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Review

JAK/STAT proteins and their biological impact on NK cell development and function

Alexander Vargas-Hernández[a,b], Lisa R. Forbes[a,b,*]

[a] Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA
[b] Texas Children's Hospital, Center for Human Immunobiology, Department of Allergy, Immunology and Rheumatology, Houston, TX, USA

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ABSTRACT

NK cells are important early effectors in the innate immune response to a variety of viral infections and for elimination of tumor cells. The JAK/STAT signaling cascade is critical for NK cell development, maturation, survival, and proliferation, therefore, it is important to understand the role of this pathway in NK cell biology. Many cytokines can activate multiple JAK/STAT protein family members, creating a severe phenotype when mutations impair their function or expression. Here we discuss the impact of defective JAK/STAT signaling pathways on NK cell development, activation and cytotoxicity.

1. Introduction

Natural killer cells are the third largest subset of lymphocytes in the peripheral blood, accounting for approximately 10–15% of all circulating lymphocytes (Cooper et al., 2001a). In peripheral blood the majority of the circulating NK cells, approximately 90% (Angelo et al., 2015), are considered the mature cytotoxic subset; these are termed $CD56^{dim}$ NK cells and are characterized functionally by their potent killing capacity. The $CD56^{bright}$ NK cell subset represents approximately 10% of peripheral blood NK cells and they are responsible for cytokine response in early viral infections (Cooper et al., 2001a, b; Freud and Caligiuri, 2006; Freud et al., 2006; Poli et al., 2009). $CD34^{+}$ NK cell precursors are found in fetal tissues, neonatal cord blood, and adult blood (Renoux et al., 2015). All stages of NK cell development described are characterized by the acquisition and/or loss of specific markers, proliferative and functional capacities, and by their in vivo trafficking (Freud et al., 2005; Freud and Caligiuri, 2006; Freud et al., 2006; J. Yu et al., 2013).

NK cell maturation through the various stages of development requires IL-15 (Becknell and Caligiuri, 2005; Huntington et al., 2009). Activation through the intracellular domain of IL-15 receptor leads to the recruitment and phosphorylation of STAT5; a member of the signal transducer and activator of transcription family (Kanai et al., 2012; Lin and Leonard, 2000). The Janus kinase (JAK)/STAT pathway transduces signals for cellular events that are critical for NK cell biology (Gotthardt and Sexl, 2016) (Table 1). In mammals, four JAK proteins (JAK1, JAK2, JAK3, and TYK2) constitute the JAK family (Vainchenker et al., 2008), and there are seven members in the STAT family: STAT1, 2, 3, 4, 5a and 5b, and 6 (Levy and Darnell, 2002; Reich, 2007, 2013).

NK cells are important early effectors in the innate immune response to a variety of viral infections and for elimination of tumor cells (Biron et al., 1999; Cooper et al., 2001a). Patients with congenital defects in NK cells have severe impairment in their NK cell function with an increased susceptibility to serious viral infections (Mace and Orange, 2016). The human STAT mutations including STAT1, STAT2 and STAT5b deficiency along with STAT1 gain of function disease (GOF) are associated with susceptibility to viral infections (Bernasconi et al., 2006; Hambleton et al., 2013; Toth et al., 2012; Toubiana et al., 2016). Importantly, JAK/STAT interactions have many implications on NK cell development and function. Our review summarizes the contributions of the canonical JAK/STAT pathway to NK cell biology. Moreover, we describe the NK cell phenotypes observed in mice and humans by each member of this signaling pathway.

2. NK cell development

The stages of NK cell development differ in their receptor expression pattern and in their in vivo trafficking (Freud and Caligiuri, 2006; Yu et al., 2013). A decade ago, five stages of human NK cell development were described according to the expression of CD34, CD117, CD94, and

Abbreviations: NK, Natural Killer cells; STAT, Signal Transducers and Activators of Transcription Factors; JAK, Janus kinase; IL-, Interleukin

* Corresponding author at: Department of Pediatrics, Immunology Allergy and Rheumatology, Center for Human Immunobiology, 1102 Bates, Suite 330, Houston, TX, 77030, USA.
E-mail address: lisa.forbes@bcm.edu (L.R. Forbes).

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Table 1
Role of JAK/STAT proteins in NK cells. JAK, Janus kinase; STAT, signal transducer and activator of transcription; TYK2, tyrosine kinase 2.

NK cell	JAK proteins associated	STATs proteins
Development	JAK1, JAK2, JAK3	STAT1, STAT5
Maturation	JAK1, JAK2, JAK3, TYK2	STAT1, STAT4, STAT5
Cytotoxicity	JAK1, JAK3, TYK2	STAT1, STAT4, STAT5 ↓ STAT3, STAT6
Survival	JAK1, JAK3	STAT5
Proliferation	JAK1, JAK3	STAT5

CD16 (Freud and Caligiuri, 2006; Freud et al., 2006; Grzywacz et al., 2006). Recently, *ex vivo* characterization in secondary lymphoid tissues (SLTs) revealed a new schema for the stages of NK cell development. This characterization was proposed according to CD34, CD117, IL-1R, CD94, NKp80, CD16 and CD57 expression (Scoville et al., 2017). This classification distinguishes the lineage commitment between NK cells and innate lymphoid cell (ILC) subsets, both of which arise from a common lymphoid progenitor (CLP) (Yang and Bhandoola, 2016). In general, NK cells are characterized by their dependence on the transcription factors T-BET and EOMES, the capacity to produce IFN-γ, and their cytolytic capacity; whereas, ILC1 cells express T-bet and secrete IFN-γ (Spits et al., 2016). Group 2 ILCs express GATA3 with higher IL-5 and IL-13 production. ILC3 cells express RORγt and produce IL-17 and IL-22 (Sonnenberg et al., 2013; Yang and Bhandoola, 2016).

