Inflammasome genetics and complex diseases: a comprehensive review

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Abstract

The inflammasome is a cytoplasmic multiprotein complex responsible for the activation of inflammatory caspases (caspase-1, -4, and -5) in response to pathogen- and/or damage-associated molecular patterns or to homeostasis-altering molecular pathways, and for the consequent release of the pro-inflammatory cytokines interleukin (IL)-1β and IL-18. Taking into account the complexity of inflammasome activation and that several regulatory steps are involved in maintaining its physiologic role in homeostasis and innate immune response, it does not surprise that several genetic variants in inflammasome components have been associated with common pathologies in the general population, such as autoimmune disorders, cardiovascular diseases, obesity and associated metabolic syndrome, neurodegenerative diseases, and cancer. Moreover, the susceptibility to infectious agents and/or to develop severe complications during infections also has been related to inflammasome genetics. In this work, we revised genetic association studies about polymorphisms of main inflammasome genes in sterile as well as infectious diseases, trying to depict the genetic contribution of inflammasome in disease pathogenesis.

Introduction

Perturbations in cellular homeostasis by microbial or endogenous danger signals are sensed by cytosolic innate pattern recognition receptors (PRRs) and trigger downstream signaling pathways leading to inflammatory response to protect the host and restore homeostasis. The same mechanisms involved in inflammation and host protection, however, can also cause (or contribute to) pathologies characterized by dysregulated (acute or chronic) inflammation. In the last decades, inflammation has been discovered to heavily contribute to the pathogenesis of the majority of complex diseases in the general population, as autoimmune diseases, cancer, cardiovascular, metabolic, and neurodegenerative diseases.

The inflammasome is a cytoplasmic multiprotein complex responsible for the activation of inflammatory caspases (namely, caspase-1, -4, and -5) in response to pathogen- and/or damage-associated molecular patterns (PAMPs and DAMPs, respectively) [1] or to homeostasis-altering molecular pathways (HAMPs) [2], and for the consequent release of the pro-inflammatory cytokines interleukin (IL)-1β and IL-18, and gasdermin-D, the effector molecule of the inflammatory cell death named pyroptosis [3] (Fig. 1).

Inflammasome sensors belong to PRRs and contain a pyrin domain (PYD) and/or a caspase-recruiting domain (CARD), by which, once activated, they become able to recruit, through the interaction with the adaptor protein ASC (a PYD and CARD containing protein), or directly (through homotypic interactions CARD–CARD) the inflammatory caspases and finally promote the autocleavage of the pro-caspases in biologically active caspases. In turn, active caspases cleave pro-IL-1β, pro-IL-18, and gasdermin-D, depending on the cytosolic availability of the respective precursors.

Rare gain-of-function variants in inflammasome genes are implicated in hereditary inflammatory diseases (hereditary auto-inflammatory syndromes) characterized by...
uncontrolled production of IL-1ß and/or IL-18, the so-called inflammasomopathies (largely reviewed by Manthiram et al. [4]). These syndromes result from genetic-determined activation of specific cytosolic receptors (NLRP1, NLRP3, NLRC4, pyrin/MEFV) therefore leading to a diminished activation threshold of inflammasome complex.

Inflammasome receptors belong to distinct PRRs families: nucleotide-binding domain (NBD or NACHT) and leucine-rich repeats (LRRs) containing receptors (NLRs), such as NLRP1, NLRP3, NLRC4, NAIP; PYD and HIN domain-containing receptors (PYHIN), such as AIM2, IFI16; or PYD domain-containing proteins, such as pyrin/MEFV (Fig. 1). They are generally present in the cytosol as conformational inactive molecules by the biochemical interaction between distinct domains (close conformation), such as NACHT and LRRs domains in NLRP3 and NLRC4, and PYHIN domains, as for AIM2 [8] and pyrin [7]. Moreover, regulatory proteins have been described to contribute for the inactive/“closed” conformation of some receptors, such as CARD8 [9] and NEK7 [10] for NLRP3 (NLRP3 inhibitor and activator, respectively).

The apparent redundancy in inflammasome sensors is partially explained taking in account their specific recognition of pathogen or damage. Some receptors detect a definite molecular pattern, such as NAIP and bacterial flagellin [11], AIM2 and IFI16, and cytosolic and/or nuclear double stranded DNA (dsDNA) [12]; while others are indirectly activated, like NLRC4, which bind the complex NAIP/flagellin [11], or NLRP1 and pyrin, which are activated in the absence of their physiologic inhibitor. Bacterial modification of small-GTP proteins, such as RhoA, affects the phosphorylation state of pyrin promoting inflammasome assembling [7]. The inhibition of the dipeptidase DPP9 leads to NLRP1 inflammasome mounting [6]. Among inflammasome receptors, NLRP3 is uniquely activated by a plethora of PAMPs and DAMPs through mechanisms not yet fully elucidated, including K+ efflux (mediated by pore-forming toxins, such as nigericin, or by the purinergic receptor P2X7 in response to increased extracellular ATP concentration); mitochondrial or phagosomal/lysosomal damage with the consequent release of organelle components (i.e., reactive oxygenous species, mtDNA, or cathepsins) [13]. According to recently introduced concept of HAMPs [2], NLRP1, NLRP3, and pyrin are activated by altered homeostasis.

Even if the final result of pathogenic variants in distinct receptors is the increased processing and liberation of pro-inflammatory cytokines IL-1ß and IL-18, patients affected by inflammasomopathies present a receptor-dependent clinical phenotype, suggesting a cell/tissue-specific expression of receptors genes (briefly summarized in Table 1).

