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Inborn errors of the development of human Natural Killer cells

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Abstract

Purpose of review—Inborn errors of human natural killer (NK) cells may affect the development of these cells, their function, or both. There are two broad categories of genetic defects of NK-cell development, depending on whether the deficiency is apparently specific to NK cells or clearly affects multiple hematopoietic lineages. We review here recent progress in the genetic dissection of NK deficiencies (NKDs).

Recent findings—Patients with severe combined immunodeficiencies (SCID) bearing mutations of *ADA*, *AK2*, *IL2RG* and *JAK3* genes present NKDs and are prone to a broad range of infections. Patients with GATA2 deficiency are susceptible to both mycobacterial and viral infections and display NKD and a lack of monocytes. Patients with MCM4 deficiency display an apparently selective NKD associated with viral infections, but they also display various non hematopoietic phenotypes, including adrenal insufficiency and growth retardation.

Summary—These studies have initiated genetic dissection of the development of human NK cells. Further studies are warranted, including the search for genetic etiologies of NKD in

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Conflicts of interest

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particular. This research may lead to the discovery of molecules specifically controlling the development of NK cells and to improvements in our understanding of the hitherto elusive function of these cells in humans.

Keywords

Natural Killer cells; Immunodeficiencies; Genetic diseases

Introduction

Natural Killer (NK) cells are innate lymphoid cells (ILCs) constituting the third most abundant lymphocyte population in the peripheral blood [1]. They are thought to play an important role in the course of pregnancy, antiviral immunity and antitumoral immunity. Unlike B and T lymphocytes, they do not express somatically rearranged antigen receptors. Instead, they bear a diverse repertoire of receptors with activating or inhibitory properties [2–4]. Imbalances between these signals trigger NK cell activation, resulting in NK cell cytotoxicity and/or the production of cytokines [5, 6]. NK cells have been extensively characterized over almost four decades, but the genetic control of human NK cell development and the function of these cells in host defense remain to be elucidated.

Major advances have been made in the dissection of NK cell development and maturation in mice (7•]. The developmental sequence from NK cell precursors to mature NK cells has been divided into seven stages, each corresponding to the expression of a different pattern of surface markers and requiring different transcription factors [8•, 9]. NK cell development begins in the bone marrow and is completed in secondary lymphoid tissues (SLT). Indeed, NK cell progenitors may leave the bone marrow at a very early stage to seed SLT within which they differentiate [10]. Some of the maturation steps require interaction with other cells, such as neutrophils and monocytes in particular [11, 12••]. The requirement of NK cells for antiviral immunity is well established in mice [13–15]. It has been recently reported that mouse NK cells also display features of adaptive immunity, particularly during viral infections [16–18]. Through their cytokine production and cytotoxic functions, NK cells can act at various steps of the immune response exerting their effects on antigen loads, dendritic cells and T cells [19•–21].

In humans, a model of NK cell differentiation has been proposed based on the expression of various markers, such as CD34, CD56, CD57, CD62L, CD94, CD117 and KIRs [22–25]. However, the development and function of these cells remain elusive, due to the rarity of pure NK cell deficiencies (NKDs) [26–28]. Inherited NKDs, in which NK cells counts are below 100 cells/mm^3, are generally associated with a lack of other lymphoid subsets, as in patients with severe combined immunodeficiency (SCID), which is defined as a lack of autologous T-cells. There are also combined NKDs associated with normal T-cell counts but low levels of myeloid cells, as in patients with the MonoMac syndrome [29, 30]. Finally, selective NKDs have been reported in individuals with no other hematopoietic phenotype and, in at least one case, the genetic basis of the deficit has been determined [31–35]. We will review here the known forms of inherited NKDs (selective or combined). We will not review the inborn errors of NK cell function in which NK cells are present, such as familial

hemophagocytic lymphohistiocytosis (e.g. perforin deficiency), which have been reviewed elsewhere [27].