Developmental stages are described on a continuum. Stage 1 ($CD34^+CD117^-IL\text{-}1R1^-ROR\gamma t^+CD1a^+CD10^+CD45RA^+$), identified in tonsils, displays a phenotype that overlaps with thymic $CD34^+CD1a^+$ T cell precursors; this finding suggests there is an overlap or intersection of the different lymphoid developmental pathways (McClory et al., 2012). Stage 2 cells ($CD34^+CD117^+ROR\gamma t^+$) were identified as residents of tonsils and intestinal lamina propia (LP). Interestingly, the capacity of these cells to differentiate into NK cells was lower in contrast to previous reports (Montaldo et al., 2014). In a subsequent study, stage 2 was further delineated and expression of IL-1β receptor (IL-1R) marked the identification of stage 2a ($CD34^+CD117^+IL\text{-}1R1^-ROR\gamma t^+CD10^-CD45RA^+$), and stage 2b ($CD34^+CD117^+IL\text{-}1R1^+ROR\gamma t^+CD10^-CD45RA^+$) in secondary lymphoid tissue (SLT)s. Both groups are functionally different, and the stage 2b cells ($IL\text{-}1R1^+$) lack the expression of *RAG1* correlating with an ILC lineage restriction. This means, in vitro, stage 2b cells are capable of giving rise to NK cells but not other leukocyte lineages (Scoville et al., 2016) **(**Fig. 1**A)**. Stage 3 ($CD34^-CD117^+IL\text{-}1R1^+CD94^-ROR\gamma t^+LFA\text{-}1^+CD45RA^+$) was identified in SLT, bone marrow (BM), as well as cord and peripheral blood. Stage 3 cells have been characterized with a multipotent capacity that can give rise to all ILC subsets, including NK cells (Freud et al., 2016; Hughes et al., 2009; Lim et al., 2017). This stage requires IL-2, IL-7, and IL-1β stimulation for differentiation to mature NK cells (Lim et al., 2017). However, in SLTs within the stage 3 N K cells and ILC3 populations exists a marked heterogeneity in the expression of numerous surface markers which makes it difficult to distinguish between subsets (Bjorklund et al., 2016).

The differential NKp80 expression during NK cell development defines stages 4a and 4b ($CD56^{bright}$) (Freud et al., 2016). Stage 4a ($CD34^-CD117^{+/low}IL\text{-}1R1^{+/low}CD94^+NKp80^-ROR\gamma t^+LFA\text{-}1^+KIR^-IFN\text{-}\gamma^-CD45RA^+$), similar to stage 3, has been characterized with an ILC3-like phenotype. This stage expresses IL-1R1, RORγt, CD127, and IL-22. However, *ex vivo* assays demonstrated that both stages lack the hallmark phenotype of mature NK cells, but have the capacity to acquire properties of mature NK cells (Freud et al., 2016). Subsequently, stage 3 and 4a giving rise to the moremature NK cell Stage 4b ($CD34^-CD117^{low/-}IL\text{-}1R1^{low/-}CD94^+NKp80^+CD16^-CD57^-Perforin^{-/low}LFA\text{-}1^+KIR^{+/-}IFN\text{-}\gamma^+CD45RA^{+/-}$) characterized by a higher expression of T-BET, EOMES, IFN-γ, and acquisition of perforin expression. (Freud et al., 2016) **(**Fig. 1**A)**. Finally, in peripheral blood, the up-regulation of CD57 expression defines two functional NK cell subsets within the $CD56^{dim}$, mature NK cell subset: the "early" $CD57^-CD56^{dim}$ (stage 5) and the "late" $CD57^+CD56^{dim}$ (stage 6). The $CD57^+CD56^{dim}$ subset is a more mature phenotype with potent cytolytic capacity (Lopez-Verges et al., 2010; Schlums et al., 2015) (Fig. 2). In addition, small functional transitional populations between $CD56^{bright}$ (stage 4b) and mature $CD56^{dim}$ NK cell subsets supports a linear model of human NK cell development. They are $CD56^{dim}CD94^{high}$ (J. Yu et al., 2010), $CD56^{dim}CD62L^{high}$ (Juelke et al., 2010), and $CD56^{dim}CD117^{high}$ (Grzywacz et al., 2006) with some expression of perforin, and a lower capacity to kill target cells compared to $CD56^{dim}$ NK cell subsets **(**Fig. 1**A)**.

In mice, NK cells develop from pluripotent hematopoietic stem cells (HSCs) through a common innate lymphoid progenitor (CILP) cell capable of giving rise to restricted common helper ILC progenitor (CHILP) cells that can differentiate into all ILC subsets but not NK cells and/or NK cell progenitor (NKPs) cells (Constantinides et al., 2015, 2014; Klose et al., 2014; Scoville et al., 2017; Yang et al., 2015; Yu et al., 2014). The murine NKPs are cells with developmental potential in response to IL-15 that lack the hallmark of mature NK cells, but can acquire NK cell lineage commitment and are defined as $Lin^-CD122^+NK1.1^-DX5^-$ cells (Rosmaraki et al., 2001). In 2011 Fathman and colleagues described a new population in the bone marrow, $Lin^{+/-}CD27^+CD244^+CD117^{low}CD127^+CD122^-CD135^-$, referred to as pre-NKP. This population represents a NKP stage between CLP and $Lin^-CD122^+NK1.1^-DX5^-$ NKP cells (Fathman et al., 2011). The acquisition of CD122 by NKP cells is an important step downstream of NK cell differentiation. As in humans, IL-15 promotes NK cell differentiation, maturation, and survival in mice as well (Becknell and Caligiuri, 2005) **(**Fig. 1**B)**.

