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Advances in IL-21 biology — enhancing our understanding of human disease

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Cytokines play critical roles in regulating the development and function of immune cells. Cytokines function by binding specific multimeric receptor complexes and activating intracellular signaling pathways that often involve JAKs and STATs. In addition to contributing to immunity, when production of cytokines is perturbed, they can contribute to disease. IL-21 is a pleiotropic cytokine produced predominantly by $CD4^+$ T cells and NKT cells. Gene-targeting studies in mice and *in vitro* analyses of human and murine lymphocytes have revealed central roles of IL-21 in regulating effector functions of T cells, NK cells and B cells. However, recent discoveries of loss-of function mutations in *IL21* or *IL21R* in humans have unveiled unexpected roles for IL-21 in immune regulation. This review will focus on recent advances in IL-21 biology that have highlighted its critical role in normal immunity and how dysregulated IL-21 production can lead to immunodeficiency and autoimmune conditions.

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Introduction

The development and function of immune cells is governed by signals delivered through surface receptors via cell-contact and soluble ligands. The latter is mediated largely by cytokines coupled to specific signaling pathways, which predominantly involve JAKs and STATs [1]. To date, more than 60 cytokines (interleukins, interferons, CSFs, TGFs, TNFs) have been identified and each play important roles in immunology. The importance of cytokines for immune cell development and function is clearly illustrated by X-linked severe combined immunodeficiency (X-SCID), caused by mutations in *IL2RG* encoding the common gamma chain (γc), a component of receptors for IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 [1,2]. X-SCID is characterized by extreme susceptibility to infection with many pathogens due to the near-absence of T and NK cells resulting from a requirement for IL-7 and IL-15, respectively, for their development. Indeed, an autosomal recessive form of SCID due to mutations in *IL7R* results in a severe lack of T cells and similar infectious susceptibility [1,2]. Although B cells develop in X-SCID, they are non-functional due to an inability to respond to the B-cell promoting cytokines IL-2 and IL-21 [3,4]. The discovery that mutations in *JAK3*, which is activated by and associates with γc, phenocopies the clinical presentation and cellular defects of X-SCID [1,2] further revealed the essential role of cytokines and associated signaling pathways in regulating immune cell biology.

While many cytokines have been identified and characterized over the past 50 years, IL-21 stands out as having broad effects that potently influence multiple aspects of immune cell function. IL-21 and its receptor (IL-21R) were identified in 2000 [5,6]. IL-21 is predominantly produced by activated $CD4^+$ T cells, while IL-21R is expressed on human B cells, NK cells, activated T cells and some non-hematopoietic cells [5,6]. Consistent with this, initial functions of IL-21 were inducing proliferation of B and T cells, and generating highly lytic NK cells [6].

These initial reports not only provided important insights into the biology of IL-21 and IL-21R, but formed the groundwork for many studies over the subsequent 15 years. Indeed, such studies demonstrated γc was a component of the IL-21R complex [7,8], and that signaling via IL21R/γc activated JAK1, JAK3, STAT1, STAT3 and STAT5 [7,8], thus implicating impaired IL-21 signaling in the pathogenesis of X-SCID and JAK3-SCID (Table 1). Detailed molecular and cellular analyses, and construction of gene-reporter mice, revealed factors and signaling pathways required for inducing IL-21 expression *in vitro* (i.e. IL-6, IL-21 itself, IL-12; STAT3) [9–16], identified the predominant sources of IL-21 to be T follicular helper (Tfh) cells [17–19], Th17 cells [9–12] and NKT cells [20], and further defined the functions of IL-21 on human and murine lymphocytes. Furthermore, analysis of transgenic, gene-targeted and autoimmune-prone mice demonstrated important functions for IL-21 in normal cellular and humoral immunity, as well as in the pathogenesis of autoimmune diseases, leading to the investigation of the clinical utility of IL-21 blockade in treating various immune dyscrasias [21••]. As several

Table 1

Immunological diseases resulting from mutations affecting the IL-21/IL-21R signaling pathway