Deficits of early hematopoiesis: AK2 and ADA deficiency

Patients with adenylate kinase 2 (AK2) deficiency (also known as reticular dysgenesis), or with adenosine deaminase (ADA) deficiency display severe immunodeficiency, with T^- B^- NK^- SCID associated with an absence of granulocytes in AK2-deficient patients and hypogranular neutrophils in ADA-deficient patients [36]. Both morbid genes are involved in metabolism: AK2 plays a key role in the adenosine diphosphate (ADP) generation and ADA is a key enzyme of the pathway for adenosine and deoxyadenosine deamination [37, 38]. The pathogenesis of the SCID phenotype in patients with AK2 and ADA deficiencies remains unclear. Moreover, NK cell lymphopenia has not been investigated in patients or the corresponding knockout mice. AK2-deficient patients have no cells developing beyond the myelocyte stage and scattered maturing lymphocytes in bone marrow (BM) and a dysplastic thymus [39, 40]. They display spontaneously high fibroblast apoptosis rates, probably due to impaired ADP flux in the mitochondrial matrix [41]. These findings suggest that NK cell differentiation in BM is sensitive to the mitochondrial control of energy balance, apoptosis, or both. In ADA-deficient patients, the accumulation of purine metabolites is toxic to thymocytes and splenic B cells leading to their apoptosis [42–44]. The BM has a normal number of NK cell progenitors, suggesting that the lack of NK cells results from high rates of apoptosis during the maturation in SLT [45, 46]. All patients display a broad spectrum of life-threatening infections, including viral, bacterial and fungal infections, with other clinical signs, probably due to the metabolic dysregulation (Table 1). The broad nature of the lymphoid and myeloid defect in these patients and their non hematopoietic phenotypes make it impossible to determine whether and which infections result from the lack of NK cells.

Deficits of early T and NK cell development: IL-2Rγ and JAK3 deficiency

Janus kinase 3 (JAK3) is the signaling adaptor associated with the common γ chain (γc), a component of the multichain receptors for IL-2, -4, -7, -9, -15 and -21 [65]. Patients with JAK3 or IL-2Rγc deficiency generally have no T and NK cells, but normal or particularly large numbers of nonfunctional B cells (T^- B^+ NK^- SCID phenotype) [47, 50, 66]. Six cytokines are known to use the common γ chain. Two of these cytokines, IL-2 and IL-7 are essential for T-cell development and function, as patients with IL-2Rα (CD25) have a T cell immunodeficiency associated with autoimmunity and those with IL-7Rα deficiency have T^- B^+ NK^+ SCID [67, 68]. By contrast, patients with IL-21R deficiency have normal numbers of T, B and NK lymphocytes, but display impaired T-cell proliferation, memory B-cell generation and NK cell antibody-dependent cellular cytotoxicity [69]. For the remaining cytokines (IL-4, -9 and -15), a defective IL-15 response is the most plausible mechanism underlying impaired NK cell development in IL2Rγ- and JAK3-deficient patients. Indeed, IL-15, alone or with stem cell factor, drives the generation of $CD56^+$ NK cells from BM $CD34^+$ progenitors *in vitro* [70, 71]. Moreover, some patients with specific *IL2RG* mutations not affecting IL-15 signaling have functional NK cells [72, 73]. Overall, the NKD probably results from IL-15 signaling failure, leading to a blockade of BM and/or SLT development. Clinically, all patients present a broad spectrum of life-threatening infections, including

viral, bacterial and fungal infections (Table 1)[48, 49]. It is difficult to determine whether and which infections result from the NKD, even by comparing these patients with patients with NK^+ SCID, in part because they have a BM transplantation very early in their life.

Impaired IL-2, IL-15 signaling: STAT5b

Signal transducer and activator of transcription (STAT)-5 is involved in the growth hormone (GH), IL-2 and IL-15 receptor signaling cascades. Following cytokine stimulation, STAT5 is phosphorylated by JAK3, inducing target gene transcription [74]. Patients with STAT5b deficiency present T and NK cell lymphopenia [51–55]. Unfortunately, their circulating and BM NK cells have not yet been thoroughly characterized. NK cell cytotoxicity is weak in basal conditions in these patients, partly due to the small number of cells, but IL-2 stimulation increases cytotoxicity and results in a normal perforin induction, suggesting that the IL-2-dependent STAT5b activation is not essential for mature NK cell activity [52, 53]. An *in vitro* study in the YT human NK cell line showed that the molecular disruption of both STAT5a and STAT5b leads to higher levels of cell death and DNA degradation, but normal progression through the cell cycle [75]. These results suggest that the NK cell lymphopenia in STAT5b deficiency results from impaired IL-15-dependent survival signaling or the inhibition of apoptotic signaling. The clinical phenotype of STAT5b-deficient patients is summarized in Table 1. They present a GH insensitivity syndrome, with facial dysmorphia and a particular susceptibility to respiratory tract infections. They also develop eczema and viral infections. The contribution of the NKD to these infectious and immunological phenotypes is unclear.

