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Role of GATA2 in Human NK Cell Development

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Abstract

Natural killer (NK) cells are major innate lymphocytes. NK cells do not require prior antigen exposure to mediate antitumor cytotoxicity or proinflammatory cytokine production. Since they use only nonclonotypic receptors, they possess high clinical value in treatment against a broad spectrum of malignancies. Irrespective of this potential, however, the transcriptional regulation that governs human NK cell development remains far from fully defined. Various environmental cues initiate a complex network of transcription factors (TFs) during their early development, one of which is GATA2, a master regulator that drives the commitment of common lymphoid progenitors (CLPs) into immature NK progenitors (NKPs). GATA2 forms a core heptad complex with six other TFs (TAL1, FLI1, RUNX1, LYL1, LMO2, and ERG) to mediate its transcriptional regulation in various cell types. Patients with GATA2 haploinsufficiency specifically lose $CD56^{bright}$ NK cells, with or without a reduced number of $CD56^{dim}$ NK cells. Here, we review the recent progress in understanding GATA2 and its role in human NK cell development and functions.

Keywords

GATA2; NK cell; NK cell development

I. INTRODUCTION

GATA2 is an essential transcription factor (TF) of the generation, survival, proliferation, and differentiation of hematopoietic stem cells (HSCs),[1–3] as well as of the formation of blood and lymphatic vessels.[4,5] This pioneer factor comprises two zinc finger (ZF) domains, two transactivation domains, one nuclear localization signal, and one negative

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regulatory domain[6,7] (Fig. 1A). The two ZF domains (N-terminal and C-terminal) are highly conserved, interacting with a network of TFs, including SPI1 (PU.1), RUNX1, TAL1, FLI1, and LMO2.[8,9] These TFs are known to be involved in specifying early hematopoietic lineage commitment.[9–12] In human HSCs, GATA2 forms a core heptad complex with six other TFs (TAL1, FLI1, RUNX1, LYL1, LMO2, and ERG) to directly impact the survival and differentiation of HSCs by regulating more than 1,000 target genes[9,13] (Fig. 1A).

GATA2 deficiency can result in monoMAC syndrome (monocytopenia with atypical mycobacterial infection),[14] DCML [dendritic cell (DC), monocyte, B cell, and NK lymphocyte deficiency],[15,16] MDS/AML (familial myelodysplastic syndrome/acute myeloid leukemia),[17] and Emberger syndrome (consisting of MDS, lymphedema, and warts from human papillomavirus infection).[4] Although GATA2 deficiency results in various clinical manifestations, the major symptoms in most patients are chronic infections, including HPV, EBV, mycobacterium, fungal and other bacterial infections, MDS/AML, cytopenia (B cell, NK cell, monocyte, DC, and $CD4^+$ T cell deficiency), and lymphedema.[18] Available patient data suggest that GATA2 is a master regulator of human NK cell development whose haploinsufficiency leads to NK cell dysfunction.[19]

In this review, we summarize the recent progress related to the overall molecular mechanisms employed by GATA2 and its role in human NK cell development and functions.

II. HUMAN NK CELL DEVELOPMENT

NK cells are the major subset of innate lymphocytes, which mediate both proinflammatory cytokine production and cytotoxicity in response to viral infections or malignant transformation.[20,21] The release of lytic granules containing perforin and granzymes results in the lysis of target cells.[22,23] Antibody-dependent cell–mediated cytotoxicity (ADCC) is another essential mechanism in recognizing infected or transformed target cells.[24,25] Since NK cell–mediated functions are not limited by clonotypic receptors,[26,27] cellular therapies can be used against a broad spectrum of cancers.[28,29]

In spite of their clinical potential, NK cells have not been utilized to their fullest in the clinic. For this reason, understanding the transcriptional regulation of the development and functions of human NK cells is paramount in formulating effective cellular therapies. Customized *in vitro* generation of mature functional human NK cells from inducible pluripotent stem cells (iPSCs) provides an exceptional opportunity for individualized front-line cancer therapy. However, lacking essential knowledge of master transcriptional regulators we are limited in our ability to fully realize the clinical potential of human NK cells. Thus, defining the role of crucial TFs, such as GATA2, in the early commitment and development of human NK cells is of high clinical relevance.