Gene mutation	Clinical features	Contribution of IL-21/IL-21R; mechanism of defect	Reference
IL2RG, *JAK3* (LOF)	• X-linked/autosomal recessive $B^+T^-NK^-$SCID • Extreme susceptibility to infection with many pathogens	• Inability of B cells to respond to IL-21 underlies poor humoral immunity	[1,4,60]
STAT3 (LOF)	• Autosomal dominant hyper-IgE syndrome • Susceptibility to infections with *S. aereus*, *S. pneumonia*, *C. albicans* • Impaired humoral immunity and memory • Vascular, musculoskeletal, dental and connective tissue defects • B-cell lymphoma	• Inability of B cells to activate STAT3 in response to IL-21 underlies poor humoral immunity • Possible contribution to generation of Tfh and Th17 cells	[15,57,58••]
IL21, *IL21R* (LOF)	• Recurrent infections of the respiratory and gastrointestinal tracts • Opportunistic infections (Pneumocystis, cryptosporidia) • Inflammatory bowel disease	• Inability of B cells to respond to IL-21 underlies poor humoral immunity • $CD4^+$ T cell derived IL-21-mediated activation of APC for protection against infection with pneumocystis, cryptosporidia • Impaired IL-21-mediated induction of IL-10, and lack of inhibition of IFNγ, may contribute to IBD	[88,89••,90••,92••]
STAT3 (GOF)	• Multisystemic autoimmunity (type 1 diabetes, enteropathy, thyroiditis, cytopenia, arthritis) • Lymphadenopathy, hepatosplenomegaly	• Possible production of auto Abs • Exacerbated repression of Treg generation	[85,86••,87]
IL21, *IL21R* SNPs	• SLE	• autoAb production	[83,84]

LOF, loss of function; GOF, gain of function; SNP, single nucleotide polymorphisms.

reviews on IL-21 have recently been published [19,21••,22], this review will briefly summarise the functions of IL-21 but focus on recent advances in IL-21 biology to emphasise its critical role in normal immunity, revealed by the discovery of genetic lesions affecting IL-21 signaling, and the contribution of dysregulated IL-21 production to the development of autoimmunity.

Functions of IL-21

$CD4^+$ T cells

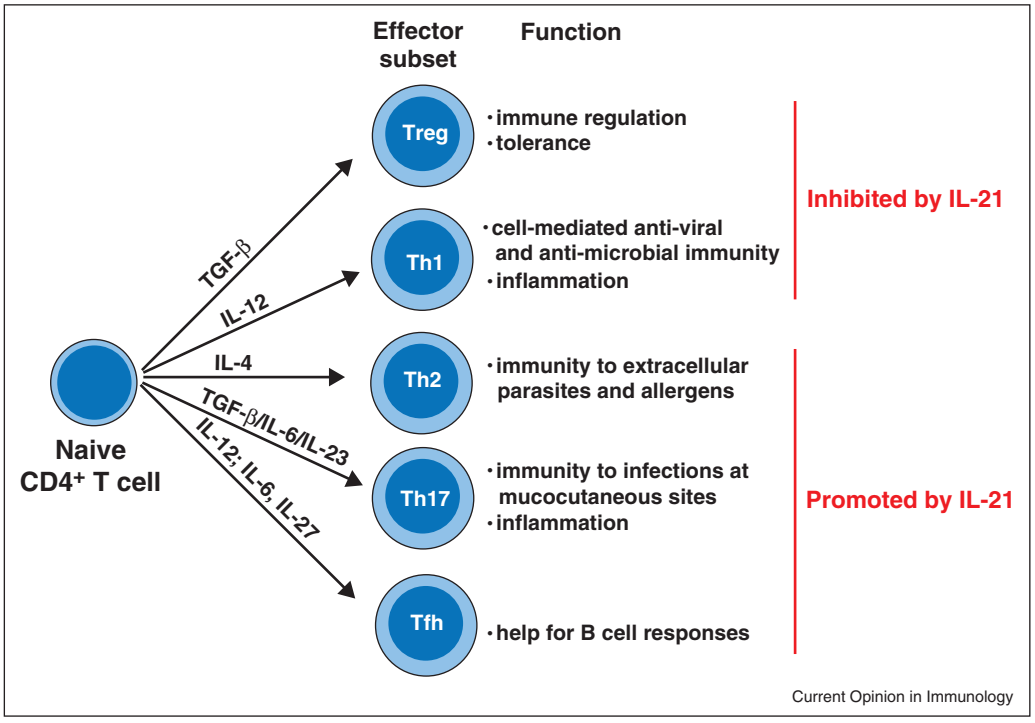
IL-21 can contribute to the generation of murine Th2 [23–25], Th17 [9–12] and Tfh [14,26] cells, while impeding development of Th1 [23,25,27•] and Treg cells [28,29,30••] (Figure 1). IL-21 is not absolutely necessary for Tfh and Th17 cell development, but rather it co-operates with other cytokines such as IL-6 and/or IL-12 (Tfh cells) [15,16,31] or IL-6, IL-23 and TGF-β (Th17 cells) [9–12,27•]. Tfh and Th17 cells can be generated *in vivo* in the absence of IL-21/IL-21R, demonstrating IL-21-independent pathways for their development [18,32,33]. Whether IL-21 functions to regulate Th9 and Th22 subsets of effector $CD4^+$ T cells remains to be determined. Thus, IL-21 appears to play a complementary, rather than obligatory, role in regulating $CD4^+$ T cell differentiation and fate.

