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Survey

The role of IL-12, IL-23 and IFN-γ in immunity to viruses

Francesco Novelli*,[1], Jean-Laurent Casanova

[a] *Laboratory of Human Genetics of Infectious Diseases, Necker Medical School, René Descartes University of Paris, INSERM U550, 156 Rue de Vaugirard, 75015 Paris, France*

Abstract

IL-12, IL-23 and IFN-γ form a loop and have been thought to play a crucial role against infectious viruses, which are the prototype of "intracellular" pathogens. In the last 10 years, the generation of knock-out (KO) mice for genes that control IL-12/IL-23-dependent IFN-γ-dependent mediated immunity (STAT1, IFN-γR1, IFNγR2, IL-12p40 and IL-12Rβ1) and the identification of patients with spontaneous germline mutations in these genes has led to a re-examination of the role of these cytokines in anti-viral immunity. We here review viral infections in mice and humans with genetic defects in the IL-12/IL-23-IFN-γ axis. A comparison of the phenotypes observed in KO mice and deficient patients suggests that the human IL-12/IL-23-IFN-γ axis plays a redundant role in immunity to most viruses, whereas its mouse counterparts play a more important role against several viruses.

Keywords: IFN-γ; IL-12; IL-23; Viral infections; Humans; Mice

Contents

1. Introduction

Humans with absent (or diminished) response to or impaired production of IFN-γ caused by nonfunctional or dysfunctional components of IFN-γ and IL-12/IL-23 signaling [the binding or signaling chains of the IFN-γ receptor (IFN-γR1 and IFN-γR2), the signal transducer and activator of transcription (STAT1), the p40 subunit of IL-12 and IL-23 (IL-12p40), the β1 subunit of the IL-12 and IL-23 receptor (IL-12Rβ1)] are highly vulnerable to infections due to nontuberculous mycobacteria (NTM) or vaccine-associated bacille Calmette-Guérin (BCG), and to a lesser extent to *Salmonella* and a few other intracellular bacteria [1–4]. In contrast, mice whose genes encoding components of the IFN-γ and IL-12/IL-23 signaling pathways are knock-out (KO) are vulnerable to infection by a broad spectrum of microorganisms, including intracellular bacteria and viruses [5–9].

* Corresponding author. Present address: Department of Medicine and Experimental Oncology, Section of Pathology, University of Turin, 10125 Turin and Center for Experimental Research and Medical Studies (CERMS), San Giovanni Battista Hospital, Via Santena 5, 10126 Turin, Italy. Tel.: +39-011-6334463; fax: +39-011-6336887.
E-mail address: franco.novelli@unito.it (F. Novelli).
[1] Wrote this review during his sabbatical leave.

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Although viruses are the prototype of "intracellular" parasites, severe viral infection has been reported in only four patients genetically deficient for IFN-γ receptor [10–12]. The discrepancies between the clinical phenotypes of patients and of mice deficient for IFN-γ and IL-12/IL-23 signaling pathway components prompted us to compare the viral susceptibility/resistance of 140 patients with IFN-γR1 and IFN-γR2 [13–31], STAT1 [32], IL-12p40 [33–35] and IL-12Rβ1 [4,36–41] mutations with the outcome of experimental viral infection in mice deficient for IFN-γ, IFN-γR1, IL-12p40 or IL-12Rβ1, or treated with antibodies neutralizing IFN-γ or IL-12 so as to provide a clearer picture of the impact of the absence of IFN-γ and IL-12/IL-23 signaling on viral infection in humans and mice.

2. Natural and experimental virus infections in the absence of IFN-γ- and IL-12/IL-23-mediated immunity

Natural infections with "common"(arbitrarily defined as 20–98% of humans seropositive at 10 years) or "rare" (arbitrarily defined as less than 10% seropositive at 10 years) DNA and RNA viruses [42] were considered in patients deficient for IFN-γ- and IL-12/IL-23-mediated immunity. Their clinical outcomes were compared with those observed after administration of natural human tropic viruses permissive in mice, or their murine-tropic counterparts, to mice KO for the genes of several components of IL-12/IL-23 signaling (IL-12p40, IL-12Rβ1 = 12KO) or IFN-γ (IFN-γ, IFN-γR1 = GKO), or treated with neutralizing mAb to IFN-γ (aG) or IL-12 (a12).