Recent studies show that human NK cells develop and mature in bone marrow and secondary lymphoid tissues (SLTs), such as lymph nodes (LNs), spleen, and tonsils.[30] Traditionally, the differential expression of surface markers defines distinct developmental stages of human NK cells. We recently summarized these markers.[31,32] Human NK cells primarily arise from self-renewing pluripotent HSCs in bone marrow.[33,34] Lineage-

negative $CD34^+$ HSCs give rise to lymphoid-primed multipotential progenitors (LMPPs) and $CD34^+CD244^+$ common lymphoid progenitors (CLPs) in sequential order. CLPs commit to the NK cell lineage, becoming NKPs (characterized by $CD117^+CD127^+CD122^+IL\text{-}1R1^+$).

Immature NK cells (iNKs) express a higher level of CD56 ($CD56^{bright}$) and IL-1R1 along with CD161 (NK1.1), CD314 (NKG2D), CD335 (NKp46), and CD337 (NKp30).[35] The maximal expression of NK1.1, NKG2D, NKp46, and NKp30 marks the commitment of iNKs to the transitional stage (TransNKs), which is separated into two substages by the expression of NKp80 (relatively immature substage a: $NKG2D^+CD337^+CD161^+NKG2A^+CD56^{bright}$ $NKp80^-$; and relatively mature substage b: $NKG2D^+CD337^+CD161^+NKG2A^+CD56^{bright}$ $NKp80^+$). TransNKs develop into the mature stage, becoming mNKs, with decreased CD56, increased CD16, and distinct expressions of CD158 (KIR) subtypes. The mNKs are $NKp80^+CD56^{dim}CD16^+KIR^{-/+}$. Expression of CD57 and increased KIR expression indicate terminally mature NK cells (TermNKs).[35,36]

Multiple cytokines in the bone marrow are responsible for the commitment, development, and maturation of NK cells (Fig. 2). Among these, stem cell factor (SCF), FMS-like tyrosine kinase 3 ligand (Flt3L), c-Kit, and IL-7 promote the early commitment of HSCs to CLPs.[37–39] IL-15 is essential for early NK cell development and survival,[40,41] and IL-2 is critical for survival, activation, and expansion.[42–44] Synergizing with IL-15 and IL-2, IL-21 enhances NK cell cytotoxicity.[45] IL-12 and IL-18 augment IFN-γ production and promote the cytotoxicity of NK cells.[46] TGF-β sustains the stemness of $CD34^+$ HSCs by blocking their commitment to the NK cell lineage.[47] However, at a later stage, it functions as a checkpoint to maintain NK cell immaturity.[48] While these and other soluble mediators play obligatory roles in the development of NK cells, the activation and functions of downstream transcriptional regulators have been only partially defined.

III. TRANSCRIPTIONAL CONTROL OF HUMAN NK CELL DEVELOPMENT

Distinct TFs drive NK cells to transition from one stage to another in sequential order.[31] The upstream and downstream regulators of GATA2 during NK cell development need to be fully determined, but, limited information is available about the select few TFs that link it with human NK cell development (Fig. 2).

Notch proteins drive HSCs into CLPs; ID2 is a member of the inhibitor of DNA-binding proteins; and RUNX3 drives CLPs into the NK cell lineage. GATA2, NFIL3, and ETS1 promote NKP transition into immature NK cells.[1,16,49–51] These TFs either positively or negatively regulate transition to maintain balanced development. Cytokine signaling pathways also play critical roles, either upstream or downstream of TFs, during human NK cell development. The constitutive expression of ID2 enhances commitment to the NK cell lineage from $CD34^+$ CLPs. High ID2 expression synergizes with IL-15 and results in an increased NKPs.[52] RUNX3 expression starts at the NKP stage, reaching its highest level in iNKs and mNKs,[53] and is essential for the commitment of NKPs.[53] RUNX3 binds the promoters of *KIR* and *NKp46* and initiates their transcription,[54] which demonstrates the role of this TF in the terminal maturation of human NK cells.