The acquisition of functional receptors in an orderly process is similarly observed in humans and mice, thereby, marking the transition to late stages of NK cell development. In mice, the NK cell developmental intermediates (NKDIs) acquire NK1.1 (only expressed in CD57BL/6 mouse strain), CD94/NKG2A, and NKp46 followed by Ly49, DX5, and, finally, CD43 and CD11b (Kim et al., 2002). The next stage, immature NK cells (iNK), is distinguished by the sequential acquisition of NK1.1 and CD94-NKG2D receptors (Yu et al., 2013). In the final stage, cells migrate to the periphery, upregulate CD11b and acquire their functional capacity. These mature NK cells produce IFN-γ and mediate perforin-dependent cellular cytotoxicity (Kim et al., 2002). CD27 expression delineates the progression of NK cell development. As the NK cells mature, they acquire CD27 expression early. Then as they become more mature, they lose CD27 expression at a later stage (Hayakawa et al., 2006; Hayakawa and Smyth, 2006) **(**Fig. 1**B)**. The relationship between NK cells and the ILC3 subset is a distinct difference in development between humans and mice. While the human stage 3 cells retain a hallmark of ILC3s, the mouse subsets are developmentally distinct (Montaldo et al., 2015).

3. IL-15 signaling and NK cell development

The JAK/STAT pathway is the principal signaling pathway for a wide range of cytokines and growth factors (Majoros et al., 2017; Rawlings et al., 2004). This pathway transduces signals for cellular events that are critical for NK cell biology (Gotthardt and Sexl, 2016). IL-15 induces NK cell development from human bone marrow-derived hematopoietic progenitor cells and is required for the terminal maturation of fully functional NK cells (Boos et al., 2008; Huntington et al., 2009; Mrozek et al., 1996; Tamzalit et al., 2014). In vitro, soluble IL-15 induces NK cell development from human BM-derived $CD34^+$ hematopoietic progenitor cells (HPCs) (Mrozek et al., 1996; Yu et al., 2013). in vivo, the trans-presentation of IL-15 to pre-NK and iNK cells promotes NK cell commitment and proliferation, respectively (Boos et al., 2008; Budagian et al., 2006; Mrozek et al., 1996; Tamzalit et al., 2014) **(**Fig. 2**A-B)**.