2.1. Common DNA viruses

Natural infection with human tropic DNA viruses was considered in deficient patients (Table 1). No clinical manifestations due to human adenovirus (HAV), human herpes virus 6 (HHV6), parvovirus B19, molluscum contagiosum virus (MCV) and human papilloma virus (HPV) infections were reported (Table 1). Many deficient patients displayed positive serology for varicella zoster virus (VZV) and herpes simplex virus (HSV) and only one case of unusually severe clinical form of HSV infection was reported in an IFN-γR2 deficient patient [10]. Although deficient patients developed a benign form of varicella, two cases of severe clinical form of VZV infections were reported [10,30]. Epstein Barr virus (EBV) and human herpes virus 8 (HHV8) are associated with lymphoma, nasopharyngeal carcinoma and Kaposi's

Table 1
Common DNA virus infection in the absence of IFN-γ- or IL-12/IL-23-mediated immunity in humans and mice

Virus family	Humans			Mice		
	Virus species[a]	No. of seropositives[b]	Severe illness (infections)[c]	Virus species[d]	Apparently normal[e]	Abnormal[f]
Adenoviridae (ds)	HAV	No data	No case reported	HAV	12KO [43]	
Herpesviridae (ds)	HSV	4/16 (25%)	One case [10]	HSV	GKO [55]	GKO [44–49]; aG [52–54]
	HCMV	14/23 (61%)	Three cases [10,30]	*MCMV*	GKO [64]	GKO [56–58]; aG [54,59,60]; 12KO [61,62]; a12 [63]
	VZV	16/20 (80%)	Two cases [10,30]	No infection		
	EBV	17/24 (71%)	No case reported	*γ-MHV68*	GKO, aG [65]	GKO [66–68]; 12KO [69]
	HHV6	2/2 (100%)	No case reported	No infection		
	HHV8	No data	One Kaposi's sarcoma [12]	No infection		
Poxviridae (ds)	MCV	No data	No lesion reported	No infection		
Parvoviridae (ss)	B19	2/3 (67%)	No case reported	No infection		
Papovaviridae (ds)	HPV	1/1 (100%)	No lesion reported	No infection		

[a] HAV, human adenovirus; HSV, herpes simplex virus; HCMV, human cytomegalovirus; VZV, varicella zoster virus; EBV, Epstein-Barr virus; HHV6, human herpes virus 6; HHV8, human herpes virus 8; MCV, molluscum contagiosum virus; B19, parvovirus B19; HPV, human papilloma virus.

[b] Data from IL-12β1, IL-12p40, IFNγR1 and IFN-γR2 and STAT1 deficient patients; mean ± S.D. age (years) of the patients in which the specific seropositivity was evaluated: HSV 13 + 6, CMV 14 + 10, VZV 17 + 10, EBV 15 + 10, HHV6 18 + 21, B19 12 + 18, HPV 33.

[c] An abnormal immune defense refers to more severe infection or disease in patients with impaired IL-12- or IFN-γ-mediated responses than in healthy individuals.

[d] Species related to human-tropic virus; non-human, mouse-tropic virus species are indicated in italics; *MCMV*, murine cytomegalovirus; *γ-MHV-68*, γ murine herpes virus 68.

[e] An apparently normal immune defense refers to a comparable disease or in vitro response between mice with or without impaired IFNγ- or IL-12- and IL-23-mediated response.