$CD8^+$ T cells, NK and NKT cells

IL-21 synergizes with other γc cytokines — IL-15, IL-7 — to induce proliferation and expression of effector molecules (IFNγ, granzyme, perforin) in $CD8^+$ T cells *in vitro* [34,35]. *In vivo* treatment of mice with IL-15 plus IL-21 improved tumor regression compared to either cytokine alone, a response requiring tumor-specific $CD8^+$ T cells [34]. Similarly, expression of IL-21 by tumor cells resulted in their prompt rejection by immunocompetent hosts, an effect dependent on $CD8^+$ T cells and perforin [36]. IL-21 is also required for the establishment of $CD8^+$ T cell memory and long-term protection against some viral infections [37–41].

IL-21 has comparable effects on NK and NKT cells, promoting increases in cell size and granularity and modulating phenotype. IL-21 potently induced production of cytokines (IFNγ, IL-10) and perforin by, and terminal differentiation of, IL-2-stimulated or IL-15-stimulated NK cells, resulting in enhanced cytotoxicity *in vitro* [35,42]. Consistent with this, *in vivo* administration of IL-21 enhanced NK cell-mediated tumor clearance in mice [36,43,44]. Interestingly, IL-21 limits expansion and viability of NK cells, suggesting it induces rapid but short-lived NK cell activation to minimize adverse cytotoxic effects occurring under these conditions [35,42]. IL-21 treatment enhanced murine NKT cell activation, inducing production of granzyme B, IL-4 and IL-13 [45]. Similar observations were observed in humans, with increased proportions of NKT cells expressing IL-4 at the expense of IFNγ following *in vivo* IL-21 administration [20].

