Review

Molecular pathways involved in human genetic susceptibility to infections: from the bedside to the bench

Vie del segnale coinvolte nella suscettibilità genetica alle infezioni: dalla clinica al laboratorio

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RIASSUNTO

Razionale. I progressi della genetica hanno favorito la scoperta di difetti in geni implicati nel funzionamento di vie del segnale non-ridondanti o tessuto-specifiche coinvolti nella patogenesi degli errori congeniti dell'immunità (IEI) intrinseca e innata. Questi disordini si manifestano in termini di suscettibilità a uno spettro ristretto di patogeni che si esprime in forma di infezioni gravi, critiche o potenzialmente letali, che generalmente si verificano in individui altrimenti sani indipendentemente da età, numero di episodi, storia infettiva familiare, patogenicità del microrganismo ed epidemiologia.

Obiettivi. Fornire elementi chiave per indagare adeguatamente IEI sottostanti in pazienti con suscettibilità infettiva ristretta a uno spettro selettivo di patogeni, descrivendo i segnali di allarme clinici meritevoli di un approfondimento genetico.

Contenuto. In questa revisione sono descritti i principali segni suggestivi di suscettibilità infettiva relativi agli IEI, con un approccio "dal capezzale al laboratorio", che parte dalla clinica e passa attraverso i meccanismi di difesa dell'ospite contro i principali patogeni coinvolti per arrivare ai test molecolari più appropriati, adottati in ragione di uno specifico sospetto diagnostico.

Implicazioni. Una diagnosi precoce di IEI intrinseca e innata si traduce potenzialmente in una pronta gestione mirata sul singolo paziente, riducendo il carico di comorbidità correlate alle infezioni e alla disregolazione immunitaria relativa agli IEI.

PAROLE CHIAVE: batteri piogeni, errori congeniti dell'immunità, funghi, micobatteri, vie del segnale, virus

SUMMARY

Background. *The widespread use of high-throughput genomic technologies has speeded up the discovery of genetic defects impairing non-redundant or tissue-specific key pathways involved in the pathogenesis of the so-called intrinsic and innate inborn errors of immunity (IEIs). These disorders manifest as susceptibility to a narrow spectrum of pathogens expressing in terms of severe, critical, or even potentially life-threatening infections, generally occurring in otherwise healthy individuals irrespective of age, number of episodes, familial infectious history, microorganism' pathogenicity and epidemiology.*

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Objectives. *We provide key elements to properly investigate underlying IEIs in patients with infectious susceptibility restricted to a selective spectrum of pathogens, describing the clinical red flags worthy of an immunologic and genetic evaluation.*
Content. *We address the main signs suggestive for IEI-related infectious susceptibility relying on a "bedside to the bench" approach, starting from clinical scenarios, going through the key determinants of host defense against the specific spectrum of pathogens involved, finishing with the proper molecular tests adopted by reason of a specific clinical- and basic laboratory-guided suspicion.*
Implications. *An early intrinsic and innate IEI diagnosis can result in prompt patient-tailored management, reducing the burden of infections- and immune-dysregulation-related comorbidities.*

KEY WORDS: *fungi, inborn errors of immunity, mycobacteria, pyogenic bacteria, signalling pathways, viruses*

INTRODUCTION

Inborn errors of immunity (IEIs) are congenital disorders due to pathogenic variants in genes involved in the development and function of the immune system. To date, more than 485 genes causative for IEIs have been identified; although singularly rare, these disorders display an overall prevalence of between 1:1000 and 5:1000 individuals [1]. IEIs show a broad spectrum of phenotypes, including infectious susceptibility and immune dysregulation in terms of autoinflammatory, autoimmune and atopic disorders, lymphoproliferative diseases (LPDs) and cancer susceptibility [2].

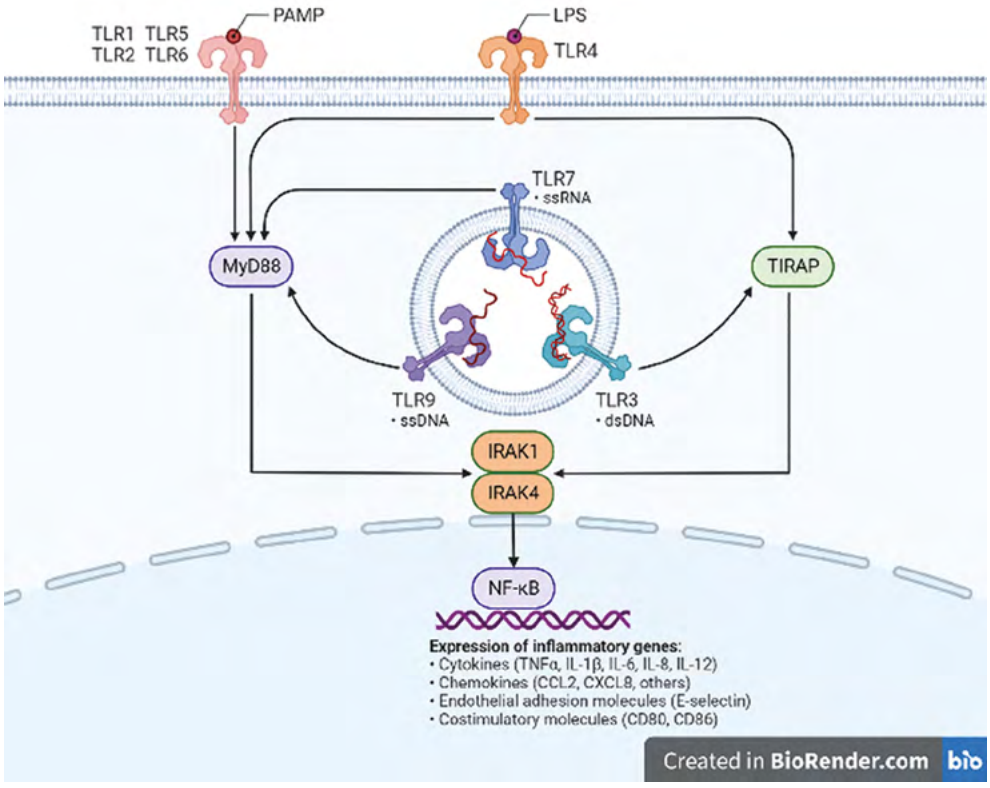

FIGURE 1. The main molecular pathways involved in human defense against pyogenic bacteria. **A.** The Toll-like receptor (TLR) pathway: TLRs, expressed in the plasma membrane (TLR1, TLR2, TLR4, TLR5, TLR6) and endosome (TLR3, TLR7, TLR8, TLR9) of leukocytes, sense molecules synthesized by bacteria and other microorganisms, called pathogen-associated molecular patterns (PAMPs), with a subsequent activation of an early innate inflammatory response. TLR intracellular domain recruits cytosolic adapters myeloid differentiation primary response protein-88 (MyD88) and TLR/interleukin 1 receptor (IL-1R) (TIR) domain-containing adaptor protein (TIRAP), leading to the Interleukin-1 receptor-associated kinase (IRAK) complex (IRAK-1 and IRAK-4)-mediated activation of nuclear factor κ-B (NFkB) 1/2. The signaling cascade leads to the release of inflammatory cytokines (IL-1β, IL-6, IL-8, IL-12 and tumor necrosis factor α (TNFα). *Le principali vie molecolari coinvolte nella difesa umana contro i batteri piogeni . **A.** La via del recettore Toll-like (TLR): i TLR, espressi sulla membrana plasmatica (TLR1, TLR2, TLR4, TLR5, TLR6) ed endosomiale (TLR3, TLR7, TLR8, TLR9) dei leucociti, riconoscono molecole sintetizzate da batteri e altri microrganismi, definite profili molecolari associati ai patogeni (PAMP), determinando l'attivazione di una risposta infiammatoria innata precoce. Il dominio intracellulare dei TLR recluta i seguenti adattatori citosolici: la proteina 88 di risposta primaria alla differenziazione mieloide (MyD88) e la proteina adattatrice contenente il dominio del recettore del TLR e dell'interleuchina-1 (TIRAP), al fine di attivare il fattore nucleare κ-B (NFkB) 1/2 attraverso il complesso dimerico delle chinasi 1 e 4 associate al recettore dell'interleuchina-1 (IRAK-1/IRAK-4). La cascata del segnale esita nel rilascio di citochine infiammatorie (IL-1β, IL-6, IL-8, IL-12 e fattore di necrosi tumorale alfa (TNFα).*