[f] An abnormal immune defense refers to a more severe disease or in vitro immune response in mice with impaired IFNγ- or IL-12- and IL-23-mediated response; GKO: IFN-γ and IFN-γR1KO mice; aG: anti-IFNγ antibody-treated mice; 12KO: IL-12p40 and IL-12Rβ1 mice; a12: anti-IL-12 antibody-treated mice. Infection routes: intranasal [43,61,67,68,69]; corneal [46,49–51,55]; intradermal [47,52]; intraperitoneal [43,45,53,54–64,66]. References for each experimental infection are indicated. The genetic backgrounds were: IFN-γKO mice: Balb/C [46–49,57,65,66]; C57BL/6 [56]; 129/SV/E [50,51]; IFN-γR1KO mice: 129/SV/E [44,45,47–51,55–57,64,66–68]; anti-IFNγ antibody-treated mice: Balb/C [52,53,59,60,65]; 129/SV/E [44]; CB17 SCID [54]; p40IL-12KO mice: Balb/C [43,61,62]; C57BL/6 [43,69]; anti-IL-12Ab-treated mice: nu/nu SCID [63].

sarcoma. Positive serology for anti EBV Ig was reported in 71% of deficient patients (Table 1). Although no clinical cases of EBV infection and mononucleosis or Burkitt lymphoma have been reported, one case of Kaposi's sarcoma occurred in an IFN-γR1 deficient patient [12], but no serological data are available. Although deficient patients displayed positive serology for cytomegalovirus (CMV), clinical forms of infections due to CMV were reported in three patients with IFN-γR1 deficiencies [10,30] (Table 1). Thus infections with HHV8 and CMV are those for which IFN-γ, but not IL-12 and IL-23, plays an important role.

Experimental infection with natural murine (and human) tropic DNA viruses in mice with IFN-γ- and IL-12/IL-23-impaired immunity was also considered (Table 1). Immune response was not compromised in the lungs of adenovirus-infected 12KO mice [43]. HSV experimental infection has been extensively described as pathogenic in both GKO [44–51] and anti-IFN-γ-treated mice [52–54], although viral replication of attenuated form of HSV in GKO mice was not different from congenic controls [55]. Experimental infections with murine cytomegalovirus (MCMV), a mouse-permissive (human nontropic) DNA virus, exacerbated infection in GKO [56–58], aG [54,59,60], 12KO [61,62] and a12 [63] mice (Table 1). However, IFN-γ is important for resistance to MCMV only, since GKO mice were protected by vaccination with an attenuated MCMV mutant [64]. Wild-type, GKO and aG cleared infectious virus from the lungs 15 days after γ-herpesvirus 68 (γ-HV68) infection, a specific mouse tropic DNA virus which is a good model for study of γ-herpesvirus (HHV6 and EBV) pathogenesis [65]. However, GKO mice died weeks to months after γ-HV68 infection from severe large-vessel arteritis [66] or developed multiorgan fibrosis [67,68]. Compared with wild-type, γ-HV68-infected 12KO mice displayed increased lytic and latent virus, and decreased IFN-γ production, but decreased splenic leukocytosis [69] (Table 1).

2.2. Common RNA viruses

Natural infection with human tropic RNA viruses was considered in deficient patients (Table 2). Most individuals are immunized against the majority of these viruses. In deficient patients, no clinical manifestations of infection by influenza virus (IV), mumps, measles, coronavirus, enterovirus, reovirus, hepatitis A virus (HAV), rotavirus or rubella virus were reported (Table 2). Positive serology for IV, enterovirus, reovirus and rotavirus (Table 2 and [70]) was reported. No positive serology for rubella virus and HAV was reported (Table 2). By contrast, although positive serology for parainfluenza virus (PIV) and respiratory syncytial virus (RSV) have been reported in deficient patients [70], clinical manifestations of PIV and RSV infections were reported in only one child with complete *IFNGR1* deficiency [10]. While IL-12 and IL-23 do not play a role in infection by common RNA viruses in humans, more patients are needed to confirm that IFN-γ plays a role in PIV and RSV infection in humans.