Inflammasome components were described in several cell types and tissues, both immune (i.e., myeloid cells and lymphocytes) and nonimmune (i.e., epithelium and endothelium), including highly specialized cells, such as neurons [1, 3, 19]. Their expression can be constitutive or inducible depending on the organ/tissue and/or the context (homeostatic vs. pathologic condition). Two main pathways lead to the transcription of inflammasome genes in inducible cells: (1) Myd88/NF-kB or (2) TRIF/IRFs signaling. The first is induced by toll-like receptors (TLRs; i.e., TLR4 and TLR5) and cytokines receptors (i.e., IL1R and TNFR), and promotes the expression of several inflammasome components such as NLRP1, NLRP3, NLRC4, NAIP, pyrin, ASC as well as biological inactive pro-forms of IL-1ß (pro-IL-1ß) and caspsases (pro-caspase-1, pro-caspase-4/5). The other is activated by TLRs (i.e., TLR3, TLR8, and TLR9) and IFNs receptors (IFNR1 and IFNR2), and induces the expression

**Fig. 1 Basic inflammasome composition and role in immune response.** Pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs), and/or homeostasis-altering associated patterns (HAMPs) are sensed by a plethora of cytosolic receptors containing a central NACHT domain, a C-terminal LRRs domain and a N-terminal PYD or CARD domain (NLRs), or a N-terminal PYD domain together with other domains such as B box zinc finger (bz, BB), coiled coil (CC) and B30.2/SPRY as for pyrin, or HIN-200 motifs as for PYD and HIN containing receptors (PYHINs). Once activated by a molecular pattern, receptors recruit directly, through homotypic CARD–CARD domains interaction, or indirectly, through the recruitment of the adaptor molecule PYD-CARD or ASC, an inflammatory caspase (namely, caspase-1,-4, and -5) which, in turn, cleaves biologically inactive forms of IL-1ß, IL-18 (pro-IL-1ß, pro-IL-18, respectively) and gasdermin-D (GSDM-D). Inflammasome activation results in the release of pro-inflammatory cytokines IL-1ß and IL-18, and a cleaved form of GSDM-D which creates pores within cellular membrane and it is responsible for cytokines release and, in some cases, for pyroptosis. IL-1ß and IL-18 mediate inflammatory process and adaptive immune response. Moreover, IL-18 is also important for epithelia and mucosal homeostasis.
of the so-called IFN-inducible proteins such as AIM2, IFI16, pro-IL-18, and pro-caspase-4/-5 [1, 3, 19].

It is important to stress that inflammasome receptors, beyond pathogen recognition, exert a wide range of biologic functions, including the maintaining of homeostasis [20, 21].

Due to the dramatic pro-inflammatory effect of inflammasome-related cytokines and cell death, the complex activation has to be strictly regulated. Several mechanisms contribute to the physiologic “break”: (a) inducible transcription of the components; (b) maintenance of “closed” conformation of the sensors; and (c) presence of inhibitory proteins. Each cell/tissue is characterized by its own activation threshold, and consequently by an inflammasome more or less prone to be activated. In general, in cells or tissues constantly exposed to environment, such as mucosa and associated immune cells (i.e., resident macrophages or dendritic cells), the activation of inflammasome is slower, compared with blood monocytes or neurons, for example [19].

Taking in account the complexity of inflammasome activation and that several regulatory steps are involved in maintaining its physiologic role in homeostasis and innate immune response, it does not surprise that inflammasome dysregulation has been pointed out as a common pathogenic mechanism not only in auto-inflammatory syndromes, but also in autoimmune disorders, cardiovascular diseases (CVD), obesity and associated metabolic syndrome, neurodegenerative diseases, and cancer [22]. Moreover, an important role of inflammasome and its specific receptors have been revealed also in infectious diseases [23, 24].

As a result, genetic variants in auto-inflammatory genes and inflammasome components may affect the individual predisposition to develop diseases common in the general population (both sterile or infectious ones). In the last decade, several polymorphisms (variants with a minor allele frequency > 1%) have been described in inflammasome-related genes and associated with multifactorial human diseases, emphasizing the key role of the complex in the pathogenesis of the diseases, and leading to the description of novel pathogenic mechanisms and pharmaceutic targets. On the other side, little is known about the functional effect of such genetic variants on inflammasome structure and function.

In this review, we summarized published genetic association studies about polymorphisms in inflammasome genes, trying to depict the genetic contribution of inflammasome in the pathogenesis of both infectious and non-infectious sterile diseases. We limited the revision to main inflammasome components, including sensors (NLRP1, NLRP3, NLRC4, pyrin, AIM2, IFI16, NLRP6, and NLRP7) and effector enzymes (caspase-1, -4, and -5). Well-known NLRP3 regulators, CARD8 [9] and NEK7 [10], were also considered. Deletions in the flagellin receptor
NAIP were detected in some patients with the acute form of spinal muscular atrophy (MIM: 253300), a rare neuromuscular disorder, however, at the present no other genetic variants have been reported as significantly associated to human diseases. Genetics of IL1B and IL18, as well as of P2X7, has been recently revised elsewhere [25, 26] and therefore it is not included in this article.

**Variability of inflammasome genes**

Both inflammasome receptors and effector molecules caspases belong to multi-gene families, and they are widely distributed within the human genome and often grouped in loci, such as in the case of AIM2 (Refseq: NM_004833.3) and IFL16 (Refseq: NM_001206567.2) in 1q23.1-2, CASP1 (Refseq: NM_033292.4), CASP4 (Refseq: NM_001225.4), and CASP5 (Refseq: NM_004347.5) in 11q22.3, indicating gene duplication events, even if apparently without redundancy in molecule function. The presence of polymorphisms and functional variants in inflammasome genes suggests that they have been selected by the environment as they give some advantage to the host.