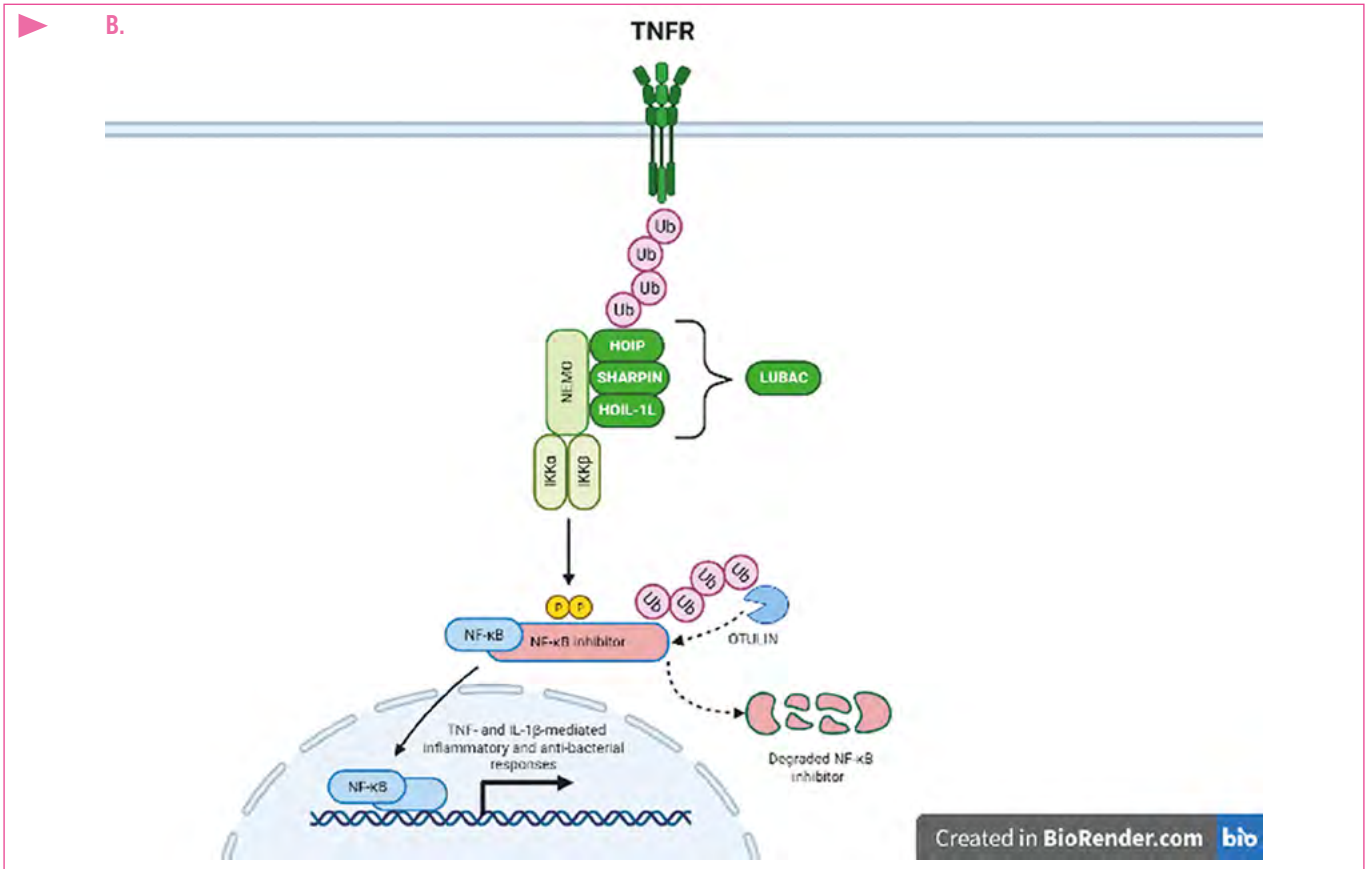

FIGURE 1. **B.** The linear-ubiquitin-chain assembly complex (LUBAC)-dependent activation of NF-kB: LUBAC is responsible for the proteasomal degradation of NF-kB inhibitors through the ubiquitin proteasome system, leading to NF-kB activation upon receptor stimulation by microbial antigens, with a subsequent NF-kB essential modulator (NEMO)/NF-kB inhibitor kinase (IKKα)/IKKβ complex-mediated phosphorylation and ubiquitin-driven degradation of NF-kB inhibitors, modulating TNF- and IL-1β-dependent inflammatory and anti-bacterial responses. LUBAC deficiency causes hyper-inflammation, muscular amylopectinosis and pyogenic susceptibility. ***B.*** *L'attivazione di NF-kB dipendente dal complesso lineare dell'ubiquitina a catena (LUBAC): LUBAC è responsabile della degradazione proteosomica degli inibitori di NF-kB attraverso il sistema ubiquitina-proteosoma, che porta all'attivazione di NF-kB dopo la stimolazione del recettore da parte di antigeni microbici, con successivo assemblaggio del complesso formato dal modulatore essenziale di NF-kB (NEMO) e dalle chinasi alfa e beta inibitrici di NF-kB (IKKα/IKKβ), che fosforila e degrada mediante il sistema ubiquitina-proteosoma gli inibitori di NF-kB, modulando l'infiammazione e la risposte antibatteriche. La carenza di LUBAC causa iperinfiammazione, amilopectinosi muscolare e suscettibilità ai piogeni.*

This constellation of phenotypes constitutes the focus of an emerging research field addressing the common pathogenic mechanisms and the complex interconnections among these apparently unlinked manifestations, often coexisting in combination in single patients [2].

The widespread use of high-throughput genomic technologies, including next generation sequencing (NGS), has led to major advances in molecular genetics, and is speeding up the discovery of novel genes and pathways involved in immune system homeostasis, defined as protective and self-limiting responses to microorganisms without immune dysregulation [2,3].

An increasing number of studies have demonstrated that genetic defects impairing non-redundant or tissue-specific key pathways are involved in the pathogenesis of intrinsic and innate IEIs, manifesting as susceptibility to a narrow spectrum of pathogens expressing in terms of severe, critical, or even potentially life-threatening infections, occurring generally in otherwise healthy individuals irrespective of age, number of episodes, familial infectious history, microorganism' pathogenicity and epidemiology. These findings gradually led to overcoming the classical so-called "immunological-first" approach, based on infectious and immunological phenotype correlations in which a wide spectrum of microbial susceptibility corresponds to detectable immunophenotype alterations deserving molecular confirmation, fitting in case of conventional primary immune deficiencies (PIDs), in favor of a first-intention genetic approach to be applied in patients with an infectious phenotype and a clinical history highly suggestive for an innate and intrinsic IEI.

These considerations hold true in particular for genetic defects impairing interleukin (IL)-6/IL-10/IL-17/IL-22, IFNγ/IL-12, and TLR3/IFNα/β/λ pathways, underlying susceptibility to invasive, both acute and chronic pyogenic/fungal [4,5], mycobacterial [6], and viral disease[7,8] in otherwise healthy individuals, respectively.

Furthermore, dysfunction of the aforementioned pathways is not always due to a genetic defect causing transcriptional or post-tran-

C.