ETS1 is predominantly a lymphocyte-specific TF.[55,56] It is first expressed in the progenitor stage of NK cells development and reaches its peak level in the NKP late stage.[57] The absolute number of NK cells is significantly reduced among ETS1-deficient human cord blood cells, although the number of NKPs is unaltered.[50] The remaining NK cells from ETS1 loss-of-function HSCs have reduced cytotoxicity and IFN-γ production.[50] ETS1 contributes to NK cell development and function by regulating the expression of several critical TFs, including GATA3, NFIL3, T-bet, BLIMP1, and HOBIT.[50] Earlier studies reported that ETS1 binds to the promoter region of GATA2 and initiates its transcription.[58]

Evidence from murine models identifies distinct TFs upstream of Ets1. Notch upregulates the transcription of *Ets1*,[59] while PU.1 directly inhibits it.[60,61] Ets1, in turn, promotes transcription of *IDB2* (the Id2 gene) and *TBX21* (the T-bet gene).[57] The activation of human NK cells with IL-2 and IL-15 upregulates the expression of ETS1.[62] NK and NKT cells, but not T or B cells, highly express NFIL3 (E4BP4).[63] NFIL3 plays an essential role in NK cell commitment from NKPs to iNKs.[63] It is involved in NK cell development as a downstream target of the IL-15–mediated signaling pathway during the commitment to iNKs.[64] Also, it directly binds to the promoter region of *IBD2* and *EOMES* and activates their transcription.[65] GATA2 binds to the promoter region of *NFIL3*,[66] which may promote iNK commitment and maintain cell survival.[67]

Eomesodermin (EOMES) and T-bet belong to the T-box family and play obligatory roles during NK cell development.[68–70] Without it, NK cell development is blocked at an immature stage.[71] However, the lack of T-bet blocks EOMES before the terminally mature stage.[72] EOMES and T-bet antagonize the each other's expression during NK cell maturation.[68,69,71] IL-12 and IL-15 stimulation upregulates the expression of T-bet. Both T-bet and Eomes are the downstream targets of IL-15R–mediated signaling.[73]

ZEB2 (zinc finger E-box-binding protein) plays a critical role in the TGF-β–mediated signaling involved in epithelial-to-mesenchymal transition through the activation of R-Smads.[74,75] Zeb2 regulates the terminal maturation of NK cells, indicating a potential role for TGF-β at the later stages of NK cell development.[76] T-bet is required to induce the expression of Zeb2, which is critical to maintaining the transcriptional activity of T-bet, implicating a mutual regulation between these two TFs.[76] Overexpression of Zeb2 partially restores NK cell defects that result from T-bet deficiency.[76] Zeb2 is downstream of NFIL3 during dendritic cell specification, implying that IL-15R–mediated activation leads to initiation of the NFIL3-Zeb2 axis during early NK cell development.[77] Mutual transcriptional repression between Id2 and Zeb2 has been found during DC lineage development which may also be operative in NKPs.[77] Thus, the transcriptional control of early NK cell development by the NFIL3-Zeb2-Id2 axis needs to be investigated.

IV. IMPACTS OF GATA2 DEFICIENCY ON IMMUNE CELLS

Patients with GATA2 haploinsufficiency possess a reduced number of $CD34^+$ cells in bone marrow (BM) but maintain maturation capability of hematopoietic stem cells.[78] However, induced pluripotent stem cells (iPSCs) derived from GATA2-deficient patients do not replicate the defects in committing to hematopoietic progenitors.[79] Patients with GATA2

deficiency also show near complete loss of B cell precursors[78] and reduced transitional and naïve B cells, while memory B cells are enriched and appeared skewed to the mature state.[80]