Experimental infection with natural mouse (and human) tropic RNA viruses was also considered (Table 2). GKO mice [71–74] as well as anti-IFN-γ and IL-12 mAb-treated mice [75,76] are resistant to IV infection (Table 2). Similarly, GKO mice were resistant to inoculation of rotavirus [77,78]. After coxackievirus B3 infection, IFN-γR1KO mice displayed exacerbated virus replication [79], whereas IFN-γKO and IL-12KO mice were resistant [79,80]. After RSV infection, GKO mice as well as anti-IFN-γ and anti-IL-12 Ab-treated mice displayed more extensive inflammation of the airways than control mice [81–84], even if no worsening of pulmonary histopathology was observed in 12KO mice [82,83]. By contrast, both GKO and anti-IFN-γ Ab-treated mice became highly susceptible to experimental measles-induced encephalitis [85–87]. GKO mice displayed no difference with wild-type after infection with myocarditis reovirus 8B, a mouse-permissive (human nontropic) virus [56] (Table 2). Moreover, autoimmune insulitis and diabetes induced by reovirus infection in mice is reduced and not exacerbated by anti-IFN-γ and anti-IL-12 antibodies [88,89].

Experimental infection with murine-specific tropic RNA viruses was also evaluated in mice with impaired IFN-γ- and IL-12/IL-23-mediated immunity (Table 2). After mouse Sendai virus (SV) infection, murine PIV1, IL-12KO, GKO and anti-IFN-γ mAb-treated mice display little or no difference with wild-type mice [90,91] and IL-12Rβ1KO mice are protected against viral-induced mortality [92].Compared to control mice, both GKO [93–100] and anti-IFN-γ mAb-treated mice [101], but not 12KO mice [95], are more susceptible to murine hepatitis virus (MHV) infection, a model for the study of coronavirus infection. In MHV-infected mice the absence of IFN-γ diminishes demyelination mediated by CD8 T cells [102] and enhances that mediated by CD4 T cells [103]. Interestingly, granulomatous peritonitis and pleuritis occur in GKO mice naturally infected with MHV [100]. Resistant GKO mice display severe encephalomyelitis with extensive primary demyelination and virus persistence following infection with Theiler's murine encephalomyelitis virus (TV) [104,105]. Administration of neutralizing Ab to IFN-γ, but not to IL-12, increased TV-induced demyelination in susceptible mice and completely abrogated resistance in resistant mice [106–108].

2.3. Rare DNA and RNA viruses

Among the rare natural human tropic viruses, only those (or their murine counterparts) tested in mice were considered. Since no infections by vaccinia virus (VV), encephalomyocarditis virus (EMCV), vescicular stomatitis virus (VSV), Semliki Forest virus (SFV), Sindbis virus (SV), equine arteritis virus (EAV), yellow fever (YF), West Nile virus (WNV) and lymphocytic choriomeningitis virus (LCMV) were reported, the vulnerability of deficient

Table 2
Common RNA virus infection in the absence of IFN-γ- or IL-12- and IL-23-mediated immunity in humans and mice

Virus family	Humans			Mice		
	Virus species[a]	No. of seropositive[b]	Severe illness (infections)[c]	Virus species[d]	Apparenly normal[e]	Abnormal[f]
Orthomyxoviridae (ss)	IV	1/1 (100%)	No case reported	IV	GKO [71–74]; aG [75]; a12 [76]	
Paramyxoviridae (ss)	PIV	Positive serology [70]	One case	*Sendai virus*	GKO [90,91]; 12KO [90,92]; ag [91]	
	Mumps virus	1/1 (100%)	No case reported	No infection		
	Measles virus	1/1 (100%)	No case reported	Measles virus		GKO [85,86]; aG [87]
	RSV	1/1 (100%)	One case	RSV	12KO [82,83]	GKO [81–83]; aG [81]; a12 [84]
Coronaviridae (ss)	HCV	No data	No case reported	*MHV*	12KO [95]	GKO [93–100]; aG [101]
Picornaviridae (ss)	Enterovirus	10/10 (100%)	No case reported	*Theilers's virus*	a12 [106]	GKO [104,105]; aG [107,108]
				Coxackievirus B3	GKO [80]; 12KO [79]	GKO [79]
	RV	Positive serology [70]	No case reported	No infection		
	HAV	0/1 (0%)	No case reported	No infection		
Reoviridae (ds)	Rotavirus	Positive serology [70]	No case reported	Rotavirus	GKO [77,78]	
				Reovirus	GKO [56]; aG [88]; a12 [89]	
Togaviridae (ss)	Rubella	0/1 (0%)	No case reported	No infection		

[a] IV, influenza virus; PIV, parainfluenza virus; RSV, respiratory syncytial virus; HCV, human coronavirus; RV, reovirus; HAV, hepatitis A virus. These RNA viruses are considered ubiquitous since >98% of individuals are seropositive at 10 years. Most individuals are immunized for Mumps, Measles, RSV, HCV, Poliovirus, Enterovirus, RV, HAV, Rotavirus, Reovirus, Rubella.