Figure 1



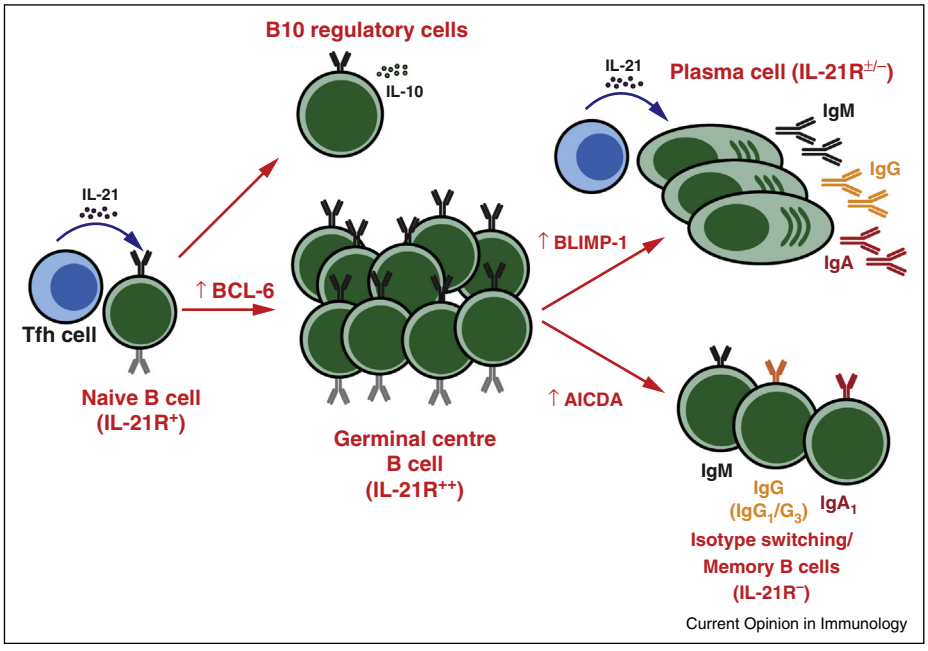
Effects of IL-21 on CD4$^+$ T cell differentiation. Naïve CD4$^+$ T cells can differentiate into numerous subsets of effector cells with distinct roles in protection against pathogen infection. CD4$^+$ T cell differentiation is regulated by cytokines provided within the stimulatory microenvironment; this can be inhibited or enhanced by IL-21. Note that several reports have indicated that Tfh and Th17 cells can be generated in the absence of IL-21.

Because of these effects on cytotoxic lymphocytes, IL-21 has been assessed clinically as a potential treatment for different malignancies. *In vivo* delivery of IL-21 increased perforin and granzyme B in NK and CD8$^+$ T cells [46–48], and NK cell cytotoxicity ex vivo [48]. Importantly, complete and partial remissions were observed in some patients [46,47]. Thus, IL-21 may have therapeutic application as an anti-cancer treatment.

B cells

The finding that IL-21 is predominantly produced by Tfh cells, and B cells express high levels of IL-21R, predicted IL-21 would have B-cell stimulatory properties. Indeed, this has been demonstrated *in vitro* and *in vivo* for both mouse and human B cells. IL-21 induced human naïve B cells to class switch to IgG3, IgG1 and IgA [49–51], and also induced these cells to become plasmablasts secreting large amounts of all Ig isotypes [50,52] (Figure 2). These latter effects were also evident when human germinal center (GC) or memory B cells were examined [50,52], consistent with upregulation of IL-21R on GC B cells *in vivo*, and on activated memory B cells *in vitro* [53] (Figure 2). The ability of IL-21 to guide class switching and plasma cell differentiation results from induction of AID and Blimp-1 [50,52,54] (Figure 2), which are required for these molecularly and functionally distinct processes. IL-21 also enhances CD86 expression on murine B cells, endowing them with superior T cell co-stimulatory capacity [55], and supports survival of human plasma cells *ex vivo* [56•]. Strikingly, heterozygous mutations in *STAT3* abrogate the stimulatory effects of IL-21 on the differentiation of human naïve B cells into plasmablasts *in vitro* (Table 1). Thus, although IL-21 can activate STAT1, STAT3 and STAT5, IL-21-mediated human B cell differentiation requires STAT3, and cannot be compensated by alternative signaling pathways, [57,58••]. The effect of IL-21 can be augmented by IL-2, IL-4 or IL-10 [49–51,59]. In the case of IL-2, this results from IL-21/STAT3 signaling inducing IL2Rα, allowing IL-21-primed B cells to respond to IL-2 [59]. These findings in humans are compatible with studies that examined IL-21 transgenic or IL-21/IL-21R-deficient mice. IL-21 transgenic mice exhibit hypergammaglobulinemia, and an increased frequency of class switched and plasma cells [54], while IL-21R-deficient mice have weak humoral responses to T-dependent Ags, with reduced GC formation due to reduced induction of Bcl-6 and reduced plasma cells, and poorly functional memory B cells [60–64] (Figure 2). Defects in humoral immunity were also observed when IL-21R was lacking only from B cells, demonstrating a B-cell intrinsic requirement for IL-21 signaling to support GC formation and