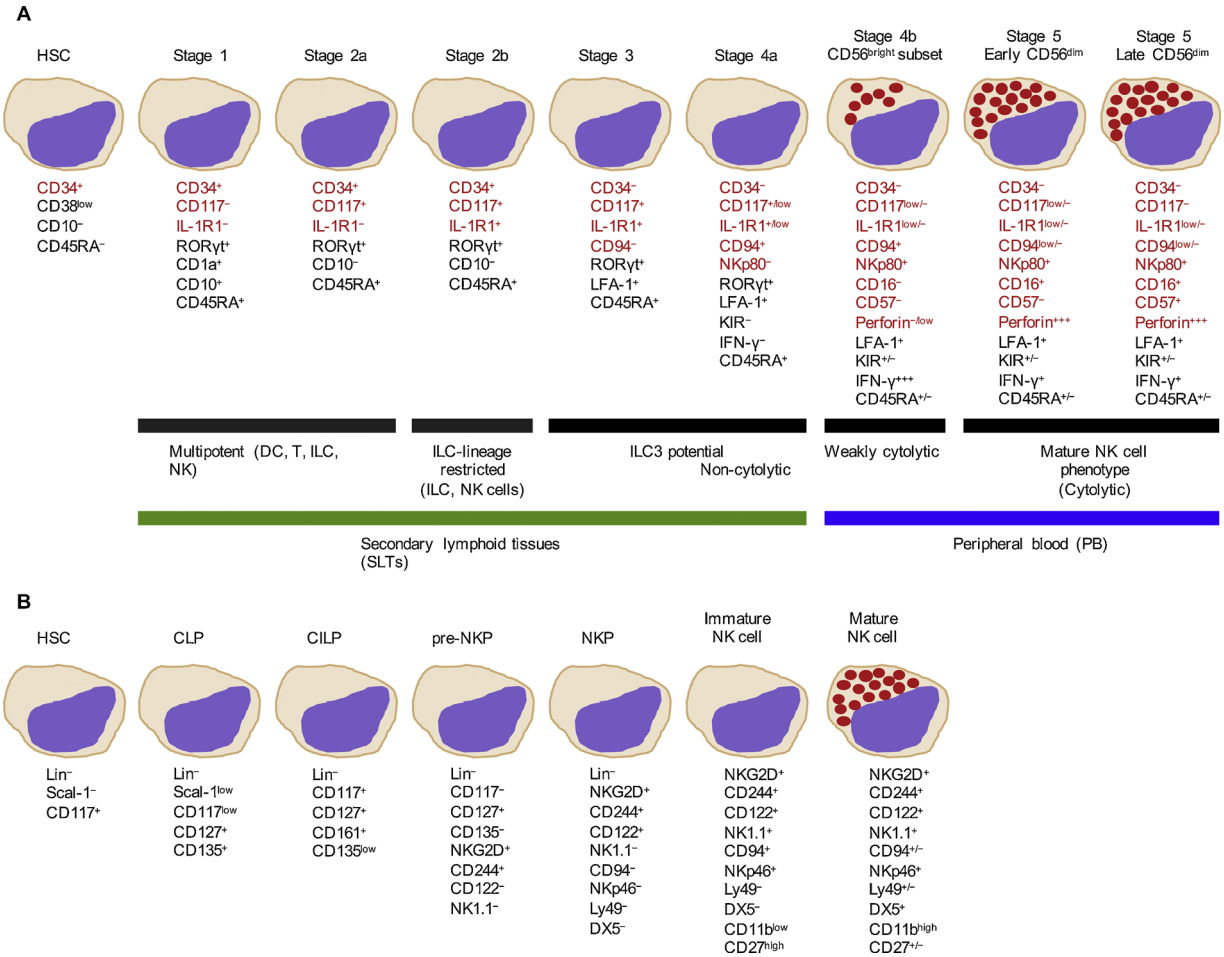

Fig. 1. Stages of A) human NK cell development according to expression of CD34, CD117, IL-1R1, CD94, NKp80, CD16, and CD57. Schematic representation based on previous report (Scoville et al., 2017). Red represents the surface receptors that define each stage. ILC, Innate lymphoid cells; LFA-1, Lymphocyte function-associated antigen 1; DC, dendritic cells; T, T lymphocytes; NK, Natural Killer cells. B) Murine NK cell development. HSC, hematopoietic stem cell; CLP, common lymphoid progenitor; CILP, common innate lymphoid progenitor; NKP, NK cell progenitor. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Activation through the IL-15 receptor induces the recruitment and phosphorylation of STAT5 proteins (Kanai et al., 2012; Lin and Leonard, 2000). The IL-15 receptor is composed of three subunits, the common γ chain (CD132), the shared IL-2/IL-15Rβ chain (CD122), and the high affinity IL-15Rα chain (CD215) (Budagian et al., 2006). Briefly, this pathway depends of a series of tyrosine phosphorylations; first, IL-15 receptor oligomerization leads to the trans-phosphorylation of JAK1 and JAK3 proteins (Fig. 2C). Next, IL-15 receptor intracellular domains are phosphorylated by JAK proteins; this phosphorylation provides binding sites for STAT5 proteins (Fig. 2D). The STAT5 proteins are then recruited to the binding sites whereupon they are phosphorylated on a single tyrosine residue (Fig. 2E). This modification induces STAT5a and/or STAT5b homo- or hetero-dimerization (even tetramerization), and finally these complexes translocate to the nucleus where they bind to consensus sequences on gene promoters (Cohen et al., 2006; Kanai et al., 2012; Levy and Darnell, 2002; Majoros et al., 2017; Soldaini et al., 2000; Vosshenrich et al., 2005) (Fig. 2F).

4. STAT proteins and NK cells

The STAT family includes seven structurally and functionally related proteins: STAT1, STAT2, STAT3, STAT4, STAT5a and b, and STAT6 (Villarino et al., 2015). STAT proteins are cytoplasmic factors that are activated by tyrosine phosphorylation in response to a variety of cytokines and growth factors (Villarino et al., 2015). After their activation STAT1, STAT3, STAT4, STAT5, and STAT6 form homodimers, while STAT1 and STAT2, and STAT1 and STAT3 can form heterodimers; STAT5 can form tetramers (Fink and Grandvaux, 2013; Levy and Darnell, 2002; Levy and Marie, 2012; Lin et al., 2012). The activation of STAT proteins is regulated by three classes of negative regulators: SOCS (suppressors of cytokine signaling), PIAS (protein inhibitors of activated stat), and PTPs (protein tyrosine phosphatases) (Rawlings et al., 2004). First, the simplest are the PTP proteins that regulate the activity of JAK proteins (Rawlings et al., 2004). Second, the SOCS proteins indirectly block STAT protein activation by their capacity to bind directly to receptor sites and/or JAKs catalytic sites (Cohney et al., 1999; Krebs and Hilton, 2001; Zhang et al., 2001). Finally, the PIAS proteins prevent the interaction of activated STAT dimers with DNA (Rawlings et al., 2004).

4.1. STAT1 and cytotoxicity

In response to type I IFNs (α/β), STAT1 and STAT2 factors dimerize; however, in response to type II IFN (γ), STAT1 forms homodimers (Reich, 2007). Many studies in mice have shown that type I IFNs have a pivotal role in the induction of NK cell cytotoxicity during viral infections (Nguyen et al., 2002; Trinchieri and Santoli, 1978; Welsh and Zinkernagel, 1977). The *Stat1*$^{-/-}$ KO mice have been characterized with a lower frequency of mature NK cells and higher susceptibility to viral and bacterial infections (Durbin et al., 1996; Gardner et al., 2012;