Specific loss of $CD56^{bright}$ NK cells is a significant and consistent feature of GATA2 deficiency.[19,80,81] T cell deficiency varies in patients. One cohort study reported that 50% of 57 patients with the GATA2 mutation displayed reduced $CD4^+$ T cell numbers.[18] Another result from a cohort study, including 30 patients with GATA2 mutation, showed reduced naïve and central memory $CD8^+$ T cells revealed by decreased CD27, CD62L, CD38, and HLA-DR.[80]

Interestingly, several groups have reported an increased $CD3^+CD56^+$ T cell population in GATA2-deficient patients.[19,80,82] These NK-like T cells play an essential role in eliminating cytomegalovirus (CMV) infections.[83] However, because the role of GATA2 in their development and functions has not been determined, and while the type of NK or B cell deficiency is well-correlated with GATA2 mutation, the developmental defects associated with T cell subtypes have yet to be fully characterized.

DC deficiency is highlighted in patients with GATA2 deficiency and may relate to elevated FLT3L in patients with GATA2 haploinsufficiency. Indeed, studies have shown the number of DCs to be inversely correlated with the level of FLT3L.[37,84] The high elevation of FLT3L is a unique serological feature of patients with GATA2 mutation, and its progressive elevation relates to the clinical advancement of associated disorders.[15,80]

Both $CD14^+$ and $CD16^+$ monocytes are significantly reduced in patients with GATA2 haploinsufficiency.[80] In addition to dysfunctional immune cells, around 75% of patients who carry the GATA2 mutation develop a malignant blood disease, including MDS, AML, and chronic myelomonocytic leukemia (CMML).[85] The acquisition of additional genetic abnormalities in GATA2 deficiency usually results in the rapid onset of hematological abnormalities with a poor prognosis for survival.[86,87] These abnormalities include monosomy 7, trisomy 8, trisomy 21, and mutations in ASXL1, CEBPA, and other genes, alone or concomitant.[86,88,89]

To date, over 350 GATA2 genomic variants have been reported on the ClinVar website (https://www.ncbi.nlm.nih.gov/clinvar/; January 2021). Around 85% of them are single nucleotide substitutions. There are three major categories of mutations present in GATA2-deficient patients: (1) the N-terminal ZF domain (amino acid 259–319), (2) the C-terminal ZF domain (amino acid 349–373), and (3) other regions (such as +9.5 intronic enhancer).[90] Somatic mutations predominately occur in the N-terminal ZF domain. $GATA2^{sLeu321Phe}$ is the most prevalent of these.[91]

All germline mutations are observed in the C-terminal ZF domain. The most common missense mutations, $GATA2^{gThr354Met}$, $GATA2^{gArg396Gln}$, and $GATA2^{gArg398Trp}$, result in loss of function.[17,92] Uniquely, $GATA2^{Leu359Val}$ is a gain-of-function mutation.[93,94] The C-terminal ZF domain of GATA2 interacts with PU.1,[95] which directly binds and drives the expression of FLT3 and granulocyte-macrophage colony–stimulating factor (GM-CSF)—essential growth factors in the development of DCs.[96] Mutated $GATA2^{Thr354Met}$ and $GATA2^{Cys373Arg}$ physically bind to PU.1 with higher affinity due to the altered C-terminal

ZF structure.[97] Interaction between GATA2 and PU.1 results in reciprocal functional antagonism through regulation of their transcription and DNA binding.[98,99]

GATA1, another GATA family member, is a crucial TF that drives the differentiation of HSCs into megakaryocytes.[100] While GATA2 is essential for maintaining stemness, it is also critical to early activation of GATA1 erythroid/megakaryocyte lineage commitment from HSCs. This phenomenon, known as the "GATA switch," facilitates the displacement of GATA2 from the chromatin by GATA1.[101–103] GATA2 can bind its own upstream promoter region and upregulate its transcription. Increased GATA2 activates GATA1, which in turn represses GATA2 expression. Both GATA1 and GATA2 are capable of autoactivating their own expression.[104] New findings have challenged this paradigm, where high DNA methylation by DNMT1, not GATA2, is responsible for an inactive *GATA1* locus.[102,105] Detailed study is required to determine the role of the GATA switch in the commitment of HSCs to the NK lineage.

