Seminars in Immunology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Seminars in Immunology

journal homepage: www.elsevier.com/locate/ysmim

What do primary immunodeficiencies tell us about the essentiality/redundancy of immune responses?

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ARTICLE INFO

Keywords:
Redundancy
Essentiality
Infections
Immunopathology
Innate immunity
Adaptive immunity
Primary immunodeficiencies

ABSTRACT

Advances in genomics and medicine have enabled the identification of (currently) 346 primary immunodeficiencies (PIDs) caused by mutations in 336 different genes. Most of these PIDs are monogenic conditions with Mendelian inheritance. Given this large number, it is possible to analyze the distribution of PIDs associated with infections and/or immunopathology according to the nature of the defect – even though this exercise can be challenging and arguable because of the pleiotropic nature of some gene products. The results of this analysis nevertheless strongly suggests that innate immune responses (mediated by pattern recognition receptor (PRR) engagement) are largely redundant, whereas adaptive immune responses are essential. Conversely, gain of function is more frequent in PRR-mediated immune responses than in adaptive immune responses – suggesting that robust innate immune pathways are less stringently regulated than energetically costly and potentially harmful adaptive immune responses.

1. Introduction

As of June 2017, a total of 346 monogenic primary immunodeficiencies (PIDs) had been described. These PIDs are caused by mutations in 338 different genes ([1] and unpublished data). By definition, the phenotypic expression of a PID reveals essentiality of their respective gene products in the execution or regulation of immune responses [2–8]. The many PID phenotypes encompass susceptibility to infectious agents (which can be broad or restricted, and permanent or transient) and immunopathologic manifestations (such as autoimmunity/inflammation, observed in 26% of PIDs [9], and allergy, observed in 20%) and lymphoproliferative disorders. As such, PIDs constitute an extraordinary *in vivo* guide to the human immune system in all its complexity.

2. Susceptibility to infections

As far as immune system cells are concerned, the analysis of PIDs has taught us that neutrophils, most of the T lymphocyte subsets, i.e. TH1, TH17, TFh, Treg and cytotoxic T cells, along with B lymphocytes and dendritic cells are essential for immune defense and/or regulation [1,2,4,5]. However, PIDs do not provide information on non-conventional T cells or macrophages because selectively impairments in these cell lineages have not been reported to date. Although a few studies have reported that susceptibility to viral infections was associated with a supposedly selective natural killer (NK) cell deficiency [10], the latter cells do not appear to be essential; after bone marrow transplantation in the absence of myeloablation, 19 patients with an NK-deficient severe combined immunodeficiency (SCID, e.g. JAK3 and γc deficiency) exhibited a T-replete NK-deficient phenotype and were healthy after a median follow-up period of 20 years [11]. The same held true for the innate lymphoid cell (ILC) subsets that these patients also lacked. This finding indicates that NK cell and ILC cell functions are redundant – at least in the context of a Western lifestyle. It is possible that an NK cell or ILC deficiency is functionally compensated for by the corresponding T cell subsets, although this remains to be unambiguously established. It would also be of interest to assess whether the absence of ILCs in the gut, skin and respiratory tract affect the microbiota. Another intriguing question is whether an NK cell or ILC deficiency modifies susceptibility to allergic, autoimmune and inflammatory disorders. However, no such manifestations have been observed to date in affected individuals. Furthermore, an ILC deficiency did not prevent fecundity in two of the women in the above-mentioned cohort – suggesting that the protective role of uterine NK cells during pregnancy is redundant. Another intriguing observation relates to the current absence of reports of selective TH2-deficiencies. TH2-mediated responses are clearly critical for

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https://doi.org/10.1016/j.smim.2017.12.001
Received 26 October 2017; Accepted 6 December 2017

Table 1
Distribution of primary immunodeficiencies (PIDs).