[b] Data from IL-12β1, IL-12p40, IFNγR1, IFN-γR2 and STAT1 deficient patients; mean ± S.D. age (years) of the patients in which the specific seropositivity was evaluated: IV, Mumps virus, Measles virus and RSV: 33, Enterovirus 19 ± 11, HAV 22, Rubella 1.

[c] An abnormal immune defense refers to more severe infection or disease in patients with impaired IFN-γ- or IL-12/IL-23-mediated responses than in healthy individuals.

[d] Species related to human-tropic virus; non-human, mouse-tropic virus species are indicated in italics; MHV, murine hepatitis virus.

[e] An apparently normal immune defense refers to a comparable disease or in vitro response between mice with or without impaired IFNγ- or IL-12/IL-23-mediated responses.

[f] An abnormal immune defense refers to a more severe disease or in vitro immune response in mice with impaired IFNγ- or IL-12/IL-23-mediated response; GKO: IFN-γ and IFN-γR1KO mice; aG: anti-IFNγ antibody-treated mice; 12KO: IL-12p40 and IL-12Rβ1 mice; a12: anti-IL-12 antibody-treated mice. Infection routes: intraperitoneal [56,73,77,88,93,95–98,101], intranasal [71,72,75,81–83,90,91,94], intratracheal [74,83,92], intracerebral [84–86,99,104–112], oral [72,73]. References for each of the experimental infection are indicated. Genetic backgrounds were: IFN-γKO mice Balb/c [79]: IFN-γKO mice: Balb/C [74,81,82,90,93,94]; C57BL/6 [71,72,77,78,87,96,98–100]; human CD46TG X IFN-γKO mice: C57BL/6 [86]; IFN-γR1KO mice: 129/SV/E [56,73,78,82,93,95,105]; C57BL/6 [97]; anti-IFNγ antibody-treated mice: Balb/C [75,81,84,106]; SJL/J [106]; C57BL/6/10NSJ [107]; A/J [100]; DBA-1 [88]; p40IL-12KO mice: Balb/C [82,90]; 129/SV/EV [83]; IL-12Rβ1KO mice: Balb/c [79]; C57BL/6 [92]; anti-IL-12 antibody-treated mice: Balb/C [76]; SJL/J [105]; DBA-1 [89]; C57BL/6 [84].

patients to these viruses remains unknown (Table 3). The same unknown status was assigned for human immunodeficiency virus (HIV) infection since neither clinical cases nor seropositivity for HIV Ag were reported in deficient patients, even though increased susceptibility to HIV replication of T cells from two IFN-γR1 and one IL-12Rβ1 deficient patient was observed in vitro (Table 3 and [109]).

Experimental infection of natural rare mouse (and human) tropic viruses was also considered (Table 3). Although some VV strains express a gene coding for IFN-γR binding chain which might play a role in virus virulence [110], IFN-γKO and anti-IFN-γ Ab-treated mice succumbed to infection with VV [111,112]. In IFN-γKO mice VV clearance was not severely affected, but it was impaired after infection with an attenuated form of VV [113]. GKO mice become more susceptible to WNV infection [114] and can no longer be protected by IL-12 from lethal EMCV infection [115] (Table 3). By contrast, wild-type, GKO [112,116,117], 12KO [118], and anti-IFN-γ Ab-treated mice [119] were equally infected by VSV, despite the fact that IFN-γ engineered to be retained in the endoplasmic reticulum mediates in vitro VSV resistance in murine fibroblasts [120]. Following SFV infection 12KO mice showed an enhanced virus replication and pathology in the brain [121], whereas GKO mice were unaffected [112]. GKO mice were also unaffected following SV [122] and YF [123] infection, even if IFN-γ mediates T cell-dependent virus clearance from CNS neurons in SV infected-mice [124]. GKO [112,118,125–129]