With the advance of genomic sequencing technology, several genetic variants have been described in inflammasome genes, including single nucleotide polymorphisms (SNPs), small deletions, variable number of tandem repeats (VNTR), and also copy number variations. However, the majority of current literature exhibits association data with SNPs, both tagSNPs or functional SNPs, even if only for a limited number of variations the effect on gene/protein is known, allowing a correct and in-depth interpretation of association data.

In Supplementary File 1, we resumed information about localization and effect of inflammasome genes polymorphisms selected to have been significantly associated with human diseases.

It is noteworthy that exonic variants are localized closed to sites important for the maintenance of “close”/inactive receptor conformation, or for enzymatic function in the case of caspases. SNPs in regulatory regions, such as promoter, 5’UTR, or 3’UTR, are also present, affecting gene transcription or mRNA stability. Intriguingly genetic variability is a characteristic of inflammasome sensors rather than of effector caspases, or of the adapter molecule ASC (PYCARD) which, differently from mice, is practically monomorphic in humans, possibly due to its central role in inflammasome assembling.

Vasseur et al. [27] have recently characterized sequence diversity in PRRs genes. Whiten NLR super-family, members with a PYD N-terminal domain (NLRPs genes) display similar or high level of genetic diversity (estimated by nucleotide diversity) that noncoding regions, whereas those with a CARD N-terminal domain (NLRCs genes) tend to show a lower diversity than expected, suggesting that NLRPs (i.e., NLRP1 and NLRP3) had evolved under strong selective pressure (purifying selection) and that their function is essential for host survival, and not redundant as supposed to be for NLRCs (i.e., NLRC4). Of note, in this analysis, authors identified a NLRP1 (Refseq: NM_033004.4) haplotype containing seven missense variations (rs11651595: c.737 C>G, p.(Thr246Ser); rs52795654: c.2345 C>G, p.(Thr782Ser); rs11657747: c.2633 C>T, p.(Thr878Met); rs34733791: c.2894 C>T, p.(Thr995Ile); rs35596958: c.3355 A>G, p.(Met1119Val); rs11653832; c.3721 G>C, p.(Val1241Leu); rs2137722: c.4096 C>T, p.(Arg1366Cys)), which fixed in worldwide populations possibly as a consequence of selective advantage against some pathogen. Another NLRP1 haplotype, including rs11651270 (c.3550 A>G; p.(Met1184Val)) and rs12150220 (c.464 T>A, p.(Leu155His)) SNPs, appeared to be more recently positively selected exclusively in Europe. Also for pyrin coding gene MEFV (Refseq: NM_000243.2), a pathogen-based selective pressure has been postulated [28]. As a consequence, several genetic variants with relative high allele frequency can be observed in the general population sometimes associated to auto-inflammatory syndrome Familial Mediterranean fever (FMF; MIM 249100).

Molecular and evolutionary analysis suggested that inflammasome genes present variants originated from past adaptation to pathogens. They are mainly gain-of-function (GoF) variations leading to increased inflammation and immune response, which nowadays could be responsible for immune disorders, such as hereditary auto-inflammatory syndromes (rare pathogenic variants in inflammasome genes), or could predispose to multifactorial diseases (common variants in inflammasome genes).

Polymorphisms resulting in increased activation of inflammasome (GoF variants) generally affect the close/inactive state or increase the expression level of the target genes. The NLRP1 SNPs rs12150220 (c.464 T>A, p.(Leu155His)), localized in a link region between PYD and NACHT domains, and rs11651270 (c.3550 A>G, p.(Met1184Val)), localized close to auto-cleavage site in FIIND, increase IL-18 processing in peripheral blood mononuclear cells especially when present in combined haplotype [29]. The missense variation rs35829419 (c. 2113 C>A, p.(Gln705Lys)) in NLRP3 (Refseq:NM_004895.4) is localized within NACHT domain and it has been demonstrated to interfere with the molecule “close” conformation resulting in constitutive activate state of the receptor and consequent decrease inflammasome activation threshold (increase IL-18 and IL-18 production) [30]. The 3’UTR variant rs10754558 (c.230 G>C) has been described by Hitomi et al. [31] as responsible for the increasing NLRP3
mRNA stability due to its localization within miR-223 binding region.

The nonsense variation rs2043211 (c.30 T>A, p.(Cys10Ter)) in the NLRP3 inhibitor CARD8 (Refseq: NM_001184900.3) results in a loss-of-function (LoF) of the inhibitor, in turn, leading to increase in inflammasome activation [32].

Several MEFV variants have been previously described as pathogenic mutations in FMF patients when found in homozygosity or combined heterozygosity (recessive pattern of inheritance), but as they have been found in general population they have been then reconsidered as likely begin variations (http://fmf.igh.cnrs.fr/ISSAID/infevers).

On the other side, LoF variants referred to polymorphisms which impaired inflammasome components availability and/or function, or caspases activation and consequently IL-1β and/or IL-18 processing and release. For example, rs4793333 (c.−119+1498 G>A) and rs385076 (c.−163 C>T) intronic SNPs in NLRC4 (Refseq: NM_021209.4) have been associated with diminished gene expression and lower plasma level of IL-18 [33, 34]. The “silent” variant rs580253 (c.766 C>T, p.(Leu256=)) and the 5’UTR SNP rs554344 (g.15661 C>G) in CASP1 (Refseq: NM_033292.4) gene have been reported to affect the enzyme processing capacity leading to diminishing IL-1β production [35].

For a portion of SNPs, we have encountered some information in public database of tissues/cells expression (i.e., GTEX Portal: The Genotype-Tissue Expression Project, https://www.GTEX.org; The Human Protein Atlas, https://www.proteinatlas.org) or in ClinVar database (www.NCBI.gov) and included in Supplementary File 1 to help the interpretation of association data. For other SNPs, tagSNP, without any available functional and/or expression information, it could be possible to take some advantage from data about linkage disequilibrium with functional SNPs (Supplementary File 1).