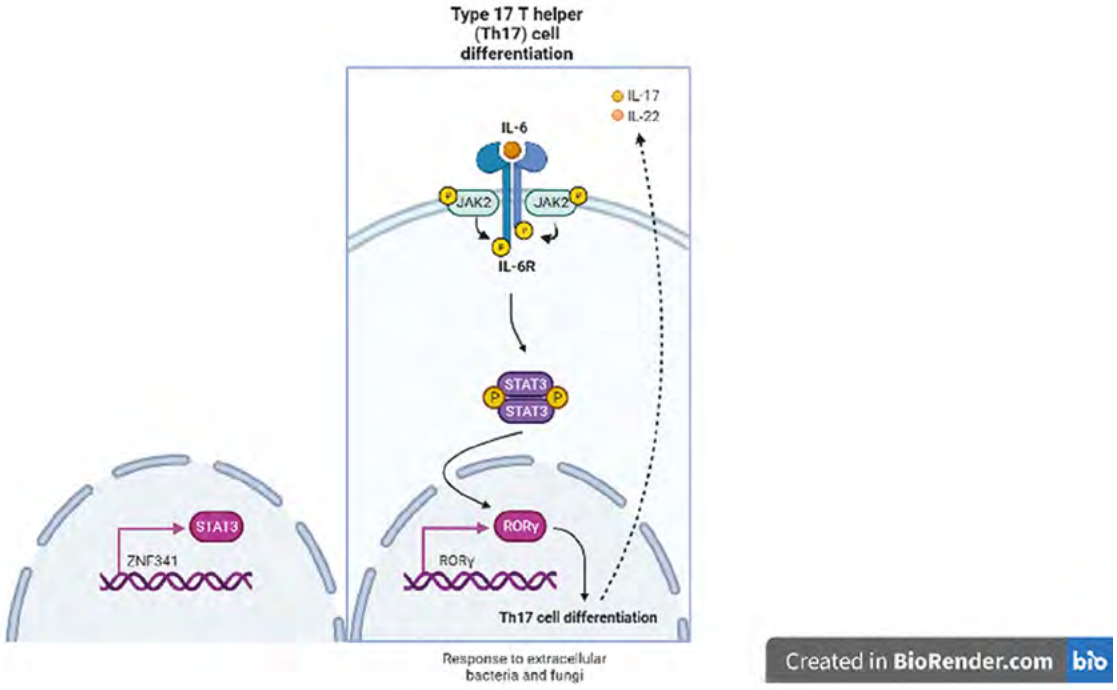

FIGURE 1. C. The IL-6/signal transducer and activator of transcription 3 (STAT3)/IL-17 signaling cascade: IL-6 signaling machinery upon IL6 receptor (IL6R) activation involves the Janus kinase (JAK2)-driven tyrosine phosphorylation of STAT3, whose transcription is enhanced by the zinc finger transcription factor ZNF341, binding to the STAT3 promoter region. STAT3 drives T helper 17 differentiation through the retinoic acid receptor-related orphan receptor γ (RORγ), encoded by RORC gene, essential for anti-bacterial and anti-fungal immunity. ***C.*** *La via del segnale formata dall'IL-6, dal trasduttore del segnale e dall'attivatore della trascrizione 3 (STAT3) e dall'IL-17: il meccanismo di segnalazione dell'IL-6, in seguito all'attivazione del recettore dell'IL6 (IL6R), coinvolge la fosforilazione dei residui di tirosina di STAT3 guidata dalle chinasi Janus (JAK2), la cui trascrizione è potenziata dal fattore di trascrizione a dita di zinco 341 (ZNF341), che si lega alla regione promotrice di STAT3. STAT3 guida la differenziazione dei linfociti T helper 17 attraverso il recettore orfano γ correlato al recettore dell'acido retinoico (RORγ), codificato dal gene RORC, essenziale per l'immunità antibatterica e antimicotica.*

scriptional abnormalities, but can sometimes be attributable to the presence of neutralizing autoantibodies against key cytokines of the signaling cascade (i.e. anti-IL-6, anti-IL-17A/F antibodies [4]) resulting in an overlapping clinical phenotype referred to as an immune phenocopy of an IEI [9]. A clarifying example of IEI phenocopy is represented by the presence of anti-interferon type 1 autoantibodies (IFN-I), which gives a particular susceptibility towards developing severe SARS-CoV-2 infection in otherwise healthy patients [8].

In this ever-changing context, the so-called conventional PIDs – such as innate IEIs affecting complement or phagocyte function or adaptive IEIs altering the cellular and/or humoral compartment diagnosable through basic first-level and second-level testing – are now only a corollary of the ever-expanding universe of IEIs, possibly presenting with shaded clinical phenotypes and blurred immunophenotypical abnormalities, detectable only by a third-line genetic work-up [10].

The purpose of this review is to provide clinicians useful clinical criteria to raise innate and intrinsic IEIs suspicion in the context of infectious susceptibility, identify subjects needing third-line investigations, and hypothesize the most likely underlying molecular defect based on clinical and laboratory data.

In fact, diagnosis of intrinsic and innate IEIs expressing with a predisposition to infections is a challenging achievement, even more than conventional PIDs, as first-level and second-level laboratory investigations often show non-relevant abnormalities or even result normal, causing an improper stop of the diagnostic process and a missed involvement of immunologists and geneticists, which is essential to guide focused third-line functional and molecular assays.

Here we performed an in-depth dissection of molecular pathways and signatures involved in genetic susceptibility to infections, offering an all-round perspective about innate and intrinsic IEIs to infections systematized for category of pathogens. We address the main signs suggestive for IEI-related infectious susceptibility relying on a "bedside to the bench" approach, starting from clinical scenarios, going through the key determinants of host defense against the specific spectrum of pathogens involved, and finishing with the proper functional and molecular tests adopted by reason of a specific clinical- and basic laboratory-guided suspicion.

INTRINSIC AND INNATE IEIs TO PYOGENIC INFECTIONS

The most frequently isolated bacteria during pyogenic infections belong to the genus *Staphylococcus*, *Streptococcus*, *Haemophilus*,

Nocardia, *Moraxella*, *Salmonella*, *Pseudomonas*, *Burkholderia* and *Serratia*.

The main clinical scenarios suggestive for an IEI-related susceptibility to pyogenic bacteria in otherwise healthy children and adults can be described by the following situations:

- occurrence of at least one severe, critical, potentially life-threatening infection, either systemic (bacteraemia) or focal (meningitis, pneumonia, deep cerebral, peritoneal, hepato-splenic or muscular abscesses, arthritis, osteomyelitis);
- occurrence of at least two episodes of diffuse/severe staphylococcal muco-cutaneous infections, such as decalvans folliculitis, blepharitis, pustules, furunculosis, cellulitis, abscesses, and suppurative lymphadenitis [4,10].

The main determinants hampering host defense against pyogenic

TABLE I. Functional and molecular testing to diagnose inborn errors of immunity-related susceptibility to pyogenic, fungal, mycobacterial and viral infections. *Test funzionali e molecolari per diagnosticare errori congeniti di suscettibilità correlata all'immunità, alle infezioni piogeniche, fungine, micobatteriche e virali.*

Spectrum of susceptibility	Functional testing	Genetic testing
Pyogenic bacterial susceptibility	• CD62L shedding assay • IL-17/IL-22 release assay • IL-6, IL-17A/F autoantibodies detection	*RPSA, HMOX, GJA1, ZIC3, IRAK1, IRAK4, MYD88, TIRAP, IL-17RA, STAT1, TLR8*, and *OTULIN, IRF4* mutations
Fungal susceptibility	• IL-17/IL-22/GM-CSF release assays • IL-12/IFNγ release assay • IL-6, IL-17A/F, GM-CSF autoantibodies detection	*IL-17F, IL-17RA, IL-17RC, TRAF3IP2, MAPK8, RORC, STAT1, STAT3, IRF8*, and *CARD9* mutations
Mycobacterial susceptibility	• L-12/IFNγ release assay • IL-12Rγ1/IFNγR1 expression and post-receptor STAT1/STAT4 phosphorylation assays • IFNγ autoantibodies detection	*CYBB, IFNG, IFNGR1, IFNGR2, IL-12B, IL12-RB1, IL12-RB2, IL-23R, IRF8, ISG15, JAK1, NEMO (IKBKG), RORC, SPPL2A, STAT1, TBX21, TYK2, ZNFX1* mutations
Viral susceptibility	• Type I IFNα/β-release assay • CD62L shedding assay • Type I IFNα/β autoantibodies detection • NK/T cell degranulation and cytotoxicity assays, along with perforin expression assays (only in case of EBV susceptibility)	*ATG4A, MAP1LC3B2, DBR1, IFNAR1, IRF3, SNORA31, TBK1, TLR3, TRAF3, TRIF, UNC93B1* mutations (severe HSV encephalitis)
		FCGR3A, POLR3A, POLR3C, POLR3F mutations (VZV neurological susceptibility)
		NOS2 mutations (disseminated CMV infection)
		CD27, CD70, ITK, MAGT1, OX40, SH2D1A, XIAP mutations (EBV susceptibility)
		TNFRSF4 mutations (HHV8-related Kaposi's sarcoma)
		DBR1, IFIH1, TLR3 mutations (enterovirus rhombencephalitis)
		IRF3, IRF7, IRF9, RIG-1, TLR3, UNC93B1 mutations (Influenza A susceptibility)
		IFIH1 mutations (RNA viruses respiratory/gastro-intestinal susceptibility)
		IFNAR1, IFNAR2, IRF3, IRF7, TBK1, TICAM1, TLR3, TLR7, UNC93B1 mutations (SARS-CoV-2 susceptibility)
		OAS1, OAS2, RNASEL mutations (SARS-CoV-2-related MIS-C)
		IL18BP mutations (fulminant Hepatitis A viral infection)
		IFNAR1, IFNAR2, IRF9, STAT2 mutations (live-attenuated vaccine strains-related severe infections)
		CD28, CIB1, CXCR4, FCGR3A, TCM6, TCM8 mutations (βHPV susceptibility)