Table 3
Rare virus infection in the absence of IFN-γ- or IL-12/IL-23-mediated immunity in humans and mice

Virus family	Humans			Mice		
	Virus species[a]	No. of seropositive[b]	Severe illness (infections)[c]	Virus species[d]	Apparently normal[e]	Abnormal[f]
Poxviridae (ds DNA)	VV	No data	No lesion reported	VV		GKO, aG [111–113]
				EV		GKO [136]; aG [135]
Picornaviridae (RNA ss)	EMCV	No data	No case reported	EMCV		GKO [115]
Rhabdoviridae (RNA ss)	VSV	No data	No case reported	VSV	GKO [112,116,117]; 12KO [118]; aG [119]	
Togaviridae (RNA ss)	*SFV*	No data	No case reported	*SFV*	GKO [112]	12KO [121]
	SV	No data	No case reported	*SV*	GKO [122]	
	EAV	No data	No case reported	LDV	GKO, aG [139,140]	
	YF	No data	No case reported	YF	GKO [123]	
Flaviviridae (RNA ss)	WNV	No data	No case reported	WNV		GKO [114]
Arenaviridae (RNA ss)	LCMV	No data	No case reported	*LCMV*	12KO [118]; a12 [132–134]	GKO [112,118,125–129]; aG [119,130,131]
Retroviridae (RNA ss)	HIV1	0/17 (0%)	No case reported Increased in vitro replication [109]	FV	12KO [145]	GKO [145,146]; aG [146]
				MMTV	GKO [147]	
				LP-BM5	aG [143,144]; a12 [143]	GKO [141,142]

[a] VV, vaccinia virus; EMCV, encephalomyocarditis virus; VSV, vescicular stomatitis virus; SFV, Semliki Forest virus; SV, Sindbis virus; EAV, equine arteritis virus; YF, yellow fever virus; WNV, West Nile virus; LCMV, lymphocytic choriomeningitis virus; HIV, human immunodeficiency virus; mouse permissive or mouse specific tropic viruses are indicated in italics. These RNA viruses are considered limited or rare since <10% of individuals are seropositive at 10 years.

[b] Data from IL-12β1, p40IL-12, IFNγR1, IFN-γR2 and STAT1 deficient patients; mean ± S.D. age (years) of the patients in which the specific seropositivity was evaluated: HIV, 22 ± 13.

[c] An abnormal immune defense refers to more severe infection or disease in patients with impaired IFN-γ- or IL-12/IL-23-mediated responses than in healthy individuals.

[d] Species related to human-tropic virus; non-human, mouse-tropic virus species are indicated in italics. *EV*, echromelia virus; LDV, lactate dehydrogenase elevating virus; *FV*, Friend virus; *MMTV*, mouse mammary tumor virus, LP-BM5 is a defective murine leukemia virus (*MuLV*).

[e] An apparently normal immune defense refers to a comparable disease or in vitro response between mice with or without impaired IFNγ- or IL-12-mediated response.

[f] An abnormal immune defense refers to a more severe disease or in vitro immune response in mice with impaired IFNγ- or IL-12/IL-23-mediated response; GKO: and IFN-γR1KO mice; aG: anti-IFNγ antibody treated-mice; 12KO: IL-12p40 and IL-12Rβ1 KO mice; a12: anti-IL-12 antibody-treated mice. Infection routes: intravenous [112,117,126,131,142]; intraperitoneal [113,114,125,126,139–141]; intradermal [112,125,135,136]; intracerebral [115,123,127,128]; intranasal [116,121]; milk [147]. References for each of the experimental infection are indicated. Genetic backgrounds were: IFN-γKO mice: Balb/C [112,125,127,128,141,149]; C57BL/6 [114,116,117,123,127,128,145,147]; IFN-γR1KO mice: 129/SV/E [112,115,122,126,136–140]; Balb/C [147]; anti-IFNγ antibody-treated mice: Balb/C [113,132,142]; C57BL/6 [112,119,135,143,144]; 129/SV/E [113]; CBA/Ht [140]; IL-12p40KO mice: C57BL/6 [118,121,145]; anti-IL-12-antibody treated mice: Balb/C [143].

and anti-IFN-γ Ab-treated [119,130,131] mice become more susceptible or succumb to LCMV infection. However, 12KO [118] or anti-IL-12Ab-treated [132–134] mice infected with LMCV showed comparable viral replication and CTL induction.