In Fig. 2, we have represented the polymorphisms distribution within principal inflammasome genes (namely, NLRP1, NLRP3, NLRC4, MEFV, Aim2, and IFI16).
When the frequency of inflammasome polymorphisms is taken in account (Supplementary File 1), we can notice that specific functional variants are present only in distinct populations, suggesting an evolutive pressure or eventually a founder effect, such as, for example, the missense variant rs12150220 (c.464 T>A, p.(Leu155His)) (MAF: 0.03–0.44) in NLRP1, the silent variation rs3806268 (c.732 G>A, p. (Ala244=)) (MAF: 0.03–0.55) and the 42 bp-VNTR (rs74163773) in NLRP3, or the three SNPs in CASP1 (rs568910, rs580253, and rs501192) (MAF: 0.01–0.25/0.26) (Supplementary File 1).

As abovementioned, inflammasome components play a main role in first line defense against infectious agents and pathogens exert a strong selection pressure on our immune system, it has been hypothesized that both acute epidemic events and/or endemic infections could be responsible for local shaping of genetic variants frequency, such as in the case of MEFV [28], or of NLRP3 42 bp-VNTR [36].

**Infectious diseases**

Association studies on genetic polymorphisms of inflammasome and infectious diseases are summarized in Table 2. Due to its role in first line defense and host/pathogen interaction [24], it is not surprising that variants which lead to heightened inflammasome activation rates and increased release of IL-1ß and/or IL-18 have been associated to protection against infections. Accordingly, these data commonly reflect the results obtained for inflammasome-related genes, such as IL1B, IL-18, or P2X7, which have been investigated also separately from inflammasome by some authors.

NLRP3 GoF variants confer protection against several viral (HCV, HIV-1, HPV, and HLV), and bacterial (pulmonary tuberculosis, renal parenchymal infections) infections (Table 2). Accordingly, GoF of CARD8 or LoF of P2X7 [59], which result in reduced activation of NLRP3 inflammasome, confer risk for pulmonary tuberculosis [60, 61]. Altogether these data emphasize that the activation of NLRP3 inflammasome is a key event in the first line immune response. It is interesting to underline that, despite both pro-IL-1ß and pro-IL-18 are substrates for caspase-1, maybe depending on cell type, NLRP3 activation generally is accompanied by a huge release of IL-1ß. Accordingly, genetic variants which lead to high amount of this cytokine also confer protection against pulmonary tuberculosis [62] and HIV-1 [63].

On the other hands, less clear is the contribution of the axis NLRP3/IL-1ß in these diseases. Several variants were described within the IL-18 promoter region, leading to reduced IL-18 plasma levels, and conferring augmented susceptibility to HIV-1 [64, 65] and tuberculosis [66], and protection against HPV infection [67].

Therefore we can deduce that while the NLRP3/IL-1ß pathway is important for HIV-1 infection, the defense against other viruses, such as HPV, is benefitted by a NLRP3-dependent IL-18 production. For M. tuberculosis, NLRP3 and both cytokines appear to be mandatory for bacterial control.

Less is known about genetic effect of other inflammasome receptors and the relative contribution in cytokines processing. GoF variants in NLRP1 and IFI16 confer protection to M. leprae [49], HPV [45], HIV-1 [44], and HSV-2 [46], respectively (Table 2).

When the progression and/or outcome of chronic infections is taken in account, results appeared to be more complex. In fact, once the pathogen has gained its entry within the host and infection has been established, inflammasome activation could be detrimental for the host due to the inflammation-mediated cells loss and tissue damage; or likely benign if we consider the homeostatic role of specific inflammasome pathways, such as the axis NLRC4/IL-18 in mucosal epithelium [3, 21, 22].

As a prototype of this hypothesis, the previously mentioned GoF variant in NLRP3 (rs10754558), which confers protection against M. tuberculosis, has been associated with severe tuberculosis in infected patients [51], suggesting that the genetic effect could change depending on the phase of immune response.

Intriguingly, NLRP1 SNPs, which were scarcely found in association with infection susceptibility, significantly affect clinical presentation and prognosis of infectious diseases such as vivax malaria [54], bacterial meningitis [56], and Chagas disease-associated cardiomyopathy [57] (Table 2).

Finally, it is interesting to remember that inflammasome SNPs have been recently investigated as modifier factors also in monogenic diseases, such as cystic fibrosis. LoF in NLRC4 receptor contributes to an increased susceptibility to lungs infections in cystic fibrosis patients [48] (Table 2).