CMV: cytomegalovirus; EBV: Epstein-Barr virus; GM-CSF: granulocyte-macrophage colony-stimulating factor; HHV8: human herpes virus 8; HPV: human papilloma virus; HSV: herpes simplex virus; IFN: interferon; IL: interleukin; MIS-C: multisystem inflammatory syndrome in children; R: receptor; STAT: signal transducer and activator of transcription; VZV: varicella zoster virus.

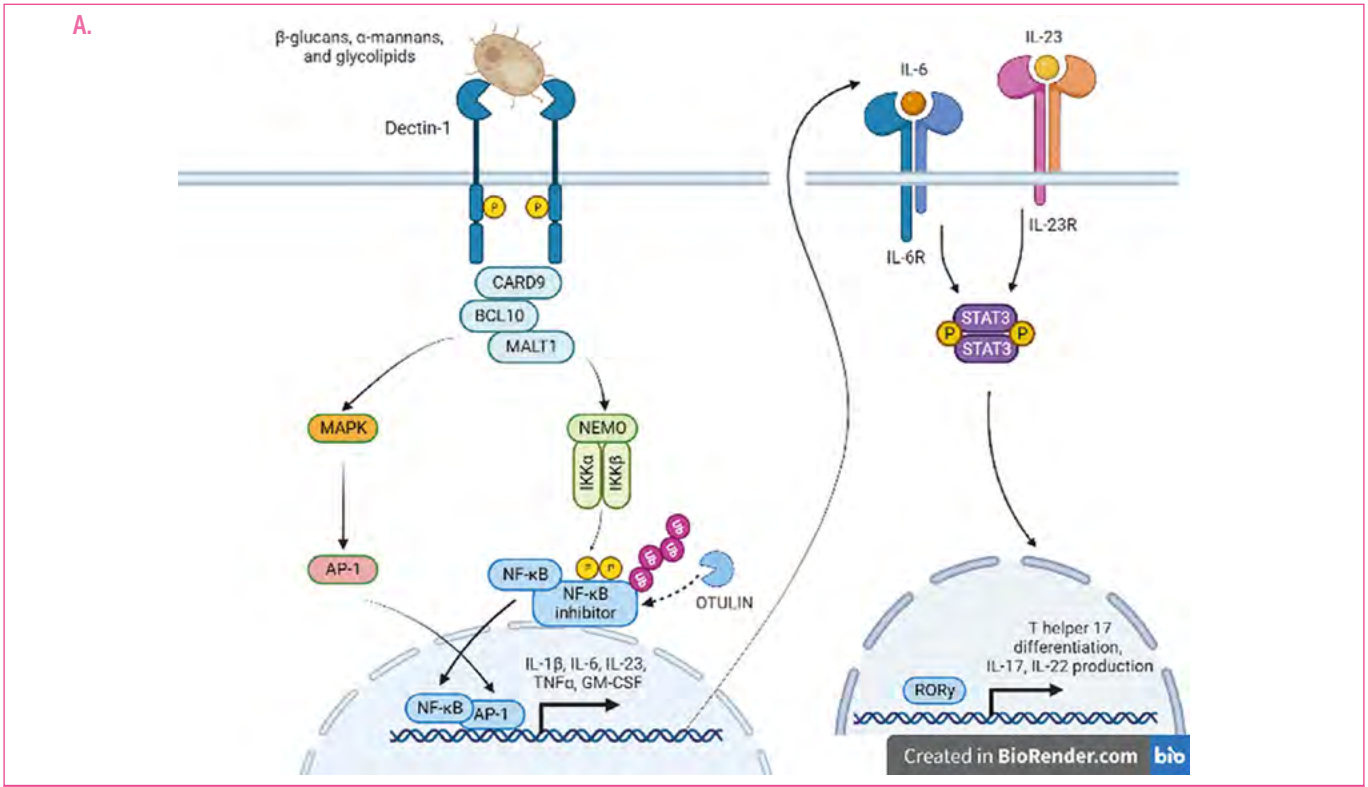

FIGURE 2. The main molecular pathways involved in human defense against fungi. **A.** Caspase recruitment domain-containing protein 9 (CARD9)-mediated immunity towards invasive fungal disease: Upon ligation of C-type lectin pattern recognition receptors (PRRs) (i.e., Dectins) with fungal β-glucans, α-mannans, and glycolipids, CARD9/B-cell leukemia-lymphoma protein 10 (BCL10)/mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1) complex assembles and activates NF-kB and mitogen-activated protein kinase (MAPK) signaling cascade, resulting in the translocation of NF-kB and activator protein 1 (AP-1) into the nucleus with the subsequent production of proinflammatory cytokines by phagocytes and epithelial cells, such as IL-1β, IL-6, IL-23, TNFα, and granulocyte-macrophage colony-stimulating factor (GM-CSF). This is the basis of a virtuous circle in which IL-23 promotes GM-CSF production in T cells, which is essential for the ability of T helper 17 cells to drive inflammation and provide an effective IL-17- and IL-22-based anti-fungal response. *Le principali vie molecolari coinvolte nella difesa umana contro i funghi.* ***A.*** *L'immunità mediata dalla proteina 9 contenente il dominio di reclutamento della caspasi (CARD9) nei confronti delle malattie fungine invasive: in seguito al legame dei recettori di riconoscimento dei profili molecolari (PRR), ossia recettori lectinici di tipo C, anche detti dectine, con i β-glucani, α-mannani e glicolipidi fungini, il complesso formato da CARD9, dalla proteina 10 del linfoma e della leucemia a cellule B (BCL10) e dalla proteina 1 di traslocazione linfoide tissutale associata alla mucosa (MALT1, si assembla e attiva la cascata del segnale di NF-kB e della proteina chinasi attivata dal mitogeno (MAPK), con conseguente traslocazione di NF-kB e della proteina attivatrice 1 (AP-1) nel nucleo e produzione da parte dei fagociti e delle cellule epiteliali di citochine proinfiammatorie, come IL-1β, IL-6, IL-23, TNFα e fattore stimolante le colonie di granulociti-macrofagi (GM-CSF). Questa è la base di un circolo virtuoso in cui IL-23 promuove la produzione di GM-CSF nelle cellule T, essenziale per la capacità delle cellule T helper 17 di guidare l'infiammazione e fornire un'efficace risposta anti-fungina.*

bacteria are represented by muco-cutaneous barrier breaches, complement deficiencies, phagocyte numeric and functional defects, humoral and cellular adaptive immunity impairment, and spleen defects, affecting both the white pulp-mediated acquired immune response, based on the crosstalk between antigen presenting cells and B/T lymphocytes, and the marginal zone-mediated innate response, driven by IgM-memory B cells responsible for a T-independent defense against encapsulated bacteria [4,10].

Focusing on innate and intrinsic IEI-related pyogenic susceptibility, the molecular pathways most frequently involved are the Toll-like receptor (TLR) signaling cascade, the linear-ubiquitin-chain assembly complex (LUBAC)-mediated activation of proinflammatory and anti-bacterial nuclear factor kappa B (NF-kB), and the IL-6/signal transducer and activator of transcription 3 (STAT3)/IL-17 signaling machinery driving T helper 17 differentiation [4,10], thoroughly described in Figure 1.