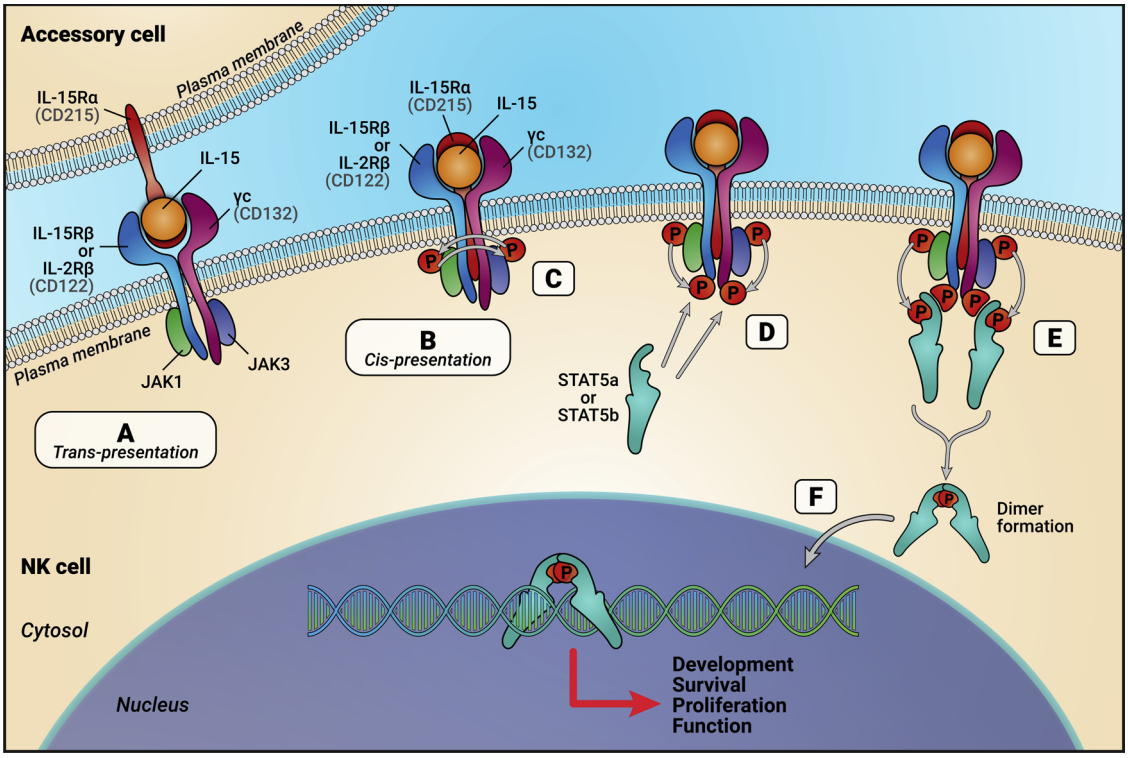

Fig. 2. IL-15 signaling pathway in NK cells. A series of tyrosine phosphorylations follow IL-15 cytokine-receptor interaction; A) trans- or B) cis-presentation of IL-15, C) JAK protein tyrosine transphosphorylation, D) phosphorylation of the intracellular domain of the IL-15 receptor and recruitment of STAT5 to the intracellular domain. E) STAT protein activation by tyrosine phosphorylation, F) Homo- or heterodimer formation and these dimers translocate to the nucleus and bind to the promoter of target genes.

Meraz et al., 1996; Robbins et al., 2005; Sugawara et al., 2004). Additionally, the splenic NK cells from *Stat1*$^{-/-}$ KO mice have an abnormal expression of NK cell maturation markers, suggesting that STAT1 has a pivotal role in the maturation of NK cells (Robbins et al., 2005) (Table 2**).** Using this mouse model following MCMV infection, the expression of IL-15 is induced by a STAT1-dependent mechanism (type I IFN stimulation), promoting the survival and/or accumulation of proliferating NK cells (Nguyen et al., 2002).

The parallel STAT1 dimer formation requires the phosphorylation of tyrosine 701 (Y701) (X. Chen et al., 1998). When this tyrosine moiety is disrupted as in the *Stat1-Y701F* mutant knock-in mouse model (Majoros et al., 2016), it results in an impairment in number and maturation of NK cells in the spleen, comparable to *Stat1*$^{-/-}$ KO mice. In addition, STAT1-S727 phosphorylation modulates dimer translocation to the nucleus and transcription (Nair et al., 2002; Sadzak et al., 2008; Wen et al., 1995). STAT1-S727 A mice display normal NK cell development witn enhanced NK cell cytotoxicity against a range of tumor cells accompanied by higher levels of perforin and granzyme B expression. This study reveals that constitutive phosphorylation of STAT1-S727 affects NK cell cytotoxic activity (Putz et al., 2013), suggesting an inhibitory role of STAT1-S727 phosphorylation in NK cell biology. These findings together suggest a complex participation of STAT1 in several NK cell processes (Table 2**).**

In humans, biallelic *STAT1* lost-of-function mutations lead to a very low or complete absence of the wild-type protein (Boisson-Dupuis et al., 2012) accompanied by defective NK cell cytotoxic activity (Vairo et al., 2011) **(**Table 2**).** Heterozygous gain-of-function (GOF) mutations in the *STAT1* gene result in a hyperphosphorylation state (Sampaio et al., 2013) where patients develop recurrent or persistent chronic mucocutaneous candidiasis (CMC) or other cutaneous mycosis, staphylococcal infections, disseminated dimorphic fungal infections (*Coccidioides immitis* and *Histoplasma capsulatum*), viral infections and autoimmune disease (Toubiana et al., 2016). Our studies demonstrated that *STAT1* GOF mutations cause a distinct NK cell deficiency characterized by an immature CD56^{dim} NK cell subset with higher levels of expression of CD117 and CD94, significantly reduced expression of CD16 and perforin, low numbers of NK cells along with decreased NK cell cytotoxicity (Vargas-Hernandez et al., 2018) **(**Table 2**).**

Treatment with the JAK 1/2 inhibitor ruxolitinib has been shown to relieve some of the clinical manifesations of the disease including NK cell abnormalities. In a patient with refractory esophageal candidiasis, treatment with ruxolitinib led to resolution of many symptoms (Higgins et al., 2015). Moreover, STAT1 GOF patients that received oral treatment with ruxolitinib showed reduced burden of CMC and hyper-responsiveness to type I and II interferons, normalized T_H1 and follicular T helper responses, and remission of autoimmune-mediated cytopenias (Mossner et al., 2016; Weinacht et al., 2017). Finally, we showed that upstream inhibition of STAT signaling with ruxolitinib restored perforin expression in CD56^{dim} NK cells and partially rescued NK cell cytotoxic function (Vargas-Hernandez et al., 2018).

4.2. STAT2: viral defense

STAT2 is activated in response to type I IFNs (Reich, 2007), dimerizes with STAT1, and together they interact with the interferon regulatory factor 9 (IRF9), (also known as IFN-stimulated gene factor 3 (ISGF3)) (Fink and Grandvaux, 2013). *STAT2*$^{-/-}$ KO mice have impaired ISGF3 activation and develop severe vesicular stomatitis viral infections (C. Park et al., 2000). Viral infections in these mice resemble the ones observed in a patient with *STAT2* deficency (Hambleton et al., 2013). Some patients with the same *STAT2* mutation do not display the same phenotype but rather remain generally healthy, without any abnormalities (Hambleton et al., 2013) **(**Table 2**).** One potential explanation for this phenotype is that STAT2 dimers have a poor DNA-binding capacity (Fink and Grandvaux, 2013). Therefore, these patients likely have normal gamma-activated transcription factor (GAF)-

Table 2
NK cells phenotypes that are caused by STAT proteins. LOF, lost of function; GOF, gain of function; GB, Granzyme B; MHC class I, Major histocompatibility complex class I; BM, bone marrow; H, human deficiency; M, knockout mice; M*, knock-in mice; Mˆ, transgenic mice (deletion of STAT3 in NK cells); M', transgenic mice (Deletion of STAT3 in hematopoietic cells); M", transgenic mice (deletion of STAT5 in NK cells); DKI mice, STAT5 tetramer-deficient mice.