**Sterile diseases**

The first association study evaluating inflammasome SNPs referred to NLRP1 and vitiligo-associated autoimmune diseases [68]. As in 2002, pathogenic variants in NLRP3 have been described in rare dominant auto-inflammatory syndromes (CAPS; MIM 606416) [15], which share some characteristics with autoimmune diseases, speculations had suggested that inflammasome genes could also contribute to autoimmunity development. Inflammation dramatic contributes to the loss of central and/or peripheral tolerance, but also mediates tissue injury once auto-reactive lymphocytes have been activated. Increased levels of pro-inflammatory cytokines IL-1ß and/or IL-18 are found in autoimmune patients. IL-1ß drives Th17-mediated tissue damage in...
| Infectious agent/disease                        | Gene     | Variant ID          | Effect on inflammasome activation | Cohort (case/controls; n)                                                                 | Association |
|-----------------------------------------------|----------|---------------------|-----------------------------------|------------------------------------------------------------------------------------------|-------------|
| C. albicans (recurrent vulvovaginal candidosis)| NLRP3    | rs74163773          | Increased                         | Europe (270/583) [37]; USA (143/182) [38]                                                | Risk        |
| C. trachomatis                                | NLRP3    | rs12065526          | Unknown                           | Germany (461/93) [39]                                                                     | Risk        |
| HCV                                           | NLRP3    | rs1539019; rs35829419| Unknown; Increased                | Egypt (201/95) [40]                                                                       | Protection  |
| HIV-1                                         | NLRP3    | rs10754558          | Increased                         | Brazil (children: 135/153; adults: 192/219) [41]; Italy (adults: 192/219) [41]; Brazil (severity) (300) [43] | Protection  |
| HPV                                           | IFI16    | rs1417806           | Increased                         | The Netherlands (365) [44]                                                                | Protection  |
| HIV-1                                         | NLRP3    | rs10754558          | Increased                         | Brazil (246/310) [45]                                                                    | Protection  |
| HSV-2                                         | IFI16    | rs2276404           | Increased                         | Sweden (227/232) [46]                                                                    | Protection  |
| HTLV                                          | NLRP3    | rs10754558          | Increased                         | Brazil (84/155) [47]                                                                     | Protection  |
| Microbial infection in lungs                  | NLRP1    | rs2670660, rs12150220, rs12137722 | Increased (Haplotype)             | Brazil (380/467) [49]                                                                   | Protection  |
| M. leprae                                     | NLRP3    | rs10754558          | Increased                         | Brazil (288/288) [50]                                                                    | Protection  |
| M. tuberculosis                               | NLRP3    | rs10754558          | Increased                         | Botswana (HIV patients; early death) (94) [51]                                           | Risk        |
| P. vivax                                      | NLRP1    | rs12150220          | Increased                         | Brazil (severe) (157) [54]                                                               | Risk        |
| Renal parenchymal infections                  | NLRP3    | rs4612666           | Increased                         | China (severity) (48/96) [55]                                                            | Protection  |
| S. pneumoniae                                 | NLRP1    | rs1651270           | Increased                         | Germany (severity) (801) [56]                                                             | Risk        |
| T. cruzi                                      | NLRP1    | rs1691270           | Increased                         | Bolivia (CAC) (38/24) [57]                                                               | Risk        |
|                                               | CASP1    | rs501192            | Unknown                           | Bolivia (CAC) (149/87) [58]                                                              | Risk        |

Inflammasome variants previously associated to infectious agents and/or diseases are briefly resumed from literature (https://www.ncbi.nlm.nih.gov/pubmed). Significantly associated polymorphisms were grouped according to the infectious agent/disease, infectious agent or disease (in alphabetical order), gene name (Gene), identification number of polymorphism (ID), resulting effect on inflammasome activation (“increased” or “decreased” or “unknown”), cohort origin (cohort) and eventually specifications (severity, etc.), sample size (n) and type (case/control or cases only), association result (“risk” or “protection”), and respective reference are reported.

HCV hepatitis C virus, HIV human immunodeficiency virus, HPV human papilloma virus, HSV herpes simplex virus, HTLV human T-lymphotropic virus, USA Unites States of America, CAC Chagas-associated cardiomyopathy.
organ-specific autoimmune diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), while IL-18 induces CD4+ T cells IFN-γ production in multiple sclerosis (MS) and RA joint inflammation and dysfunction of endothelial progenitor cells in SLE, impairing vascular repair. Therefore, it has been hypothesized that GoF polymorphisms in inflammasome genes, leading to constitutive augmented levels of IL-1ß and/or IL-18, could represent risk factors for the predisposition and/or for the prognosis of autoimmune disorders [69]. Intriguingly, as inflammasome receptors are redundant in immune cells but tissue specific in nonimmune compartments, studies showed that some receptors are preferentially associated to organ-specific diseases, such as NLRP1 and autoimmune skin diseases (vitiligo and psoriasis) (Table 3), letting us hypothesizing a sensor-specific contribution in disease pathogenesis.

The majority of the studies reported a significant association for inflammasome polymorphisms and increased risk to develop autoimmune diseases (Table 3). GoF SNPs in IL1B and increased IL-1ß are considered a risk factor for vitiligo (Zurawek et al. Supplementary File 3; Additional References), autoimmune thyroiditis (Zhao et al. Supplementary File 3; Additional References), SLE (Polo et al. Supplementary File 3; Additional References), RA (Kastbom et al. Supplementary File 3; Additional References), MS (Alkhateeb et al. Supplementary File 3; Additional References), ankylosing spondylitis (as largely reviewed in (Schoultz et al. Supplementary File 3; Additional References)). However, some results are discordant, such as from our group (i.e., NLRP3 rs10754558 and type-1 diabetes (Cheng et al. Supplementary File 3; Additional References); NLRP3 rs35829419 and celiac disease (Voet et al. Supplementary File 3; Additional References)) (Table 3). It could be an ethnicity-based effect, or it could be taken in account as a new aspect of inflammasome pathways in autoimmunity. It is interesting to emphasize that some autoimmune diseases have been associated to viral or bacterial infection in early infancy (Roberts et al. Supplementary File 3; Additional References), thus, considering the role of inflammasome in pathogen detection and response, we can speculate that a genetic background that better defend against infections could also decrease the risk of early infections, removing a contribution factor in autoimmune pathogenesis. Another hypothesis involved the homeostatic role of inflammasome receptors in mucosa and epithelium [21] and in detecting endogenous DNA inappropriately located outside cell nucleus (Roberts et al. Supplementary File 3; Additional References). Both mechanisms play key role in autoantigens exposition and heavily contribute to autoimmunity. Once again it appears that inflammasome pathways leading to preferential IL-18 production could exert a protective role also in autoimmunity. As it has been reported for NLRP1 variants and diabetes kidney disease in T1D patients (Ravimohan et al. Supplementary File 3; Additional References), or NLRC4 and MS (Feitosa et al. Supplementary File 3; Additional References) (Table 3), and in accord to literature about LoF IL-18 SNPs and risk for T1D (Hanaei et al. Supplementary File 3; Additional References, Zhang et al. Supplementary File 3; Additional References, Cummings et al. Supplementary File 3; Additional References,) and MS (Villani et al. Supplementary File 3; Additional References).