Experimental infection with rare murine-specific tropic viruses was considered (Table 3). GKO and anti-IFN-γ Ab-treated mice succumbed to infection with mousepox virus, and ecromelia virus (EV) [135,136]. Inhibition of EV replication is due to the ability of IFN-γ to induce nitric oxide synthases [137,138]. By contrast, infection with lactate dehydrogenase (LDV)-elevating virus had no effect in either GKO or anti-IFN-γ treated mice [139,140]. Murine AIDS (MAIDS) is induced by LP-BM5 murine leukemia retrovirus (MuLV) in susceptible mice. After LP-BM5 infection, GKO mice displayed accelerated neurodegeneration [141] and the therapeutic effect of IL-12 on mice with MAIDS was absent in GKO and anti-IFN-γ mAb-treated mice [142]. However, anti-IFN-γ mAb-treated mice displayed delayed progression of MAIDS [143,144] and knocking out of IFN-γ gene or anti-IL-12 mAb treatment did not induce disease in resistant mice [144]. 12KO mice were comparable to wild-type mice in their ability to control murine Friend retrovirus (FV) infection [145]. In contrast, GKO and anti-IFN-γ-treated mice were unable to maintain long-term control over FV infection [146]. No differences between wild-type and GKO mice were observed after mouse mammary tumor virus (MMTV) infection [147].

3. A tentative picture of the role of IL-12/IL-23-IFN-γ axis in natural and experimental viral infections

Nine years after the discovery of the first germline mutations in IFN-γ-mediated immunity in man [13,14] an attempt can be made to illustrate the protective impact of the IL-12/IL-23-IFN-γ axis by comparing the phenotypes of naturally infected deficient patients and experimentally infected deficient mice. Experimental viral infection is conducted with pure, homogeneous laboratory strains, in inbred mice via artificial routes and generally is effective. By contrast, natural infection is the result of incidental exposure to clinical samples of one or more species and is often repelled. It may occur in vaccinated individuals or individuals with a history of other related or unrelated infections [148]. Viral infections in humans are associated with primary immunodeficiency diseases or are idiopathic. In patients with deficiencies in the IFN-γ- and IL-12/IL-23-mediated immunity, viral illness may be favored by previous mycobacterial disease, which results in poor clinical status and low CD4 counts. Several viruses may be associated with resistance in mice, but vulnerability in humans.

Four phenotypes were assigned to deficient patients to define their vulnerability to natural infections: normal (absence of clinical cases, with positive serology or no serological data), moderate (clinical cases, with positive serology or no serological data), high (occurrence of severe or lethal cases with positive serology or no serological data) and unknown (absence of clinical cases reported with no positive serology or no serological data). Three phenotypes were assigned to KO mice to define their vulnerability to experimental viral infection: normal (enhanced morbidity or mortality), moderate (enhanced subclinical infection or enhanced mortality or morbidity in GKO or 12KO mice only), and high (enhanced mortality or morbidity in both GKO and 12KO).

For common DNA viruses, the vulnerability of deficient patients is moderate to HSV and VZV, and high to HCMV and HHV8, whereas that of deficient mice is moderate to γ-MHV68 and high to HSV and MCMV. In both settings, the IL-12/IL-23-IFN-γ axis is required for protection against HSV, but not HAV. For natural infections only, it is not required for protection against EBV, HHV6, MCV, B19, and HPV, whereas only IFN-γ is required for protection against HCMV and HHV8. For experimental infection only, the axis is required for protection against γ-MHV68.