Genotype	Biological effects in NK cells	References
Stat1$^{-/-}$ (M)	Impaired NK cell maturation Low expression of MHC class I and maturation markers	(Robbins et al., 2005)
Stat1-Y701F (M*)	Impaired NK cell maturation	(Putz et al., 2016; Majoros et al., 2016)
Stat1-S727A (M*)	Higher numbers of mature NK cells Minor NK cell phenotype changes Higher expression of perforin and GB Enhanced cytotoxic capacity Enhanced NK cell-dependent tumor surveillance	(Putz et al., 2013)
STAT1 LOF (H)	Low NK cell cytotoxicity	(Vairo et al., 2011)
STAT1 GOF (H)	Impaired NK cell development Decreased NK cell cytotoxicity Low Perforin and CD16 expression	(Vargas-Hernandez et al., 2018)
Stat2$^{-/-}$ (M)	NK cell function	(Park et al., 2000)
STAT2 (H)	NK cell function (?)	(Hambleton et al., 2013)
Stat3$^{-/-}$ (Mˆ)	Normal NK cell development Reduced tumor burden NK cell-dependent High expression of perforin and GB	(Gotthardt et al., 2014)
Stat3$^{-/-}$ (M')	Normal NK cell development Enhanced cytotoxic capacity	(Kortylewski et al., 2005)
STAT3 GOF (H)	Low NK cells number in peripheral blood Low NK cell cytotoxicity Low IFN-γ production	(Haapaniemi et al., 2015; Milner et al., 2015)
Stat4$^{-/-}$ (M)	Abrogated NK cell cytotoxicity Lower IFN-γ production Coordinated regulation in NK cell response (Type I IFNs, IL-12, and IL-15)	(Kaplan et al., 1996; Nguyen et al., 2002)
Stat5a$^{-/-}$ (M)	Impaired NK cell development	(Villarino et al., 2017)
Stat5b$^{-/-}$ (M)	Impaired NK cell development Impaired NK cell maturation	(Imada et al., 1998; Villarino et al., 2017)
Stat5$^{-/-}$ (M")	Impaired NK cell maturation in BM Impaired NK cell viability Impaired NK cell-dependent tumor surveillance	(Eckelhart et al., 2011)
DKI mice	Low NK cells number in peripheral blood	(Levy and Marie, 2012; Lin et al., 2012)
STAT5b (H)	Low NK cells number in peripheral blood NK cell development, maturation, and function	(Vargas-Hernandez et al., unpublished; Bernasconi et al., 2006)
Stat6$^{-/-}$ (M)	Normal NK cell development Normal NK cell phenotype Higher NK cell cytotoxic capacity Resistance to viral infections Higher IFN-γ production	(Katsumoto et al., 2004; Mahalingam et al., 2001; Bream et al., 2003)

dependent signaling, hence, the absence of viral infections.

4.3. STAT3: NK cells and cancer

STAT3 regulates many aspects of NK cell function, including cytotoxic capacity, cytokine-mediated effects, and interactions with other members of the immune system (Cacalano, 2016). Studies have show that tumor-infiltrating cells display constitutive STAT3 phosphorylation to include NK cells. (Kortylewski et al., 2005). In mice, the contribution of STAT3 to NK-specific antitumor response was studied in a model with an exclusive deletion of STAT3 in NK cells. This deletion does not affect NK cell development and correlates with a normal expression of developmental and functional NK cell receptors (Gotthardt et al., 2014). In addition, the deletion of STAT3 in NK cells enhances tumor surveillance with a reduction of tumor burden that was associated with increased levels of DNAM-1, perforin, and granzyme B expression. Similar findings were observed in adult mice with STAT3 deletion in hematopoietic cells using the *Mx1-Cre-loxP* system (Kortylewski et al., 2005) **(**Table 2**)**.

In cancer patients, the constitutive activation of STAT3 affects the expression of NK cell activation molecules including DNAM-1, NKp30, NKp44, NKG2D, perforin, and granzyme B resulting in a decrease in cytotoxic activity leading to an impairment in tumor immune surveillance (Cacalano, 2016; Carrega et al., 2008; Gotthardt et al., 2014; Rocca et al., 2013; Zhu et al., 2014). Alternatively, germline heterozygous *STAT3* GOF mutations were described in patients with autoimmunity and lymphoproliferation, including large granular lymphocytic (LGL) leukemia (Haapaniemi et al., 2015; Milner et al., 2015). Haapaniemi et al. showed *STAT3* GOF mutations affect the NK cell number in peripheral blood along with low cytotoxic capacity and decreased IFN-γ production, without affecting expression of perforin and granzyme B **(**Table 2**)**. This may suggest that constitutive STAT3 activation affects NK cell function by regulating the expression of important NK cell receptors.

4.4. STAT4

IL-12 stimulation activates STAT4, which then induces IFN-γ production and contributes to increased NK cell cytotoxicity alone or in combination with IL-2 (Orange and Biron, 1996; Wang et al., 2000). Upon IL-12 stimulation, STAT4 has the ability to bind two enhancers located in the 5' region of the *PRF1* gene and induces the expression of perforin (Yamamoto et al., 2002; Yu et al., 1999). Studies in mice demonstrated that NK cells from *Stat4*$^{-/-}$ KO mice exhibit reduced

cytotoxicity with lower IFN-γ production in the presence of IL-12 (Kaplan et al., 1996). Furthermore, upon viral infection type I IFNs, IL-12, and IL-15 have a harmonized regulation of the NK cell response; while IL-12 induces IFN-γ production through STAT4 activation, type I IFN stimulation induces cytotoxicity with the critical participation of STAT1. Moreover, through a STAT1-dependent mechanism, type I IFNs induce the expression of IL-15, which promotes survival and proliferation of NK cells (Nguyen et al., 2002).

4.5. STAT5, the driver of NK cell development

In mammals, there are two STAT5 homologs (STAT5a and STAT5b) and both genes are located on chromosome 17 (Crispi et al., 2004). More than 90% of the peptide sequence of these homologs is similar (Boucheron et al., 1998).