It is worth considering that IL-6/STAT3/IL-17 pathway alterations could be explained by the detection of anti-IL-6 and anti-IL-7A/F antibodies interrupting the signaling cascade, in the absence of detectable genetic defects [4,9].

A few examples of functional tests exploring the abovementioned pathways reported in the literature are listed below:

- CD62L shedding assay upon TLR stimulation, dosing by flow cytometry an adhesion molecule enzymatically cleaved from the surface of activated blood granulocytes, inflammatory monocytes, and naïve T cells, deficient in subjects with impaired TLR signaling [10–12];
- IL-6 and IL-17A/F autoantibodies determination, especially in case of association with polyendocrine disorders/thymoma[9,10,12,13].

However, these investigations, generally developed for research purposes and not for clinical practice, are available only in a few third-level centers.

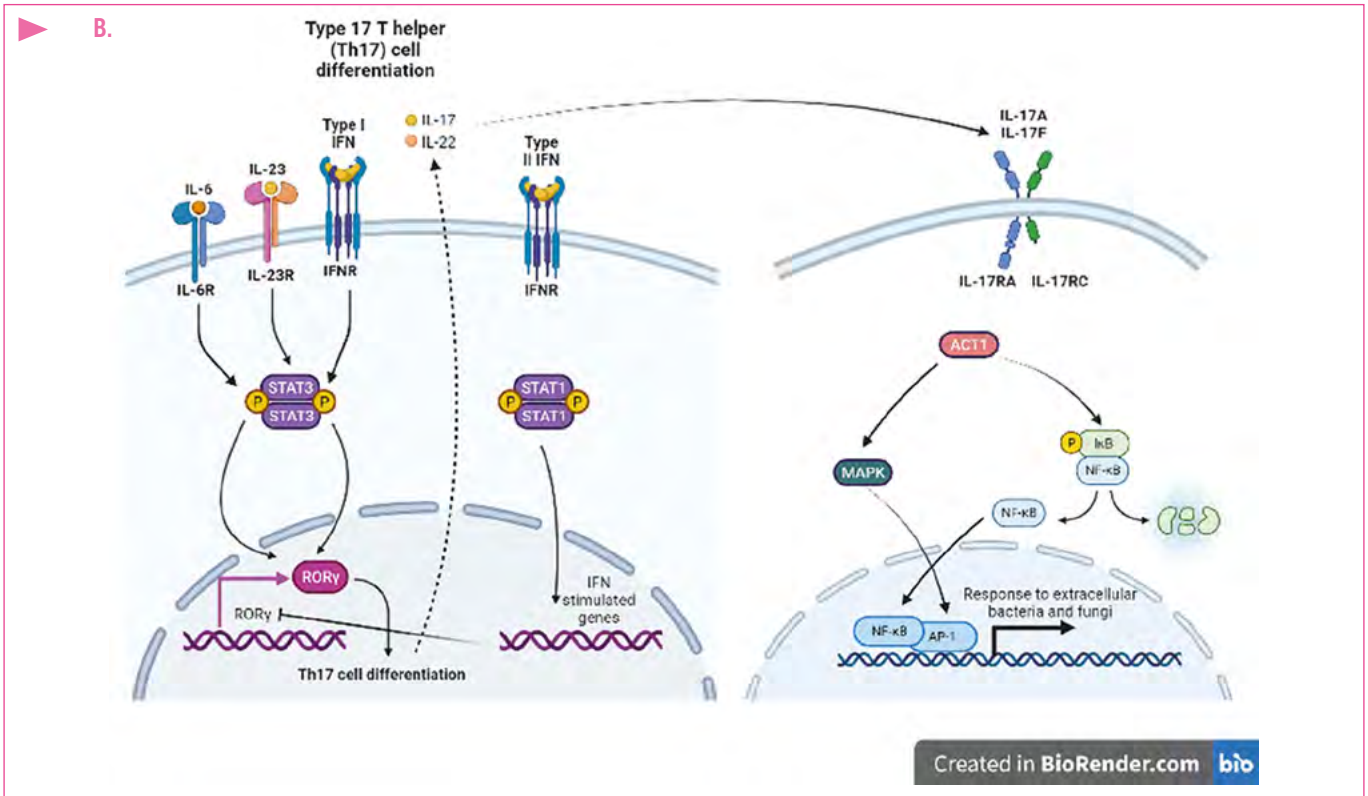

FIGURE 2. **B.** T helper 17-mediated immunity against chronic mucocutaneous candidiadis (CMC): Upon binding of IL-17A and IL-17F to IL-17RA/IL-17RC receptors, nuclear factor-kappa-B activator 1 (ACT1) is recruited, with subsequent activation of NF-kB and MAPK signaling, hesitating in the production of pro-inflammatory cytokines and chemokines, antimicrobial peptides, and matrix metalloproteinases. In T cells, upon IL-6R, IL-23R, and interferon receptors (IFNRs) activation by their ligands, JAK is recruited activating STAT1 and STAT3 signaling through phosphorylation. T helper 17-mediated immunity depend on a delicate balance existing between STAT1 and STAT3 pathway, respectively hampering and promoting an IL-17 signature, to guarantee an effective but self-limiting anti-fungal response through the induction of the maturation of CD34+ hematopoietic precursors into neutrophils. ***B.*** *Immunità mediata dai T helper 17 verso la candidosi mucocutanea cronica (CMC): in seguito al legame dell'IL-17A e IL-17F con i recettori IL-17RA/IL-17RC, l'attivatore nucleare del fattore kappa-B 1 (ACT1), è reclutato con successiva attivazione della via del segnale di NF-kB e MAPK, che esita nella produzione di citochine e chemochine pro-infiammatorie, peptidi antimicrobici e metalloproteasi della matrice. Nelle cellule T, successivamente all'attivazione dei recettori IL-6R, IL-23R e dell'interferone (IFNR) da parte dei rispettivi ligandi, JAK viene reclutato per attivare la via del segnale di STAT1 e STAT3 attraverso la loro fosforilazione. L'immunità mediata dai linfociti T helper 17 dipende da un delicato equilibrio esistente tra la via di STAT1 e STAT3, rispettivamente inibitrice e promotrice del segnale dell'IL-17, che garantisce una risposta antimicotica efficace ma al contempo autolimitantesi, attraverso l'induzione della differenziazione dei precursori emopoietici CD34+ in forma di neutrofili.*

Eventually, confirmatory molecular testing useful in the diagnosis of innate and intrinsic IEI-related pyogenic susceptibility should evaluate the presence of *RPSA*, *HMOX*, *GJA1*, *ZIC3*, *IRAK1*, *IRAK4*, *MYD88*, *TIRAP*, *IL-17RA*, *STAT1*, *TLR8*, and *OTULIN* mutations[4,10,14], taking into account that Whipple's disease by *Tropheryma whipplei* can also be traced back to *IRF4* mutations [15] (Tab. I).

INTRINSIC AND INNATE IEIs TO FUNGAL INFECTIONS

The main clinical scenarios suspicious for IEI-related susceptibility to fungi can be summarized by the following set of criteria occurring in otherwise healthy children and adults:

- chronic mucocutaneous candidiadis (CMC);
- non-central line-related invasive candidiasis or fungemia;
- central nervous system (CNS), respiratory, abdominal, osteo-articular and mucocutaneous invasive fungal infections by *Aspergillus*, *Blastomyces*, *Coccidioides*, *Cryptococcus*, *Histoplasma*, *Mucormycetes, Paracoccidiodes*, *Pneumocystis*, and *Talaromyces*;
- persistent positive fungal culture refractory to appropriate therapy;
- deep/extensive dermal and lymph-nodal dermatophytosis (*Microsporum*, *Epidermophyton*, *Tricophyton*);
- infection by rare yeasts (i.e., malasseziosis, trichosporonosis) and rare moulds (i.e., fusariosis, phaeohyphomycosis) [5,10].

The main host defense mechanisms against fungi are dampened by muco-cutaneous barrier breaches, an ineffective pathogen recognition receptor (PRR)-driven early inflammatory response involving phagocytes and opsonins, and an impaired innate-adaptive immune cells crosstalk resulting in T helper 17 and regulatory T cells numeric and functional defects, failing to provide a protective but self-limiting anti-fungal response [5,16,17].