Deficits of myeloid, B-, and NK-cell development: GATA2 deficiency

Autosomal dominant GATA2 deficiency was first described in 2011 [56, 57]. It causes the monocytopenia and mycobacterial infections (MonoMAC) syndrome [29, 30], which typically combines deficiencies of dendritic cells, monocytes, B and NK lymphocytes [29, 30,56–60]. A *GATA2* mutation was identified in the first case report for a patient with an apparently selective NKD [61], who has since developed many other cytopenias [62••]. In humans, NK cells can be identified by the surface expression of CD56 or neural cell adhesion molecule (N-CAM). In the linear differentiation model for human NK cells, $CD56^{bright}$ and $CD56^{dim}$ NK cells correspond to sequential steps in NK cell differentiation. $CD56^{bright}$ NK cells are immature and only weakly cytolytic but have a high cytokine production capacity, whereas $CD56^{dim}$ NK cells exert both effector functions [24, 76]. The NK cell phenotype in GATA2-deficient patients is characterized by the lack of the $CD56^{bright}$ population and a strong decrease in the size of the $CD56^{dim}$ [62••], suggesting a survival defect of the $CD56^{bright}$ population. Moreover, despite the normal expression of maturation markers, the $CD56^{dim}$ population is also functionally impaired [62••]. Analyses of BM from patients frequently show hypocellularity, myeloid dysplasia, and an absence of multilymphoid progenitors and $CD38^+$-$CD10^+$ B/NK cell precursor [29,59]. The NKD in patients with GATA2 deficiency probably results from a series of failures in (i) the maintenance of primitive NK progenitors, (ii) the survival and homeostasis of $CD56^{bright}$ cells in SLT and blood and/or (iii) the maintenance of circulating $CD56^{dim}$ cells. Further studies are required to determine whether GATA2 is involved in IL-15-dependent survival

signaling for NK cell development. Clinically, these patients present viral infections, leukemia and cytogenetic abnormalities (Table 1). The contribution of the NKD to these manifestations is unclear.

Isolated NK deficiency: MCM4 deficiency

Mini chromosomal maintenance (MCM)-4 is a member of the highly conserved hexameric MCM complex involved in DNA replication [77]. Patients with autosomal recessive MCM4 deficiency have normal numbers of T and B cells but very few circulating NK cells [31, 63••, 64]. The biochemical defect is partial as the homozygous mutation is hypomorphic. In these patients, the NK $CD56^{bright}$ population is present at normal levels but NK $CD56^{dim}$ cells are almost completely absent. The NK $CD56^{bright}$ subset displays a strong proliferation defect following IL-2 or IL-15 stimulation and an excess of spontaneous apoptosis [63••]. By contrast, the few NK $CD56^{dim}$ cells proliferate normally upon stimulation with IL-2 and IL-15, but present excess spontaneous apoptosis, that is not prevented by IL-2 or IL-15 activation [63••]. These findings confirm that the NK $CD56^{dim}$ subset originates from the NK $CD56^{bright}$ population and indicate that this last step of differentiation requires the hyperproliferation of NK $CD56^{bright}$ cells. Partial MCM4 deficiency affects DNA replication, by disrupting control of the prevention of re-replication, and leads to genomic instability, characterized by an accumulation of chromosomal aberrations, potentially accounting for the loss of the $CD56^{dim}$ NK cell subset. Clinically, patients present growth retardation, adrenal insufficiency due to abnormal adrenal morphology [64] and susceptibility to viral infections, probably resulting at least partly from the NKD, although better documentation is required to confirm this (Table 1). It is interesting that partial MCM4 deficiency results in such a specific hematopoietic (NK $CD56^{dim}$ cell deficiency) and endocrine (adrenal insufficiency) phenotype, reflecting different requirements for MCM4 in different tissues.

Other isolated NK deficiencies

Finally, several case reports for patients with unexplained NKD have been published. One such patient was an Israeli consanguineous patient who developed a severe varicella [33]. She presented an isolated NKD with normal numbers of T and B cells and normal T-cell proliferation. Functional studies showed a normal IL-15 response in T cells, implying that the genetic defect affects an IL-15-independent pathway in NK homeostasis [33]. A similar clinical case, with severe varicella and a total absence of NK cells, was reported in a non consanguineous family [34]. Another report concerned a French, multiplex, non-consanguineous family in which one patient died from severe cytomegalovirus infection [78]. Like STAT5b- and MCM4-deficient patients, the two patients from this family had an intra- and extrauterine growth retardation, without autoimmunity or adrenal insufficiency [78]. They also had neutropenia, but to a lesser extent than GATA2-deficient patients. Studies of the patients' T cells *in vitro* showed impaired IL-2- and IL-15-dependent survival [32], but no genetic etiology has yet been identified. Another recently reported case of NKD concerned a patient with normal number of T and B lymphocytes and normal T-cell proliferation [35]. This patient has. bilateral adrenal EBV-associated smooth muscle tumors, as described in GATA2-deficient patients. Both $CD56^{bright}$ and the $CD56^{dim}$ NK cells are

detectable, but with particularly high levels of CD117 (human homolog of c-kit) expression [35], suggesting incomplete development, as the $CD56^{bright}$ and the $CD56^{dim}$ NK cells are $CD117^{+}$ and $CD117^{-}$, respectively [79]. However, some cases have been identified during the first infectious episode. They have to be considered carefully as some herpes viruses may lead to a decrease of NK cell count [80].