Both *Stat5a*$^{-/-}$ and *Stat5b*$^{-/-}$ mice have a low frequency of NK cells, but only the *Stat5b*$^{-/-}$ NK cells exhibit a profound decrease in their activity after IL-2 and IL-15 stimulation. Furthermore, *Stat5b*$^{-/-}$ knockout mice have significantly lower levels of perforin expression with greatly decreased cytolytic function (Imada et al., 1998). The *Stata5*$^{f/f}$ *Ncr1*- iCre transgenic mice have a restricted deletion of STAT5 in NK cells (Eckelhart et al., 2011). This mouse model is characterized by impaired NK cell development at an early NK cell stage in bone marrow, decreased NK cell viability, and impaired NK cell dependent tumor surveillance. Using a mouse model with decreasing number of *Stat5* alleles (from four to one), it was demonstrated that STAT5 promotes NK cell maturation. The deletion of *Stat5b* alleles had a dramatic impact on NK cell development in comparison to the deletion of *Stat5a* alleles. Interestingly, both mice were characterized with a significant reduction of NK cell numbers in spleen, liver, and intestine but not in the bone marrow. Further, the deletion of *Stat5b* alleles had a greater impact on the generation and accumulation of all ILC subsets than deletion of *Stat5a* alleles (Villarino et al., 2017) demonstrating that STAT5 is necessary for development and/or homeostasis of both NK cells and ILCs. STAT5 can also form tetramers and the STAT5 tetramer-deficient mice (DKI mice) have lower numbers of peripheral NK cells (Levy and Marie, 2012; Lin et al., 2012) (Table 3). These mice also exhibited abnormal T cell development and poor function in response to IL-2 (Table 2).

Human STAT5b deficiency is characterized by severe growth retardation, chronic diarrhea, eczema, chronic lung disease and chronic interstitial pneumonia as well as a combined immunodeficinecy (Bernasconi et al., 2006; Hwa et al., 2007, 2011; Nadeau et al., 2011). STAT5b-deficient patients have a dramatic reduction of circulating NK cells that translates into lower cytotoxicity (Bernasconi et al., 2006). Recently, we identified a non-functional CD56^{dim} NK cell subset in these patients (unpublished data). The non-functional CD56^{dim} NK cell subset has decreased expression of perforin and CD16 and a higher frequency of immature NK cells markers, including CD94, CD117, and IL-15Rα. Furthermore, the absence of STAT5b in the CD56^{bright} NK cell subset leads to impaired cytokine production. This phenotype was accompanied by decreased expression of co-stimulatory and activating receptors, including CD11a, CD18, DNAM-1, and NKp46, affecting the lytic granule convergence to the MTOC (unpublished data) (Table 2). STAT5 is an important transcripton factor in NK cell development both in humans and mice along with influencing early activation events in NK cell lytic synapse formation.

4.6. STAT6

STAT6 is a common downstream effector of IL-4 (H. C. Chen and Reich, 2010). In mice, the absence of STAT6 in NK cells affects IL-15 and IL-13 production, but does not affect their development and surface marker expression (Katsumoto et al., 2004). *Stat6*$^{-/-}$ mice also exhibit increased resistance to ectromelia virus (EV) by a hightened cytolytic capacity (Mahalingam et al., 2001). Interestingly, the absence of STAT6 enhanced IFN-γ production in NK cells after costimulation with IL-4 and IL-2 (Bream et al., 2003). These findings allow speculation that blocking STAT6 can augment NK cell activity.

5. JAK proteins in NK cells

In mammals, four JAK proteins (TYK2, JAK1, JAK2, and JAK3) compose the JAK family (Vainchenker et al., 2008). The Janus kinase (JAK) family is a group of non-receptor tyrosine kinases that are important for immune cells and hematopoietic cell biology (Ghoreschi et al., 2009). JAK signaling is regulated by a negative feedback loop mediated by suppressor of cytokine signaling proteins (SOCS) and cytokine inducible SH-2 domain containing (CIS) proteins (Ghoreschi et al., 2009; Hookham et al., 2007).

5.1. TYK2

The type I interferons (IFNs) transduce signals through TYK2 and

Table 3
NK cell phenotypes that are caused by JAK proteins. PV, polycythemia vera; ET, essential thrombocythemia; PMF, primitive myelofibrosis; SCID, severe combined immunodeficiency; GOF, gain of function; H, human deficiency; M knockout mice; M', Jak1Spade/Spade mice (constitutively active JAK1-R878H); M", Jak2f/f Mx1-Cre conditional knockout mice.

Genotype	Biological effects in NK cells	References
Tyk2$^{-/-}$ (M)	Decreased NK cell function Impaired IL-12 signaling	(Shimoda et al., 2002; Stoiber et al., 2004; Prchal-Murphy et al., 2015)
TYK2 (H)	Decreased NK cell function Impaired IL-12 signaling	(Kreins et al., 2015; Minegishi et al., 2015)
Jak1$^{-/-}$ (M)	Perinatal lethal	(Roding et al., 1998)
Jak1 (M')	Dermatitis, NK cell function (?)	(Yasuda et al., 2016)
JAK1 GOF (H)	NK cell function (?) Susceptibility to viral infections	(Del Bel et al., 2017)
Jak2$^{-/-}$ (M)	Embryonic lethal Severe erythropoiesis	(Neubauer et al., 1998; Krempler et al., 2004)
Jak2$^{-/-}$ (M")	Severe erythropoiesis Abnormal NK cell maturation Low DNAM-1 expression	(Park et al., 2013; Bottos et al., 2016)
JAK2 GOF (H)	Associated with PV, ET, and PMF	(Vainchenker et al., 2008; Hookham et al., 2007)
Jak3$^{-/-}$ (M)	Impaired NK cell development	(Park et al., 1995)
JAK3 (H)	Impaired NK cell development (X-linked SCID phenotype)	(Brugnoni et al., 1998; Notarangelo et al., 2001)

JAK1-mediated STAT1 and STAT2 activation, while IFN-γ signaling requires JAK1/JAK2 with STAT1 activation exclusively (Majoros et al., 2017). On the other hand, IL-12 stimulation induces the activation of TYK2 and JAK2 with downstream activation of STAT4 (Bacon et al., 1995a, b). *Tyk2*$^{-/-}$ mice have been characterized with impaired IL-12/IL-18 signaling that affects STAT4 activation leading to impaired IFN-γ production in NK cells (Shimoda et al., 2002). The absence of TYK2 does not affect the frequency of NK cells in peripheral blood (Shimoda et al., 2002) **(**Table 3**)**. However, these *Tyk2*$^{-/-}$ NK cells show impaired cytotoxic capacity with decreased efficiency to clear infections (Schleicher et al., 2004) along with inefficient tumor surveillance (Prchal-Murphy et al., 2015; Stoiber et al., 2004).