Figure 2



IL-21 guides the differentiation of B cell into multiple effector fates. The provision of IL-21 by Tfh cells induces naive B cells to undergo proliferation and then differentiation into GC B cells, with the latter dependent on induction of Bcl-6. GC B cells subsequently yield plasma cells, following acquisition of Blimp-1, and memory B cells. IL-21 also induces expression of AICDA, which guides class switch recombination, predominantly to the IgG1, IgG3 and IgA subclasses. IL-10-producing murine B cells — termed B10 cells — have immunoregulatory properties and these cells are also induced by IL-21. It is unknown whether this is dependent or independent of GC reactions.

plasma cell differentiation [61,62,64]. IL-21 can also induce granzyme B and IL-10 in human and murine B cells [59,65,66•] (Figure 2), an effect dependent on STAT3. IL-10-expressing B cells are termed B10 cells, and have immunoregulatory function evidenced by ameliorating disease in models of autoimmunity [66•]. Generation of murine B10 cells *in vivo* is IL-21 dependent (Figure 2); thus IL-21 is required for B10-mediated protection against autoimmunity [66•]. While this further highlights the broad effects of IL-21 on B-cell biology, it remains to be determined whether human B10 cells similarly require IL-21 for their development, and whether IL-10 produced in this setting is immunoregulatory, given its ability to induce plasmablasts, albeit to a lesser extent than IL-21 [50,52].

Overall, IL-21 has potent effects on all lymphocytes. This is achieved by influencing fate-specification of $CD4^+$ T cells, inducing acquisition of cytolytic mediators and cytotoxic function of $CD8^+$ T and NK cells to provide these cells with anti-viral and anti-tumor effector functions, and inducing B cells to robustly differentiate into memory and plasma cells, hallmarks of long-lived humoral immunity. Given these potent effects, it is perhaps not surprising that several disease conditions are caused by aberrant IL-21 function.

Immunological dyscrasias associated with aberrant IL-21/IL-21R signaling

Autoimmune diseases

The early findings that IL-21 was highly produced by Tfh and Th17 cells, which have key roles in B-cell differentiation and inflammatory responses, and overproduced in autoimmune prone mice, led to many studies assessing the contribution of IL-21 to the pathophysiology of murine models of human autoimmune diseases. The severity of lupus in BXSB-Yaa and MRL^{lpr} mice [67–69], type 1 diabetes in NOD mice and other relevant models of diabetes [19,29,70–73], rheumatoid arthritis [74] and experimental uveitis [75] was ameliorated in the absence of IL-21/IL-21R signaling. Remarkably, a lack of IL-21R from only B cells protected BXSB-Yaa mice from disease [76], revealing the important role of autoAbs in this model. However, IL-21 also promoted disease by concomitantly inducing pro-inflammatory autoAg-specific $CD4^+$ and $CD8^+$ T cells [19,29,69–73]. The pathogenic effects of IL-21 were not restricted to lymphocytes, as IL-21R-deficient DCs were defective in trafficking from inflamed tissues to lymph nodes, thereby limiting their ability to stimulate autoAg-specific $CD4^+$ and $CD8^+$ T cells [73]. Thus, pleiotropic functions of IL-21 underlie disease severity in these animal models.

These findings have been extended to humans, where serum levels of IL-21, IL-21 production by $CD4^+$ T cells, and proportions of circulating Tfh-like cells are increased in patients with SLE [77–81], rheumatoid arthritis [82–84] and type-1 diabetes [85,86••]. Notably, increases in serum IL-21 and circulating Tfh-like cells positively correlated with disease activity [79–85]. As these parameters could be attenuated by immunosuppressive treatments [79,80,82,84,85], excessive production of IL-21 is likely to directly contribute to disease severity. These cellular findings extend those from GWAS that identified polymorphisms in both *IL21* and *IL21R* that associated with SLE [87,88] (Table 1). Yet it is unclear whether these polymorphisms result in hypermorphic function, and how they contribute to disease.