More recently several genetic variants in inflammasome components have been associated with common pathologies in the general population, such CVD, obesity and associated metabolic syndrome, neurodegenerative diseases, and cancer. Detailed literature revision is reported in Supplementary File 2. Association results for most studied genes (NLRP1, NLRP3, CARD8, MEFV, CASP1, and CASP5) are graphically represented in Fig. 3.

Tumorigenesis could be affected by inflammasome activation in several stages by regulating cell cycle (proliferation or death), innate and adaptive response and the consequent tumor micro-environment, as well as through the direct response to mucosal microbiota, cancer associated pathogens (i.e., HPV and HCV), or inorganic molecules (i.e., asbestos and nicotine). Depending on cancer type, the activation of inflammasome has been reported to promote tumor growth and/or metastasis (i.e., breast cancer and gastric carcinoma) (McGovern et al. Supplementary File 3; Additional References) or to protect against cancer development by the maintenance of tissue homeostasis and/or supporting NK activation status, principally through IL-18 production (Germain et al. Supplementary File 3; Additional References). Accordingly, individuals carrying variants in NLRP1, NLRP3, CARD8, or CASP1 leading to increase inflammasome activation rate are more susceptible to cancer development and/or worse prognosis (Fig. 3; Supplementary File 2). On the other side, variants associated to a decrease noncanonical caspases activity represent generally a risk factor for several cancer types (Fig. 3; Supplementary File 2). Curiously, GoF variants in NLRP1 protect against the malignant transformation of HPV+ lesions [45] (Fig. 3; Supplementary File 2). However, in that specific context we have to remind that NLRP1 is the main inflammasome receptor in keratinocytes and its role is important in mucosal response against pathogens (Yang et al. Supplementary File 3; Additional References). Moreover, in keratinocytes the activation of NLRP1 lead to IL-18 production, which as abovementioned is crucial for mucosal homeostasis and antitumoral activity [25].

Inflammation and inflammasome activation are involved in the pathogenesis of CVD, such as atherosclerosis, myocardial infarction and heart failure. After ischemia, the myocardial cells death lead to a huge release of DAMPs
### Table 3: Genetic polymorphisms in inflammasome components and autoimmune and polygenic auto-inflammatory diseases.

| Disease/Condition | Gene | Variant ID | Effect on inflammasome activation | Cohort (case/controls, n) | Association |
|-------------------|------|------------|-----------------------------------|---------------------------|-------------|
| Addison disease   | NLRP1| rs12150220 | Increased                         | Norway (333/3273) (70); Polish (101/254) (Patel et al. Supplementary File 3; Additional References) | Risk        |
| Ankylosing spondylitis | NLRP3| rs4612666  | Increased                         | China (200/200) (Takahashi. Supplementary File 3; Additional References) | Risk        |
|                    | MEFV | rs22404    | Unknown                           | Spain (456) (van Hout et al. Supplementary File 3; Additional References) | Risk        |
|                    | CARD8| rs2043211  | Increased                         | Sweden (492/793) (Artlett. Supplementary File 3; Additional References) | Protection  |
| Autoimmune thyroiditis | NLRP1| rs12150220 | Increased                         | Jordan (207/220) (Dehghan et al. Supplementary File 3; Additional References) | Risk        |
| Bečht disease     | AM2  | rs55873    | Unknown                           | Spain (371/1854) (Péroncés et al. Supplementary File 3; Additional References) | Risk        |
|                   | IFI16| rs6940     | Decreased                         | Unknown                    | Risk        |
| Celiac disease    | NLRP3| rs35829419 | Increased                         | Brazil (59/902) (Cheng et al. Supplementary File 3; Additional References); Italy (504/256) (Voet et al. Supplementary File 3; Additional References) | Risk; Risk  |
| IBD: Crohn disease (CD) and ulcerative colitis (UC) | NLRP3| rs35829419 | Increased                         | Sweden (CD) (498/742) (Pontillo et al. Supplementary File 3; Additional References); New Zealand (CD) (507/517) (Tan et al. Supplementary File 3; Additional References) | Risk (men)  |
|                   | MEFV | rs182671, rs24217, rs224225, rs224224, rs224223, rs24222 | Decreased; Unknown          | Unknown                    | Risk        |
|                   | CARD8| rs2043211  | Increased                         | Unknown                    | Risk        |
|                   | MEFV | rs3743930  | Unknown                           | Korea (CD, UC) (650/688) (Bouchard et al. Supplementary File 3; Additional References) | Risk        |
| HS purpura        | MEFV | rs3743930  | Unknown                           | China (320/342) (Grandeman et al. Supplementary File 3; Additional References); China (78/189) (Canna et al. Supplementary File 3; Additional References) | Risk        |
| Kawasaki disease  | NLRP1| rs11651270, rs8079034, rs37447117, rs11078571, rs16954813, rs8079727 | Increased (Haplotype)      | Japan (356/215) (Romberg et al. Supplementary File 3; Additional References) | Risk        |
| Multiple sclerosis | NLRP3| rs3806265  | Unknown                           | Japan (150/100) (Ksentivjevich et al. Supplementary File 3; Additional References) | Risk        |
|                   | NLRC4| rs35829419 | Increased                         | Brazil (severity) (209) (Feitosa et al. Supplementary File 3; Additional References) | Risk        |
|                   | CARD8| rs479333   | Decreased                         | Switzerland (82/100) (Ekman et al. Supplementary File 3; Additional References) | Protection  |
| Psoriasis         | NLRP1| rs8079034  | Unknown                           | Sweden (1847/802) (Zhang et al. Supplementary File 3; Additional References) | Risk        |
|                   | NLRP3| rs3806265  | Unknown                           | China (540/612) (Jaegcr et al. Supplementary File 3; Additional References) | Risk        |
Inflammasome variants previously associated to autoimmune or polygenic multifactorial auto-inflammatory diseases are briefly resumed from literature (https://www.ncbi.nlm.nih.gov/pubmed). Disease or pathologic conditions (in alphabetical order), gene name (Gene), identification number of polymorphism (ID), resulting effect on inflammasome activation ("increased" or "decreased" or "unknown"), cohort origin (cohort), eventually specifications (severity, etc.), sample size (n), type (case/control or cases only), association result ("risk" or "protection"), and respective reference are reported. 