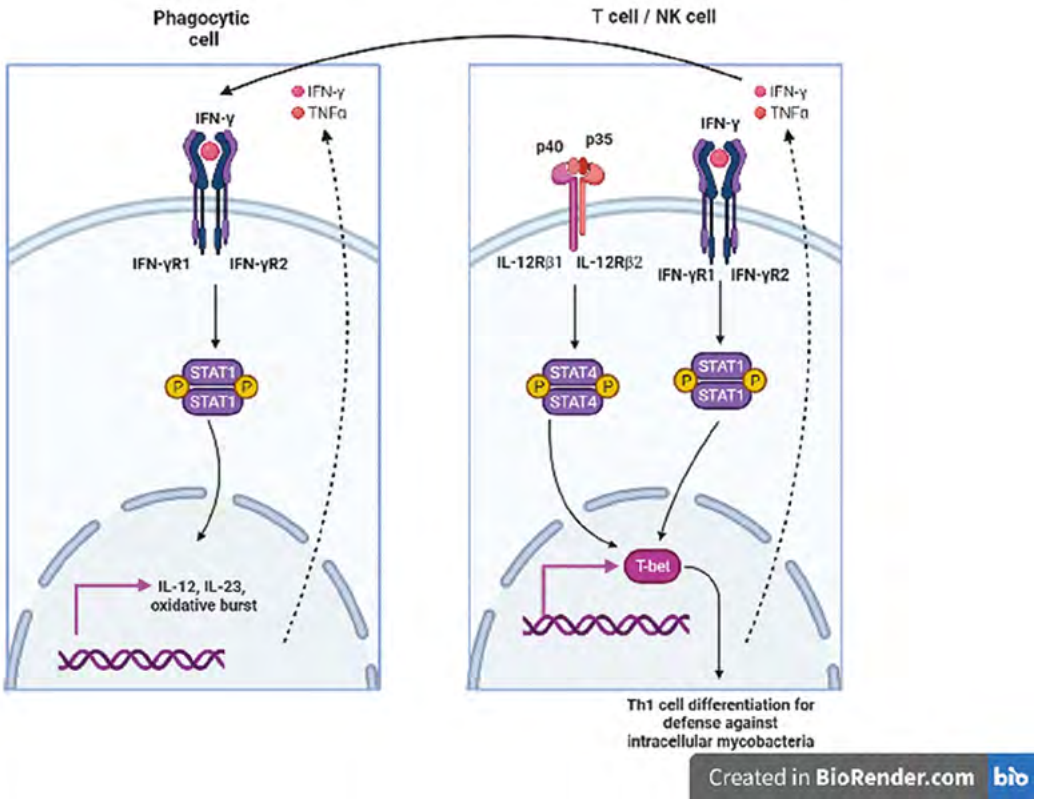

FIGURE 3. The main molecular pathways involved in human defense against mycobacteria. The IL-12/IFNγ axis: Innate immune recognition of mycobacteria by phagocytes results in IL-12 secretion and signalling via heterodimeric receptors IL-12Rβ1/IL-12Pβ2 for IL-12. IL-12 receptor signalling results in IFNγ production by T helper 1 (Th1) cells and natural killer (NK) cells, driving Th1 cell polarization of CD4+ T cells. IFNγ binding to its heterodimeric receptor IFNγR1/IFNγR2 on phagocytes leads to phagocyte activation, including oxidative burst, further IL-12 production, and control of the intracellular mycobacteria infection. *Le principali vie molecolari coinvolte nella difesa umana contro i micobatteri. L'asse IL-12/IFNγ: il riconoscimento immunitario innato dei micobatteri da parte dei fagociti determina la secrezione di IL-12 e l'attivazione della trasduzione del segnale tramite i recettori eterodimerici IL-12Rβ1/IL-12Rβ2 dell'IL-12. L'attivazione del recettore dell'IL-12 determina la produzione di IFNγ da parte delle cellule T helper 1 (Th1) e delle cellule natural killer (NK), guidando la polarizzazione delle cellule T CD4+ a favore dei Th1. Il legame dell'IFNγ al suo recettore eterodimerico IFNγR1/IFNγR2 sui fagociti porta all'attivazione di questi ultimi in termini di potenziamento del burst ossidativo, di ulteriore produzione di IL-12 e di controllo dell'infezione da parte di micobatteri intracellulari.*

The molecular pathways most frequently involved in innate and intrinsic IEI-related fungal susceptibility, comprehensively described in Figure 2, are embodied by the C-type lectin PRRs-mediated caspase recruitment domain-containing protein 9 (CARD9)/B-cell leukemia-lymphoma protein 10 (BCL10)/mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1) complex machinery, which is responsible for the control of invasive fungal disease through NF-kB and mitogen-activated protein kinase (MAPK) activation, and the IL-6/STAT3/IL-17 cascade driving T helper 17 differentiation against CMC, potentially hampered by *STAT1* gain of function (GOF)-driven IFNγ production and by the presence of anti-IL-6 and anti-IL-7A/F antibodies interrupting the signaling mechanism [5,16,17].

Functional tests performed in a few third-level centers for research purpose in patients presenting with clinical signs and a history suggestive for an innate and intrinsic IEI-related fungal susceptibility are the following:

- IL-17/IL-22/GM-CSF release assay upon stimulation of T helper 17 cells, reduced in individuals with altered IL-6/STAT3/IL-17 signaling [10,12].
- IL-12/IFNγ release assay, showing an increased IFNγ production in carriers of *STAT1* GOF [5,10,12];
- IL-6, IL-17A/F and GM-CSF autoantibodies determination, especially in case of association with polyendocrine disorders/thymoma [9,10,12,13].

Eventually, molecular testing to confirm the diagnosis of innate and intrinsic IEI-related fungal susceptibility should search for the presence of *IL-17F*, *IL-17RA*, *IL-17RC*, *TRAF3IP2*, *MAPK8*, *RORC*, *STAT1*, *STAT3*, *IRF8*, and *CARD9* mutations[5,10,14] (Tab. I).

INTRINSIC AND INNATE IEIs TO MYCOBACTERIAL INFECTIONS

The main clinical scenario consistent with an IEI-related susceptibility to mycobacteria can be described by the occurrence of severe,

A.