For common RNA viruses the vulnerability of deficient patients is moderate to PIV and RSV, whereas that of deficient mice is moderate to RSV, MHV and enterovirus and high to measles virus. In both settings, the IL-12/IL-23-IFN-γ axis is required for protection against RSV, but not IV, rotavirus and enterovirus. For natural infections only, it is required for protection against PIV, but not mumps virus, measles virus, coronavirus, reovirus, HAV and rubella virus. For experimental infections only, it is not required for protection against PIV and reovirus, but it is required for protection against measles virus, coronavirus, and (confined to IFN-γ only) to enterovirus.

Due to the absence of clinical cases and/or negative serological data, the vulnerability of deficient patients to rare viruses is unknown. For these viruses the vulnerability of deficient mice is moderate to SVF, LCMV, FV and LP-BM5 and high to VV, EV, WNV and EMCV. For experimental infections only, the IL-12/IL-23-IFN-γ axis is not required for protection against VSV, SV, LDV, YF and MMTV, but is required for protection against VV, EV, WNV and ECMV. IFN-γ only is required for protection against LMCV and FV whereas IL-12 and IL-23 only are required for protection against SVF.

The vulnerability of natural and experimental infection with rare viruses cannot be compared. The vulnerability of mice to rare viruses and common viruses is much the same (58% versus 54%).

4. Conclusions

In experimental infections, the IL-12/IL-23 and IFN-γ axis displays a conspicuous redundancy, since KO mice display vulnerability to about 60% of the rare and common viruses considered. In natural infections, this redundancy is much more pronounced, since deficient patients display modest vulnerability to about 20% of common viruses. This indicates that non-IFN-γ and non-IL-12/IL-23 mechanisms are certainly involved in the control of viral infections, particularly natural infections.

IL-12 and IL-23 share a common p40 subunit, yet they comprise unique p35 and p19 subunits, respectively [149]. IL-12 and IL-23 receptor complexes share a common IL-12Rβ1 subunit, yet they comprise unique IL-12Rβ2 and a specific IL-23R component [9]. Since IL-12p40 and IL-12Rβ1 mutants, in mice and man, lack both IL-12 and IL-23 immunity [4,9,150], we do not know whether the antiviral effects detected (particularly in natural infections) are caused by the lack of IL-12 or IL-23. A possible unique role of IL-12 in antiviral immunity is suggested by the observation that IL-12p35 KO mice display an enhanced susceptibility following infection with MCMV, SV and VV [61,90,113] and that mice deficient in STAT4, which is mainly induced by IL-12 rather than IL-23 [9], are more susceptible to RSV and VSV infection [84,151]. However, the simplest explanation for the absence of patients identified as being genetically deficient in p35IL-12- or IL-12Rβ2 is the lack of an infectious phenotype, suggesting that IL-12 alone is entirely redundant in protective immunity against all microorganisms in humans.

IFN-α/β is considered to play a major role in antiviral defense [152]. For experimental infections, anti-IFNα/β antibody-treated mice [152] and IFNα/β receptor KO mice [104,112,153–157], as well as mice deficient in both IFNα/β and IFN-γ receptors [5,55], STAT1 [158,159] and STAT2 [160] showed marked sensitivity to a broad range of DNA

and RNA viruses. However, the IL-12/IL-23 and IFN-γ axis is interconnected with IFNα/β in the antiviral defense. IL-12 is essential for antibody-mediated protection of HSV-infected mice without a functional IFN type I system [161] and IFNα/β directly activates STAT-4 which is required for IFN-γ production during viral infection [162]. For natural infection, while patients with a heterozygous *STAT1* mutation that impairs IFN-γ, but not IFNα/β-mediated activation, are susceptible only to mycobacterial disease [32], two patients with a heterozygous *STAT1* mutation that impairs both IFN-γ and IFNα/β-mediated activation suffered from mycobacterial disease but, unlike patients with IFN-γR deficiency, died of disseminated HSV-1 infection with recurrent encephalitis [163]. These data indicate that human IFNα/β plays a pivotal role for immunological control of HSV, and probably other viruses in vivo.

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