One of the critical TFs in lymphocyte development, Ets1, can bind to the GATA2 promoter and positively regulate its expression on erythroid differentiation.[58] GATA2 protein directly binds to the *NFIL3* promoter region, a TF that is essential in developing T, B, NK, and dendritic cells.[106,107]

GATA2$^{-/-}$ mice are embryonically lethal and die at day 10.5 (E10.5) due to loss of vascular integrity and anemia.[1] Following tamoxifen-induced deletion, *GATA2*$^{fl/fl}$*ER*^{Cre} adult mice display depleted splenic B cells, T cells, NK cells, monocytes, and DCs, along with impaired DC differentiation.[108] Notably, CD-49b^{+}NK1.1^{+} NK cell numbers are significantly reduced in these mice.[108] However, the extent of the reduction in defective NK cell development and the impaired signaling pathways is not known. Mice with *GATA2* haploinsufficiency display a reduced number of HSCs and granulocyte-macrophage progenitor (GMP) cells as well as an impaired ability to differentiate to monocytes[109]; however, they do not exhibit defects in DC numbers or DC differentiation,[108] the development of MDS, or leukemia.[109]

Further studies are required to determine if NK cells display impaired development in *GATA2*$^{+/-}$ mice. Overexpression of GATA2 inhibits hematopoiesis through defective cell cycle pathways.[110] Elevated GATA2 correlates with an adverse prognosis for patients with AML.[111,112] Thus, a fine-tuned balance of functional GATA2 protein is critical to the self-renewal and differentiation of HSCs into lineage-committed progenitors. Although *GATA2*$^{fl/fl}$ *ER*^{Cre} and *GATA2*$^{+/-}$ mice can mimic some GATA2-deficiency features, a better disease model is necessary to define the molecular mechanisms of GATA2-mediated transcriptional regulations.

V. ROLE OF GATA2 IN HUMAN NK CELL DEVELOPMENT

GATA2 is an essential TF in lineage commitment and early NK cell development in humans.[16] The specific loss of the CD56^{bright} NK cell population is a striking feature of GATA2-deficient patients[19] with or without reduced total CD56^{dim} NK cells.[19,81,82] Earlier, we reported that upregulated apoptosis is potentially the mechanism behind reduced NK cell numbers, supported by the augmented expression of the proapoptotic genes *GIMAP4* and

GIMAP7.[35] In an *in vitro* culture, purified $CD34^+$ hematopoietic precursors from GATA2-deficient patients failed to differentiate into $CD56^{bright}$ NK cells but gave rise to $CD56^{dim}$ NK cells, albeit in significantly lower numbers than expected.[19,81]

iPSCs derived from GATA2-deficient patients do not show significant defects in differentiating to NK cells.[79] The reasons for these differences are not understood. GATA2 is predominately expressed in $CD56^{bright}$ cells, which may indicate its vital role in maintaining this early immature subset.[19] However, it has been shown that $CD56^+$ NK cells only express GATA3 and that GATA2 is detected uniquely on HSCs.[81] Thus, the expression of GATA2 on the $CD56^{bright}$ NK subset requires detailed analyses to substantiate its role in early developmental stages.

NK cells in patients with GATA2 haploinsufficiency exhibit severe functional defects, including cytotoxicity of remaining $CD56^{dim}$ cells.[19] Severe HPV or EBV infection in these patients further indicates dysfunctional mature $CD56^{dim}$ NK cells at multiple levels, although precise molecular defects are so far unknown. A reduced expression of effector molecules, such as perforin and different granzymes, could be due to a reduction in responsible TFs, including T-bet and EOMES.[81] NK cells in these patients also express less PLZF, FceRg, and SYK, which define adaptive NK cells.[81] Adaptive NK cells persist longer term, but it is not clear whether increased adaptive NK cells can protect patients from viral infections. NK cell development is not significantly altered in PLZF-null mice, suggesting other transcription factors downstream of GATA2.[113] NK cells from these patients have lower levels of CXCR4 and dysfunctional CXCL12/CXCR4-mediated chemotaxis.[35,82] Proper functioning of the CXCL12/CXCR4 axis is essential for the bone marrow homing of NK cells.[114]