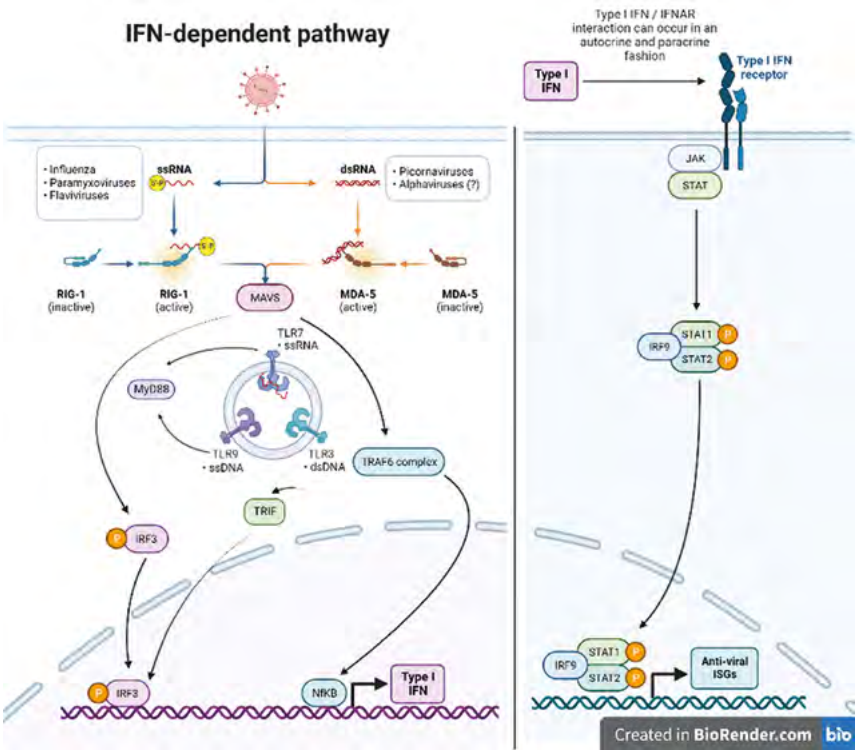

FIGURE 4. The main molecular pathways involved in human defense against viruses. **A.** The IFN-dependent pathway: Membrane-bound (TLRs) and cytosolic (retinoic acid inducible gene 1 [RIG-1], melanoma differentiation association factor 5 [MDA5]) PRRs sense viral nucleic acids, with subsequent production of proinflammatory cytokines and type I IFN upon NF-kB and IFN regulatory transcription factors (IRFs) activation. Type I IFNs bind to IFNAR1 and IFNAR2 receptors in an autocrine and paracrine manner, promoting the expression of antiviral IFN-stimulated genes (ISGs) through the JAK-STAT pathway. *Le principali vie molecolari coinvolte nella difesa umana contro i virus.* ***A.*** *La via del segnale IFN-dipendente: i PRR legati alla membrana (TLR) e i PPR citosolici (codificati dal gene 1 inducibile dall'acido retinoico [RIG-1] e dal gene 5 associato alla differenziazione del melanoma [MDA5]) rilevano gli acidi nucleici virali, con una successiva produzione di citochine proinfiammatorie e IFN di tipo I in seguito all'attivazione di NF-kB e dei fattori di trascrizione regolatori dell'IFN (IRF). Gli IFN di tipo I si legano ai recettori IFNAR1 e IFNAR2 in modo autocrino e paracrino, promuovendo attraverso la via del segnale di JAK-STAT l'espressione di geni ad azione antivirale stimolati dall'IFN (ISG).*

persistent, unusual, recurrent (SPUR) infections by tuberculotic (TB)/non-tuberculotic mycobacteria (NTM), including diseases caused by Bacillus Calmette-Guérin vaccine strains (BCG-osis), in otherwise healthy children and adults[6,10,18].

The main determinant of host defense against mycobacteria is represented by a virtuous innate-adaptive immune system cross-signaling, modulated on a molecular basis by the IL-12/IFNγ axis, in which IL-12-producing activated phagocytes drive IFNγ-synthesizing T helper 1 cell polarization of CD4+ T cells with a subsequent enhanced phagocytic oxidative burst, disrupted in case of *CYBB*-related nicotinamide adenine dinucleotide phosphate oxidase complex dysfunction, leading to an impaired phagocytic respiratory burst limited to monocyte-derived macrophages not affecting monocytes or granulocytes, differently from chronic granulomatous diseases (Fig. 3) [6,19].

The IL-12/IFNγ pathway is regulated at both a transcriptional and post-transcriptional level by 18 different genes, whose defects are responsible for mendelian susceptibility to mycobacterial diseases [6]. Furthermore, IL-12/IFNγ axis can be impaired at a non-molecular level by the presence of IFNγ autoantibodies [9].

Functional tests performed in a few third-level centers for research purpose in patients with a clinical suspicion of innate and intrinsic IEI-related mycobacterial susceptibility are the following:

- sequential IL-12/IFNγ pathway assessment first through Quantiferon-Plus system to detect IFNγ/IL-12 secretion defects and then by flow-cytometry to assess impaired receptor protein expression (IL-12Rγ1/IFNγR1) and to quantify post-receptor STAT1/STAT4 phosphorylation, especially in case of association with invasive fungal infections [10,12,20,21];
- IFNγ autoantibodies detection, especially in case of late-onset susceptibility to BCG/NTM associated with varicella zoster virus (VZV) reactivation and salmonellosis [9,10,12,13,22].

Confirmatory molecular testing is useful in the diagnosis of innate and intrinsic IEI-related mycobacterial susceptibility and should evaluate the presence of *CYBB*, *IFNG*, *IFNGR1*, *IFNGR2*, *IL-12B*, *IL12-RB1*, *IL12-RB2*, *IL-23R*, *IRF8*, *ISG15*, *JAK1*, *NEMO* (*IKBKG*), *RORC*, *SPPL2A*, *STAT1*, *TBX21*, *TYK2*, and *ZNFX1* mutations[6,10,14] (Tab. I).

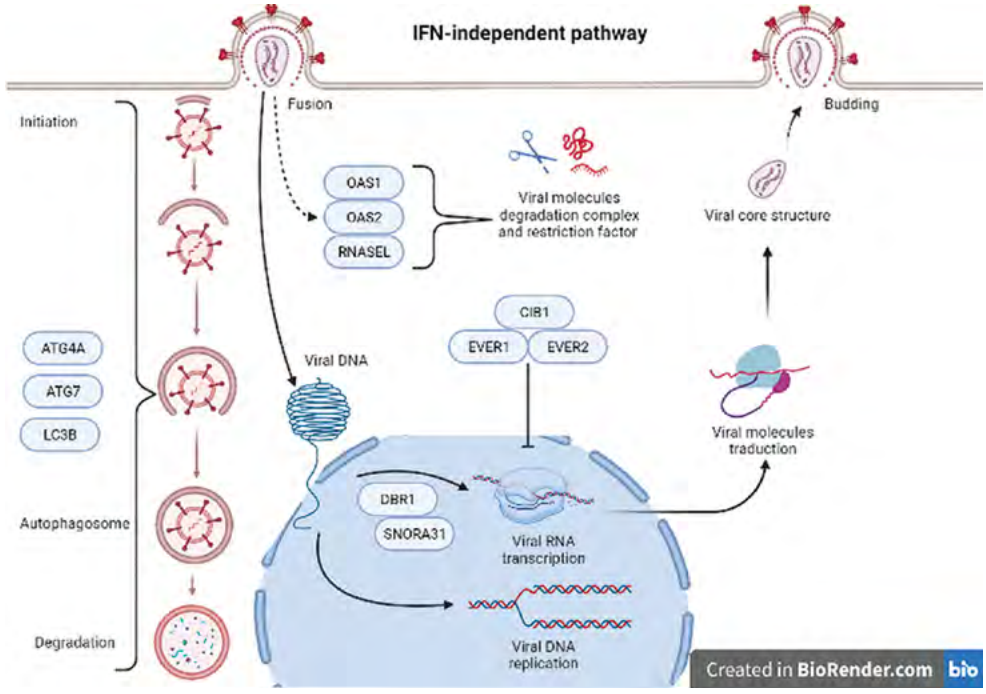

FIGURE 4. B. The IFN-independent pathway: Defects in the *ATG4A*, *ATG7* and *LC3B* genes disrupt autophagic viral degradation, playing a key role in some viral infections of the central nervous system (CNS). Impairment of cellular RNA lariat formation and disturbed uridine to pseudouridine isomerization of small nucleolar RNA and ribosomal RNA, respectively, due to DBR1 and SNORA31 mutations, affect regulatory RNA-mediated blockade of viral RNA transcription, thus impacting the severity of some viral CNS infections. The calcium- and integrin-binding protein-1 (CIB1)/Epidermodysplasia verruciformis protein 1 (EVER1)/EVER2 complex assembles in keratinocytes restricting the transcription of β human papilloma virus (HPV) minichromosome, avoiding severe βHPV complications. The cytosolic dsRNA-sensing oligoadenylate synthetase 1 and 2, encoded by OAS1 and OAS2 genes, activate the ssRNA-degrading RNase L (RNASEL gene), acting as viral restriction factor and modulating phagocytic inflammatory response to viruses, including SARS-CoV-2. ***B.*** *La via del segnale IFN-indipendente: i difetti nei geni ATG4A, ATG7 e LC3B interrompono la degradazione virale autofagica, svolgendo un ruolo chiave in alcune infezioni virali del sistema nervoso centrale (SNC). A livello cellulare, la compromissione della formazione dell'RNA lariat e dell'isomerizzazione da uridina a pseudouridina dell'RNA nucleolare e ribosomiale, rispettivamente a causa delle mutazioni a livello dei geni DBR1 e SNORA31, ostacolano il blocco della trascrizione dell'RNA virale da parte dell'RNA regolatorio, impattando sulla gravità di alcune infezioni virali del sistema nervoso centrale. Il complesso formato dalla proteina 1 legante il calcio e l'integrina (CIB1) e dalle proteine 1 e 2 dell'epidermodisplasia verruciforme (EVER1/EVER2) si assembla nei cheratinociti limitando la trascrizione del minicromosoma del virus del papilloma umano beta (βHPV), evitando gravi complicanze infettive. L'oligoadenilato sintetasi 1 e 2 citosolica sensibile al dsRNA, codificata dai geni OAS1 e OAS2, attiva la RNasi L degradante il ssRNA, codificata dal gene RNASEL, agendo come fattore di restrizione virale e modulando la risposta infiammatoria dei fagociti ai virus, incluso il SARS-CoV-2.*