Recently, gain-of function mutations in *STAT3* have been identified to cause an early onset multi-organ autoimmune disease. Although the clinical presentation is diverse, and fewer than 20 patients have currently been reported, features of this condition include lymphoproliferation, lymphadenopathy, hepatosplenomegaly, type 1 diabetes, autoimmune-mediated enteropathy, thyroiditis, arthritis and cytopenias [89••,90••,91•]. Pathogen infections and hypogammaglobulinemia have also been observed, as has a reduction in Tregs, which likely contributes to the autoimmune pathology [89••,90••,91•]. •]. Whilst STAT3 can be activated by a multitude of cytokines [1], thereby implicating numerous pathways in pathophysiology, aberrant signaling via IL-21/STAT3 probably contributes to some aspects of this condition. For instance, as autoimmune hemolytic anemia improved following treatment with rituximab [90••], IL-21 may underlie autoAb production (Table 1). Similarly, reduced Tregs may result from IL-21-mediated repression of Treg formation [28,29,30••]. This monogenic autoimmune disorder will provide opportunities to further dissect the role of IL-21/STAT3 signaling in health and disease.

Immunodeficiency

Whilst genetic association studies implicated polymorphisms in *IL21/IL21R* in SLE [87,88], indisputable evidence for the critical functions of this signaling pathway in immune regulation has come from the study of primary immunodeficiencies. In the past 2 years, several individuals have been identified with disease-causing loss-of function mutations in *IL21R* [92••,93•,94•,95] or *IL21* [96•]. Common features of most described individuals include poor humoral immune response evidenced by recurrent infections of the gastrointestinal and respiratory tracts; this is accompanied by reductions in memory B cells, class-switched B cells, and serum IgG and/or IgA [58••,92••,93•,94•,95,96•]. This reveals the non-redundant function of IL-21/IL-21R in establishing or maintaining long-lived serological memory (Table 1), and is consistent with previous proposals that IL-21 is the main inducer of human B-cell differentiation [50,52], and that an inability to signal through IL-21R/γc underlies impaired humoral immunity in X-SCID patients [4,60]. Interestingly, circulating Tfh cells were only mildly reduced or unaffected [92••,93•,94•,96•], suggesting IL-21 acts directly on B cells to establish humoral memory and is dispensable for generating Tfh cells. Several of the patients also exhibited increases in serum IgE [92••,93•,94•,96•]. These perturbations to B-cell differentiation in the absence of IL-21/IL-21R resemble those in patients with loss-of function mutations in *STAT3*, however serum IgE levels are much greater in STAT3 deficiency [57,58••]. Since IL-21 is a strong activator of STAT3, it is likely that impaired responses of STAT3-deficient B cells to IL-21 underlie compromised humoral immunity, and at least contribute to the hyper-IgE phenotype, of STAT3-deficient individuals (Table 1).

Despite the consistent B-cell defects in the absence of IL-21/IL-21R signaling, the main clinical complication of this primary immunodeficiency is susceptibility to pathogens such as Cryptosporidia, resulting in severe liver disease, and *Pneumocystis jirovecii* [92••,93•,94•,95] (Table 1). Infection with these pathogens is typically observed in the setting of severe reductions in the number or function of $CD4^+$ T cells (MHC class II deficiency, CD40L-deficiency, HIV infection). This suggests IL-21 plays a central role in regulating activation of APCs required to control these pathogens — most likely due to the preferential production of IL-21 by $CD4^+$ T cells. However, the mechanism underlying susceptibility to *Cryptosporidia* and *Pneumocystis* in IL-21/IL-21R-deficiency remains unknown. Infections with fungal pathogens in some patients have also been observed [94•,95], which may reflect a contributory role for IL-21 in Th17 cell function [9–12,27•]. Alternatively, the lack of prominent candida infections in all patients could argue against an obligatory role for IL-21 in Th17 cell generation [32,33]. Remarkably, several patients also have features of IBD-like disease or gut-related pathology [92••,93•,94•,95,96•]. This may result from the ability of IL-21 to induce IL-10 [27•,97] and suppress IFNγ [23,25,27•]; reduced IL-10 in IL-21/IL-21R-deficient patients could precipitate severe early onset IBD, as observed in individuals with mutations in the IL-10/IL-10R pathway [98], and this could be exacerbated by dysregulated IFNγ. This finding was somewhat surprising given previous observations that IL-21 (a) is over-produced by $CD4^+$ T cells in inflamed intestinal tissue of individuals with IBD [22], (b) can induce expression of IFNγ in human $CD4^+$ T cells [22], (c) suppresses Treg cells [28,29,30••], and (d) is considered a target to treat Crohn's disease [21••]. Thus, understanding the exact role of IL-21 in inducing or preventing IBD in humans will await the identification of additional patients with mutations in *IL21/IL21R*, and the outcomes of clinical trials targeting IL-21 in different human pathologies.