The susceptibility to viral and opportunistic infections described in mice is recapitulated in patients. Human TYK2 deficiency is characterized by susceptibility to viral and intracellular infections (Kilic et al., 2012; Kreins et al., 2015; Minegishi et al., 2006). The human *Tyk2*-deficient NK cells have an impaired but not abolished IL-12 response **(**Table 3**)**. Impaired IFN-γ production after IL-12 stimulation predisposes these patients to the viral and intracellular infections observed (Kreins et al., 2015). Moreover, the absence of TYK2 affects the signaling of many cytokines and interferes with activation of multiple STAT proteins (Kreins et al., 2015; Minegishi et al., 2006).

5.2. JAK1 and JAK2

While JAK3 is restricted to hematopoietic tissues, JAK1 and JAK2 have a more ubiquitous expression; this could explain why there is a more severe phenotype of perinatal and embryonic lethality in *Jak1*$^{-/-}$ and *Jak2*$^{-/-}$ knockout mice, respectively (Neubauer et al., 1998; Rodig et al., 1998). *Jak1*$^{-/-}$ mice are characterized by a profound defect in their lymphopoiesis (Rodig et al., 1998). Alternatively, mice that harbor a constitutively active JAK1 mutation (R878H mutation) develop pruritic dermatitis which leads to skin barrier malfunction (Yasuda et al., 2016). The dermatitis described in these mice resembles that observed in the human germline *JAK1*-A634D gain-of-function mutation. These patients developed severe atopic dermatitis, hypereosinophilia, hepatosplenomegaly, and autoimmunity (Del Bel et al., 2017). NK cell functional analysis has yet to be reported in these patients, but they did develop recurrent viral infections which could suggest abnormal NK cell function **(**Table 3**)**. The *Jak2*$^{f/f}$ *Mx1-Cre* conditional knockout mice also exhibit a severe erythropoiesis similar to the *Jak2*$^{-/-}$ conventional knockout mice (Krempler et al., 2004; S. O. Park et al., 2013). The *Jak2*$^{f/f}$ *Mx1-Cre* conditional knockout mice have abnormal NK cell maturation, reduced splenic NK cell numbers and reduced expression of DNAM-1 (Bottos et al., 2016) **(**Table 3**)**.

In humans, the activating *JAK2*-V617 F mutation is associated with polycythemia vera (PV), with essential thrombocythemia (ET), and primitive myelofibrosis (PMF) (Vainchenker et al., 2008) **(**Table 3**)**. JAK2-V617 F is spontaneously active with a capacity to escape negative regulation by SOC3, an important regulator of JAK/STAT function (Hookham et al., 2007). Ruxolitinib is a specific inhibitor of JAK1 and JAK2 and approved for the treatment of PV and myelofibrosis (Harrison et al., 2012b). The JAK 1/2 inhibition leads to control of symptoms and reduction of spleen size in patients with myelofibrosis (Harrison et al., 2012a; Verstovsek et al., 2012). However, in patients with myeloproliferative neoplasms (MPN), ruxolitinib treatment impairs NK cell maturation, generating an accumulation of immature NK cells causing an increased susceptibility to viral infections (Schonberg et al., 2015). Additionally, it is thought that ruxolitinib affects NK cell cytotoxicity in this particular subset of patients because the ruxolitinib treated NK cells have decreased expression of CD16, granzyme B, and activation receptors seen on mature NK cells (Schonberg et al., 2015).

5.3. JAK3

JAK3 is a JAK family member that is involved in NK cell development, proliferation, and function (Ghoreschi et al., 2009). In contrast with other JAK members, JAK3 expression is restricted to hematopoietic tissues (Thomis and Berg, 1997). In addition to its restricted expression, JAK3 only binds the common gamma chain (γ_c) receptor, the common signaling subunit of the IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 receptors (Matthews et al., 1995). Since the commitment to the NK cell lineage is promoted by IL-15, the absence of NK cells in peripheral blood from *Jak3*$^{-/-}$ knockout mice and in human JAK3 deficiency results from an inability to signal throught the IL-15 receptor (Notarangelo et al., 2001; Park et al., 1995) **(**Table 3**)**. The immune abnormalities observed in *Jak3*$^{-/-}$ mice are recapitulated in patients with JAK3 deficiency (X-linked SCID phenotype) **(**Table 3**)** and include severe recurrent infections in early life, lack of T and NK cells, and functionally deficient B cells in peripheral blood, (Brugnoni et al., 1998; Notarangelo et al., 2001) Interestingly, a similar NK cell phenotype was observed in mice deficient of IL-15 or its downstream effector STAT5a/b (Eckelhart et al., 2011; Imada et al., 1998; Park et al., 1995).

6. Conclusion

In this review, we focused on the JAK/STAT signaling defects that affect NK cell biology. This signaling pathway is highly conserved and integral to NK cell development in humans and mice. That being said, there are distinct differences in NK cell development between the species. Therefore, recognizing the different roles for each part of this signaling pathway in NK cell development is paramount to understanding the impact of genetic alterations on NK cell biology. Further deliniatiton of the biological functions of JAK/STAT proteins in NK cells will enhance the development of new therapeutic approaches for human disease.

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Conflict of interest

The authors declare no conflict of interest

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