It is not clear whether impairment of the CXCL12/CXCR4 axis results in reduced cell numbers in the bone marrow of patients with GATA2 haploinsufficiency. As a master regulator, GATA2 may cooperate with a network of TFs to govern human NK cell development. ETS1, one GATA2 upstream regulator,[58] NFIL3, a GATA2 downstream target,[106,107] and several other TFs interacting with GATA2, such as PLZF[115] and PU.1,[95] all play critical roles in NK cell development and functions. Future studies should focus on whether an ETS1-GATA2-NFIL3 transcriptional axis governs human NK cell development (Fig. 2).

VI. SUMMARY AND FUTURE DIRECTIONS

Human NK cells account for around 10%–20% of circulating lymphocytes in the peripheral blood. Their ability to kill malignant cells without prior sensitization indicates a promising role in immunotherapeutic applications. Driving the full functional potential of NK cells in patients or *ex vivo* is essential for successful clinical application. Achieving success in immunotherapy requires a thorough understanding of the TF network and its potential mechanisms of action in human NK cell development. Most known TFs of NK cells are based on murine models, which have not been fully replicated on human NK cells. The human disease conditions that specifically lack either a $CD56^{bright}$ or a $CD56^{dim}$ population provide a unique opportunity to understand human NK cell development.

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ABBREVIATIONS:

ADCC	antibody-dependent cell–mediated cytotoxicity
AML	acute myeloid leukemia
CLP	common lymphoid progenitor
DC	dendritic cell
HSC	hematopoietic stem cell
iNK	immature NK cell
iPSC	inducible pluripotent stem cell
MDS	myeloid dysplastic syndrome
mNK	mature NK cell
NK	natural killer
NKP	NK cell progenitor
TF	transcription factor
ZF	zinc finger

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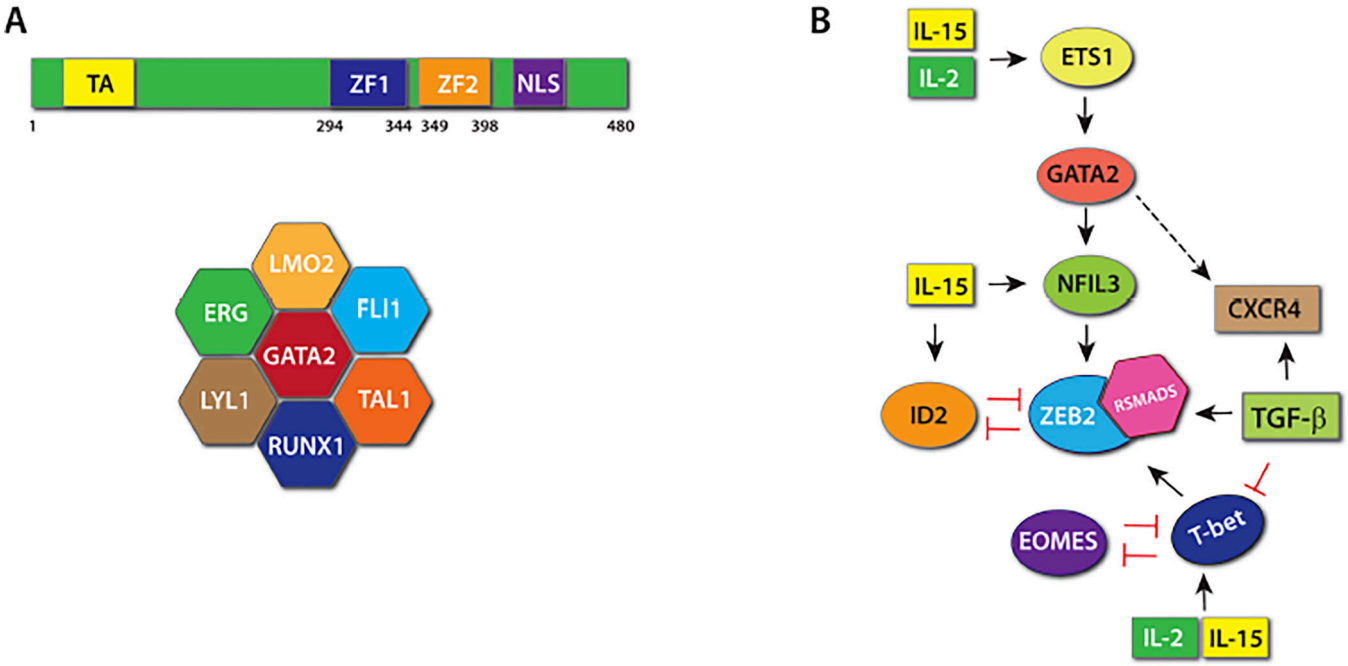