INTRINSIC AND INNATE IEIs TO VIRAL INFECTIONS

The main clinical scenarios suspicious for an IEI-related susceptibility to viruses in otherwise healthy patients are the following:

- severe herpes simplex virus (HSV) encephalitis (*ATG4A*, *MAP1LC3B2*, *DBR1*, *IFNAR1*, *IRF3*, *SNORA31*, *TBK1*, *TLR3*, *TRAF3*, *TRIF*, *UNC93B1* genes);
- severe CNS infection by VZV (*FCGR3A*, *POLR3A*, *POLR3C*, *POLR3F* genes);
- disseminated cytomegalovirus (CMV) infection (*NOS2* gene);
- disseminated Epstein-Barr (EBV) infection-related haemophagocytosis, malignant and non-malignant lymphoproliferation (*CD27*, *CD70*, *ITK*, *MAGT1*, *OX40*, *SH2D1A*, *XIAP* genes);
- human herpes virus 8-related Kaposi's sarcoma (*TNFRSF4* gene);
- childhood life-threatening enterovirus rhombencephalitis (*DBR1*, *IFIH1*, *TLR3* genes);
- childhood primary influenza A-related infection complicated by acute respiratory distress syndrome (ARDS) (*IRF3*, *IRF7*, *IRF9*, *RIG-1*, *TLR3*, *UNC93B1* genes);
- childhood recurrent enterovirus, rhinovirus and respiratory syncytial virus (RSV) infections of the respiratory/gastro-intestinal tract requiring a prolonged hospitalization with continuous positive airway pressure/invasive ventilation and/or parenteral rehydration (*IFIH1* gene);
- SARS-CoV-2-related ARDS (*IFNAR1*, *IFNAR2*, *IRF3*, *IRF7*, *TBK1*, *TICAM1*, *TLR3*, *TLR7*, *UNC93B1* genes) and multisystem inflammatory syndrome in children (MIS-C) (*OAS1*, *OAS2*, *RNASEL* genes);
- fulminant hepatitis A viral infection (*IL-18BP* gene);
- live-attenuated vaccine strain-related severe infections (*IFNAR1*, *IFNAR2*, *IRF9*, *STAT2* genes);
- β human papilloma virus (HPV) infection-related tree-man syndrome, mucocutaneous carcinoma, and diffuse/recurrent skyn warts and mucous condyloma/papillomatosis (*CD28*, *CIB1*, *CXCR4*, *FCGR3A*, *TCM6*, *TCM8* genes) [7,8,10,23].

The main host defense mechanisms against viruses are represented by muco-cutaneous barriers, both structural and immunological through the cellular restriction factor complex of viral genes, innate immunity-driven autophagy pathways, cellular RNA lariat formation and small nucleolar/ribosomal RNA isomerization blocking viral RNA transcription, TLR-driven type I IFN release upon innate-adaptive immune system cross-talk, and cytotoxic killing of infected cells by NK and T cells [7,24–27].

The molecular pathways most frequently involved in innate and intrinsic IEI-related viral susceptibility, comprehensively described in Figure 4, can be divided into a type I IFN-dependent and -independent mechanism.

The former, responsible for the control of HSV, Influenza A, SARS-CoV-2, RSV, Rhinovirus and Enterovirus infections, is activated by membrane-bound and cytosolic PRRs sensing viral nucleic acids, with a subsequent production of proinflammatory cytokines and type I IFN governed by NF-kB and IFN regulatory transcription factors.

The latter on the one hand avoids severe CNS infections by HSV relying on both autophagic viral degradation and regulatory RNA-mediated blockade of viral RNA transcription. On the other hand it prevents destructive βHPV infections through the calcium- and integrin-binding protein-1 (CIB1)/Epidermodysplasia verruciformis protein 1 (EVER1)/EVER2 complex, restricting the transcription of the viral minichromosome [7,24–2].

It is worth noting that cases of critical SARS-CoV-2 infection in otherwise healthy patients can be attributed to type I IFN autoantibodies impairing the IFN-dependent antiviral response [8], whose hyperactivation due to a deficiency in cytosolic PRRs and/or in viral nucleic acid degrading enzymes can result in a SARS-CoV-2-related MIS-C [23].

IL-18BP mutation-related fulminant A hepatitis and *NOS2* mutation-related disseminated CMV infection deserve a separate discussion, as *IL-18BP* defect results in an exaggerated IFNγ-driven NK cytotoxicity towards infected hepatocytes [28], while *NOS2* function needs to be further investigated, although being probably involved in an IFNγ-mediated pathway [29].

Regarding EBV susceptibility, it is not included in the spectrum of innate and intrinsic IEIs, being defined a disease of immune dysregulation due to impaired granule-dependent and -independent CD8+/NK-mediated cytotoxic killing of EBV-infected B cells and apoptotic defects, with protracted T and NK cells expansion, cytokine overproduction and persistent hyperinflammation [26,30,31].

Functional tests performed in a few third-level centers for research purposes in patients with a suspected intrinsic and innate IEI-related susceptibility to viral infections, such as type I IFN release assay and/or CD62L shedding assay, as well as type I IFN autoantibodies determination, are reliable only in patients with an impaired IFN-dependent signaling pathway, and is normal in subjects with a defective IFN-independent antiviral defense, which can be detected only by molecular analysis [10,12,32].

Functional tests to explore EBV susceptibility are NK/T cell degranulation and cytotoxicity assays, along with perforin expression assays [10,12,26].

Genetic testing to confirm the diagnosis of IEI-related viral susceptibility should rely on different targeted gene panels or single gene sequencing applied according to a clinically and functionally oriented IEI suspicion [7,8,10] (Tab. I).

CONCLUSIONS

The genetic theory of infectious diseases considers susceptibility to infections and pathogenic mutations as a continuum in the ever-expanding universe of IEIs, including conventional and non-conventional forms. While the former, the so-called PIDs, often display a wide spectrum proneness to infections and associated with immune dysregulation and altered lymphocyte typization, the latter, affecting intrinsic and innate immunity, present with a predisposition to a restricted spectrum of pathogens in otherwise healthy patients in absence of relevant immunophenotype aberrations; thus, it is likely that the infectious disease physician is the first medical professional encountered by patients with an intrinsic and innate IEI, diagnosable only by third-level functional and genetic testing.

In this context, we provide clinically useful hints on when and how to refer patients with infections to advanced immunological and molecular diagnostics, available in only a few third-level centers, highlighting the importance of a multidisciplinary approach involving geneticists, immunologists, microbiologists and infectious disease specialists, given that to date large size studies reliably assessing clinical and laboratory risk factors for intrinsic and innate IEIs are lacking.

The two main future challenges are to design further studies addressing the complex interplay between microbiological, immunological, and genetic factors in IEI patients, and to translate these findings into a clinical benefit, such as a prompt patient-tailored management, as occurs in subjects with an impaired IFN-dependent response receiving supplementary IFN therapy during SARS-CoV-2 and mycobacterial infections and in individuals with *STAT1* GOF treated with Janus kinase inhibitor for CMC [33].

TAKE HOME MESSAGES

- When should an infectious disease clinician suspect an intrinsic and innate inborn error of immunity (IEI) and ask for immunologic counselling in a patient referred for an infection?
  - In case of susceptibility to a narrow spectrum of pathogens expressing in terms of severe, critical, or even potentially life-threatening infections, generally occurring in otherwise healthy individuals irrespective of age, number of episodes, familial infectious history, microorganism' pathogenicity and epidemiology.
- What diagnostic tests should be performed?
  - After an extremely accurate medical history, if the clinical scenario is consistent with an intrinsic and innate IEI, the immunologist can rely on a first-intention genetic approach exploring the molecular pathways most frequently involved in the patient's spectrum of infectious susceptibility.

Contributed by the Authors

F.C. conceived the idea. M.M. drafted the manuscript. M.M., D.Z. and F.C. conceptualized the aims for this manuscript and reviewed it, providing critical feedback. All authors have read and agreed to the published version of the manuscript.

Ethical statement

The article is unpublished, not simultaneously submitted to another journal and complies with current legislation on research ethics.

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