| Disease/condition         | Gene     | Variant ID | Effect on inflammasome activation | Cohort (case/controls; n) | Association |
|---------------------------|----------|------------|------------------------------------|---------------------------|-------------|
| Psoriatic JIA             | NLRP3    | rs35829419 | Increased                          | Swedish (174/360)          | Risk        |
|                           |          | rs10754558 | Increased                          | Brazil (128)               | Risk        |
|                           |          | rs10159239 | Increased                          | UK (12782/33)              | Risk        |
|                           | CARD8    | rs2043211  | Increased                          | Sweden (174/360)           | Risk        |
|                           |          | rs9651713  | Unknown                            | Norway (308/273)           | Risk        |
|                           | NLRP1    | rs12150220 | Increased                          | Brazil (144/158)           | Risk        |
|                           |          | rs98132352 | Unknown                            | Germany (532)              | Risk        |
|                           | NLRP1    | rs2670660  | Increased                          | Norway (1086/327)          | Risk        |
|                           |          | rs10754558 | Increased                          | Brazil (196/192)           | Protection  |
|                           | NLRP1    | rs12150220 | Increased                          | USA/UK (333/323)           | Risk        |
|                           |          | rs8182352  | Unknown                            | Romania (66/69)            | Risk        |
|                           |          | rs602867   | Unknown                            | India (537/645)            | Risk        |
|                           |          | rs1008588  | Unknown                            | Jordan (269/61)            | Risk        |
| Rheumatoid arthritis      | NLRP1    | rs878329   | Unknown                            | China (190/190)            | Risk        |
|                           |          | rs3806265  | Unknown                            | UK (59072/8)               | Risk        |
|                           | MEFV     | rs2276405  | Unknown                            | China (900/500)            | Risk        |
|                           |          | rs224204   | Unknown                            | China (118)                | Risk        |
|                           |          | rs2043211  | Increased                          | Sweden (174/360)           | Risk        |
|                           |          | rs2043211  | Increased                          | Switzerland (218/307)      | Risk        |
|                           |          | rs9651713  | Unknown                            | Romania (66/69)            | Risk        |
|                           |          | rs2670660  | Increased                          | USA/UK (333/323)           | Risk        |
|                           |          | rs1008588  | Unknown                            | Jordan (269/61)            | Risk        |

**Inflammasome variants previously associated to autoimmune or polygenic multifactorial auto-inflammatory diseases are briefly resumed from literature (https://www.ncbi.nlm.nih.gov/pubmed).**

**Disease or pathologic conditions (in alphabetical order), gene name (Gene), identification number of polymorphism (ID), resulting effect on inflammasome activation ("increased" or "decreased" or "unknown"), cohort origin (cohort), eventually specifications (severity, etc.), sample size (n), type (case/control or cases only), association result ("risk" or "protection"), and respective reference are reported.**

**HS** Henoch–Schönlein, **IBD** intestinal bowel disease, **PFAPA** periodic fever with aphthous stomatitis, pharyngitis, and cervical adenitis, **JIA** juvenile idiopathic arthritis **SLE** systemic lupus eritematosus.

*aVitiligo-associated multiple autoimmune disease.*
(i.e., ATP, mtDNA, etc.) and the consequent activation of inflammation and leukocytes infiltration within the hearth. This response could result in an exaggerated inflammatory response, tissue damage, adverse cardiac tissue remodeling, and worse prognosis (Xiong et al. Supplementary File 3; Additional References). Moreover, a high fatty acid diet and the consequent increased levels of plasma oxidized low-density lipoproteins, as well as alterations in glycolytic pathways, are known pro-inflammatory factors and have been associated to atherosclerosis, obesity and insulin resistance, in part due to the activation of NLRP3 inflammasome (He et al. Supplementary File 3; Additional References).

In this scenario, it does not surprise that genetic variants that increased inflammasome activation have been described as possible risk factors for CVD or metabolic diseases. As could be appreciated in Fig. 3 (and detailed in Supplementary File 2), accordingly to its uniquely expression in cardiomyocytes, cardiac fibroblasts, and cardiac microvascular endothelial cells (Onoyama et al. Supplementary File 3; Additional References), it is mainly NLRP3 genetics that represents a predisposing factor for CVD. Recent evidence about the use of specific NLRP3 inhibitor MCC-950 in CVD treatment support the central role of the receptor in this group of diseases (Imani et al. Supplementary File 3; Additional References).