FIG. 1:

GATA2, its transcriptional partners, and their transcriptional role in human NK cells. (A) GATA2 comprises two zinc finger (ZF) domains, two transactivation domains, one nuclear localization signal, and one negative regulatory domain (Top). GATA2 forms a core heptad complex with six other TFs (TAL1, FLI1, RUNX1, LYL1, LMO2, and ERG) to directly impact the survival differentiation of HSCs by regulating more than 1,000 target genes (Bottom). (B) Multiple potential upstream and downstream factors of GATA2 and cytokines. This predicted pathway was assembled using findings from NK and other cell types.

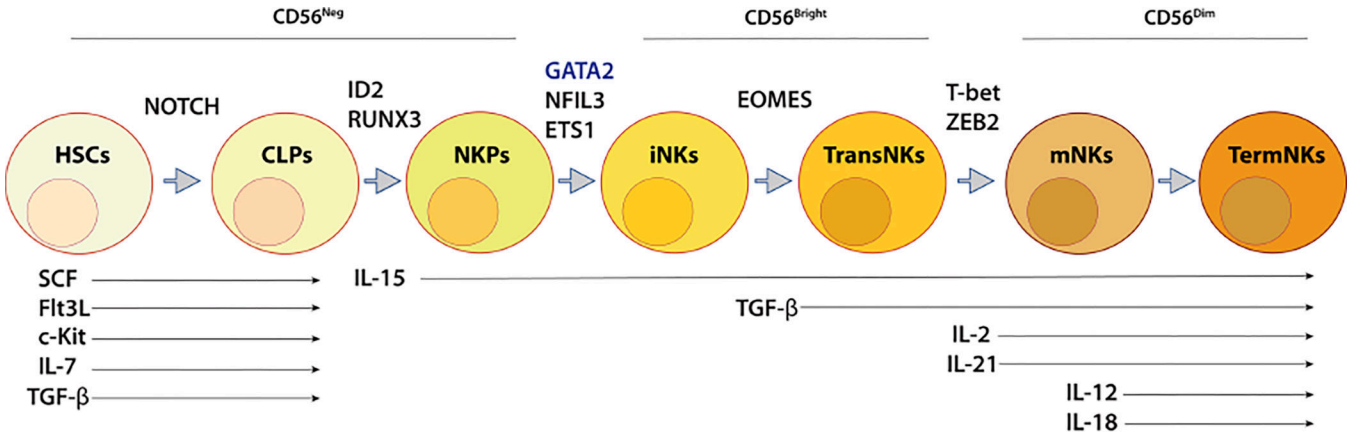

FIG. 2:

Role of major transcription factors, including GATA2, in human NK cell development. Transcription factors and the specific developmental stages of human NK cells are indicated. GATA2 plays an essential role in the transition of NKPs into immature NKs. The role of GATA2 in the early commitment of CLPs into NKPs is yet to be established.