Conclusion

NK cells were first described, 40 years ago, as cytotoxic lymphocytes of the innate immune system [81–83]. Their function has recently been re-evaluated, as they also display adaptive behaviors [18]. The development of NK cells and the function of these cells, in antiviral immunity in particular, have been studied in detail [8, 19•]. However, we still know little about the development and function of NK cells in humans, due partly to the rarity of inherited forms of NKDs. Recent discoveries in this field have confirmed previous findings but have also provided new insights. First, the IL-15/JAK3-and GATA2-dependent signaling pathways are essential for NK cell development, through mechanisms that are only partially understood. Second, the final step in NK maturation involves a hyperproliferation of the $CD56^{bright}$ NK cells that is highly dependent on MCM4. However, further investigations are required in patients with NKD: (i) in-depth phenotyping, including evaluations of the expression of different markers, such as CD34, CD117 and CD94, in the $CD56^{bright}$ population in blood and SLT [24], (ii) studies of proliferation and apoptosis in response to IL-15 activation, (iii) *in vitro* differentiation assays of $CD34^{+}$ precursors, from patients or from controls transfected with siRNA, upon activations with various molecules, including IL-15. These investigations should shed light on the precise mechanism underlying human NK cell development. Needless to say, the search for new genetic etiologies of NKD is also important. Identification of the genetic defects underlying NKD will provide new insight into the development and function of NK cells in humans. Clinically, the only phenotype common to all patients with NKD, whether isolated or combined, is predisposition to viral infections, especially herpes virus infections (Table 1), contributing to the concept of primary immunodeficiencies associated with a restrictive susceptibility to infection [84–87]. GATA2-deficient patients display susceptibility to papillomaviruses, but it is unclear to what extent this is due to the NKD. Some patients with MCM4 and GATA2 deficiencies have also developed cancers suggesting a possible role of NK cells in antitumoral immunity. However, these patients also present genomic instability, which may be responsible for these cancers. Long-term clinical and immunological monitoring is required to evaluate the patient outcome, changes in the immune system and correlations between the NKD and clinical signs.

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Key points

This article provides an overview of the genetic etiologies of isolated or combined NK deficiency in humans.

Recent studies have revealed an unexpected role for GATA2 and MCM4 in human NK cell development.

The genetic dissection of various forms of inherited NK cell deficiency should make it possible to decipher the factors controlling human NK cell development.

These genetic studies should also help to define the hitherto elusive function of human NK cells in host defense.

Table 1

Combined and isolated quantitative NK cells deficiencies

Mode of transmission Disease	**Mutated Gene**	**NK cell number/phenotype**	**Other immunological abnormalities**	**Other clinical phenotypes**	**Infectious susceptibility**	**Cancer phenotype**	**References**
Autosomal recessive Metabolic T-B-SCID	ADA	Markedly decreased	No T and B cells Hypogranular neutrophils	Autoimmunity Hepatic and renal diseases Neurological abnormalities Skeletal alterations	Multiple life-threatening infections		36
Autosomale recessive Reticular dysgenesis	AK2	Absent	No leukocytes	Deafness	Multiple life-threatening infections		39–41
X-linked T-B+ SCID	IL2RG	Markedly decreased	No T cells		Multiple life-threatening infections		47, 48, 49
Autosomal recessive T-B+ SCID	JAK3	Markedly decreased	No T cells		Multiple life-threatening infections		48, 49, 50
Autosomal recessive Growth hormone insensitivity syndrome	STAT5b	Decreased	Low T cell numbers T_{reg} dysfunction Hyper-gammaglobulinemia	Growth retardation Autoimmunity Allergy	Chronic pulmonary diseases Herpes infections Eczema		51–55
Autosomal dominant Mono-Mac syndrome	GATA-2	Markedly decreased No $CD56^{bright}$ Fewer $CD56^{dim}$	Few or no monocytes, dendritic cells, B lymphocytes	Autoimmunity Primary lymphedema Pulmonary proteinosis	Papillomavirus infections Herpes infections Non-tuberculous mycobacteria Fungal infections	Myelodysplastic syndrome Leukemia EBV-associated smooth muscle tumors	29, 30, 56–62
Autosomal recessive	MCM4	Markedly decreased Normal $CD56^{bright}$ Fewer $CD56^{dim}$		Growth retardation Adrenal insufficiency	Herpes infections	EBV lymphoma	31, 63, 64