Interestingly, there was no consistent defect in NK cell function in patients with *IL21* or *IL21R* mutations [92••,93•,94•,95,96•]. Similarly, neither viral infections nor malignancy are common features of these patients, suggesting relatively intact anti-viral and anti-tumor immunity, mediated by NK and $CD8^+$ T cells, in the absence of IL-21 signaling [92••,93•,94•,95,96•]. Thus, IL-21 may be redundant for these aspects of cell-mediated immunity in humans. Alternatively, defects in immunity against chronic viral infections and tumor surveillance may not yet have manifested in these patients, given their relatively young age.

The prognosis for patients with *IL21* or *IL21R* mutations is poor, with most patients succumbing either to infection or dying of complications relating to organ or stem cell transplant (SCT) [92••,95,96•]. Notably, several of the genotyped patients are from families where other siblings died at a young age of similar disease but were not molecularly characterized [92••,96•]. Taking all of these individuals into account, mortality is ~70%. However, there has been one successful SCT performed, with the patient being relatively healthy 6 months post-SCT [93•]. The success of this procedure probably results from performing SCT prior to development of secondary complications, such as liver disease, following pathogen infection [93•]. Thus, early SCT may be curative for IL-21/IL-21R deficiency, even though IL-21R is also expressed on non-hematopoietic cells [21••].

It is clear that loss-of function mutations in either *IL21* or *IL21R* cause severe and significant disease in humans characterized by immunodeficiency and autoimmunity/inflammation, the clinical features of which were not entirely predicted from corresponding gene-targeted mice. The pathological consequences of abolished IL-21 signaling in humans highlight the critical role of IL-21 in host defense and immune regulation and reveal possible unanticipated and undesired outcomes of IL-21 blockade in treatments of human malignancies and autoimmune diseases [21••,22].

Conclusions

Since its discovery in 2000, IL-21 has emerged as a critical immunomodulatory cytokine with pleiotropic effects on all populations of lymphocytes, but also some myeloid cells. The importance of IL-21 in immunity is evidenced not only from its ability to potently induce the activation and differentiation of these different cell types, but also from the consequences of the absence of IL-21/IL-21R signaling on normal TD immune responses as well as in animal models of pathogen infection, autoimmunity and malignancy. However, the most convincing evidence for the criticality of IL-21 is the discovery of humans with loss-of function mutations in *IL21* or *IL21R* who develop severe immune dysregulation, characterized by infectious susceptibility to opportunistic pathogens and, paradoxically, autoimmunity. The discovery of these genetic defects as causes of human disease unquestionably establish non-redundant functions of IL-21 in immunity, and provide new opportunities to further dissect the impact of IL-21/IL-21R deficiency on the development of humoral and cell-mediated immunity, infectious disease, malignancy and autoinflammatory conditions. It also reminds us of unanticipated outcomes of therapeutic IL-21 blockade. Continuing research into IL-21 biology will no doubt reveal more functions for this dynamic cytokine, and uncover new avenues whereby amplifying or alleviating its effects could have clinical application for the treatment of diverse human immunological conditions.

Acknowledgements

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