	Vulnerability to infection	
	Total number of genes	Genes mutated in PIDs
Total	1854	287
Adaptive immunity	515	189
Innate immunity	1540	59
− neutrophils		33
− others		26
Mixed/unknown		39

Table 2
Characteristics of susceptibility to infections as a function of the PID.

a) The main categories of adaptive immunity PIDs causing susceptibility to infection

Total	189		
T cells	106		
B cells	54	permanent	100%
Antigen presentation	12	broad spectrum	91%
Effector function − > innate	17	high penetrance	100%

b) Characteristics of innate immunity PIDs causing susceptibility to infections

Phagocytic cells	n = 32
- permanent	100%
- broad spectrum	94%
- high penetrance	100%

c) Characteristics of PRR-related innate immunity PIDs causing susceptibility to infections

PIDs not restricted to hematopoietic cells[a]	n = 15
− permanent	0
− broad spectrum	0
− high penetrance	0[a]

[a] Not known for 9.

Table 3
Monogenic diseases causing autoimmunity and/or inflammation.

		% with gain of function	
	n	Gene product	pathway
Adaptive immunity	75	7	10
Innate immunity	58	29	64

defense against helminths but are associated with allergy in the Western world. One can thus legitimately speculate that for people living in a helminth-free environment, the absence of TH2 responses would not be harmful and might even be an advantage by precluding the development of allergy!

3. Genetic studies

As previously reported [2] and presented here (Table 1), the great majority of the PIDs associated with susceptibility to infections are caused by defects in adaptive immunity and not by defects in innate immunity. Approximately 40% of the genes associated with adaptive immunity are seen to be mutated in infection-linked PIDs, whereas this is the case for only 3.8% of the genes associated with innate immunity. Interestingly, the characteristics of infections associated with adaptive immunity deficiencies (Table 2) and those observed in patients with phagocytic cell disorders (Table 2) differ from those observed in patients with innate immune defects related to pattern recognition receptors (PRRs) and their downstream signaling cascade and effector pathways (Table 2). Indeed, the rare PIDs associated with immune defects in a PRR signaling pathway usually have a very narrow pattern of susceptibility to infection. In addition, the susceptibility can be tissue – and/or time-restricted; for example, patients with a deficiency in the Toll-like receptor 3 (TLR3) pathway are susceptible to HSV1 infection in the brain (but not in other tissues) and only in the first years of life (but not thereafter) [3]. In contrast, the PIDs associated with adaptive immunity deficiencies and phagocytic cell disorders create a state of life-long susceptibility to a broader spectrum of infectious agents. Taken as a whole, these observations strongly suggest that PRR-related immunity − which relies on many receptors (among them 11 TLR genes and 22 nucleotide oligomerization domain-like receptor genes, etc.) and even more effectors (with more than 300 interferon signaling genes) – is both robust and redundant. The latter hypothesis is supported by the recent finding that people with deficiencies in IRAK1 and TIRAP (key molecules involved in signal transduction from TLRs) are not abnormally susceptible to infections [12,13]. Furthermore, these observations confirm the critical, tissue-restricted role of these pathways, and indicate that essentiality/redundancy is not an all-or-nothing concept.

Table 4
The relative proportions of disease genes causing immunopathologies or susceptibility to infections as a function of the immune pathway.

	Immunopathology (gain of function)	Susceptibility to infection (loss of function)
TLRs	0	8
NLRs	6	1
CLRs	0	1
RLRs	4	1
DNA sensing	9	0
Interferon response	7	5
Interleukin 1	7	0
TNF	2	0
Interleukin 6	1	0
Interleukin 17	1	9
Interferon γ	0[a]	6
Total		
Innate immunity	36	15
Adaptive immunity	1	15

TLR: Toll-like receptor; NLR: nucleotide oligomerization domain-like receptor; CLR: C-type lectin receptor; RLR: RIG-I-like receptor.

[a] Excluding HLH and related conditions characterized by excessive interferon γ production, which is an indirect consequence of defects in T/NK cell cytotoxicity.

4. Immunopathology

As of June 2017, mutations in 139 different genes were known to lead to PIDs associated with an immunopathology (i.e. allergy, autoimmunity and/or inflammation; Tables 3 and 4). It is noteworthy that many of these PIDs are also leading to susceptibility to infection [2]. The overall distribution indicates that genetic abnormalities affecting adaptive immunity and those affecting innate immunity can cause immunopathologies. Strikingly, gain-of-function mutations in genes (or, more broadly gains in effector functions in pathways) are more frequently linked to innate immune system defects. Details of the relative contributions of innate immunity defects and adaptive immunity defects to infection susceptibility and immunopathologies are given in Table 4. Strikingly, gain-of-function mutations in innate immunity (PRR