alters the transcriptional landscape in response to environmental and developmental challenges. While GATA2 may not be a viable therapeutic target due to its central role in hematopoiesis, identification of the transcription factors and signaling pathways which regulate GATA2 expression may allow for the therapeutic targeting of GATA2 in the many diseases where its expression serves a pathological role.

Author contribution AA authored most of the manuscript. BH contributed to the writing and editing of the manuscript and oversaw its preparation. Both authors read and approved the final manuscript.

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Data availability This is a review and therefore contains no new data. All materials used to prepare this manuscript can be found in the reference section.

Declarations

Ethics and informed consent Not applicable.

Conflict of interest The authors declare no conflict of interests.

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