For what concerns studies about inflammasome genetics and metabolism, some GoF SNPs resulted associated to hyperlipidemia and/or hyper glicemia (Fig. 3; Supplementary File 2). However, these data have to be carefully interpreted as metabolic alteration could be sensed by NLRP3—or maybe other receptors—inducing a response trying to report the cell to homeostasis, therefore an excessive inflammatory response could cause metabolism-related pathologies, however, the contrary is far to be demonstrated.

Fibrotic response and collagen deposition have been showed to be guided by inflammasome activation (Cheung et al. Supplementary File 3; Additional References). Therefore researchers wondered whether inflammasome genetics could contribute to the predisposition observed in some individuals to develop fibrosis and fibrosis-related diseases. A half-dozen SNPs have been significantly associated to coal workers’ pneumoconiosis, chronic renal disease and silicosis (Fig. 3; Supplementary File 2), however, no functional data are available for a deeper discussion. Of note individuals carrying the tagSNP rs1539019 present an increased level of fibrinogen (Yu et al. Supplementary File 3; Additional References), which can at least in part explain the association results.

As expected, hyper-sensibility reactions have been associated with GoF variants in inflammasome genes (Fig. 3; Supplementary File 2) accordingly to those related to increased IL-1ß production (Carlstrom et al. Supplementary File 3; Additional References). IL-18 is considered homeostatic in airways and lung epithelium, as well as in skin, and concordantly IL-18 GoF have been reported as protective factors against asthma (Zuo et al. Supplementary File 3; Additional References).

Besides, animal models suggest that both NLRP1 and NLRP3 are involved in inflammasome activation and in the pathogenesis of neurodegenerative diseases (Yang et al. Supplementary File 3; Additional References), from a genetic point of view data appear more complicated. Amyloid and misfolded proteins have been demonstrated to cause neuroinflammation, through the activation of NLRP3 (and maybe NLRP1) inflammasome both by ER stress or direct binding to some PRRs (i.e., scavenger receptors and TLRs) (Yang et al. Supplementary File 3; Additional References). However, a protective role of GoF SNPs in NLRP1 and NLRP3 toward the development of Alzheimer disease (AD) was reported (Fig. 3; Supplementary File 2) (Day et al. Supplementary File 3; Additional References, Sui et al. Supplementary File 3; Additional References).
Accordingly another study showed that variants that decrease caspase-1 activity accelerate AD progression (Goh et al. Supplementary File 3; Additional References). How a constitutive increased activation of inflammasome could protect from neurodegeneration is still unclear.

On the other side, a synonymous variant which decreases NLRP3 stability represents a protective factor in Parkinson disease (PD) (Kastbom et al. Supplementary File 3; Additional References), suggesting a pathologic role of NLRP3 inflammasome activation in PD, as also confirmed by the positive association between GoF IL1B SNPs and PD development (Jenko et al. Supplementary File 3; Additional References). Intriguingly, genetic variants leading to increasing inflammasome activity (NLRP3, NLRC4, and IL-18) were associated to worse progression of MS (Feitosa et al. Supplementary File 3; Additional References), that, besides the distinct pathogenesis, is characterized by neuroinflammation and neurodegeneration.

Few studies have been performed investigating inflammasome genetics and pregnancy disorders, however, it is interesting to emphasize some results, for example, hypertension complication during pregnancy (preeclampsia) was more frequent in women carrying GoF polymorphisms in NLRP1 (Addobbati et al. Supplementary File 3; Additional References) and NLRP3 (Mathews et al. Supplementary File 3; Additional References) (Fig. 3; Supplementary File 2).

Finally, a low number of reports have been published about genetic variants in dsDNA receptors AIM2 and IFI16 and significant association with sterile diseases, including Bechet disease, psoriasis, and periodontal diseases (Supplementary File 2). Of note, while GoF SNPs have been associated to periodontal disease, suggesting that they lead to increased inflammasome activation contributing to the periodontal pathologic inflammation, for autoimmune conditions it seems that a decreased activity of these receptors could negatively affect the development of the autoreactivity (Padron-Morales et al. Supplementary File 3; Additional References).

Half a dozen studies reported the significant association between SNPs in inflammasome genes and response to treatment (Table 4). Curiously all but one showed that GoF variants in NLRP1 or NLRP3 inflammasome had a negative effect on treatment response, glucocorticoids, or IFN-based therapies.

### Concluding remarks and perspectives

Pathogenic variants in inflammasome genes have been described as cause of rare inherited auto-inflammatory syndromes (http://fmf.igh.cnrs.fr/ISSAID/infevers), characterized by a constitutive activation of inflammasome and a dramatic production of IL-1β and/or IL-18 [4].

Increasing evidence have demonstrated the genetic association between polymorphisms in inflammasome genes and multifactorial diseases, both infectious and sterile diseases. Data about the functional effect of these variants are available only for a limited number of disease-associated polymorphisms. In general, they affect inflammasome constitutive activation and/or its activation rate. It is interesting to underline that, as previously observed for rare syndromes [4], inflammasome components, especially the receptors, have a unique cell and/or tissue expression profile. Therefore the effect of polymorphisms in specific genes may alter the clinical phenotype and the systemic or organ-specific presentation, depending on the circumstances. It makes sense that, for example, variants in NLRP1, which is expressed in keratinocytes, brain, and kidney tubular cells (from https://www.proteinatlas.org),
have been associated to HPV infection (Table 2), vitiligo and psoriasis (Table 3), AD or renal impairment (Fig. 3; Supplementary File 2). Moreover, we would like to emphasize that, even if the exact mechanism is still unknown, genetic association studies point out a preferential receptor/cytokine axis in the contribution to multifactorial diseases etiology, which could be taken in account that inflammasome genes have often distinct cell/tissue-specific expression.

Finally it is important to remember that beyond the key role in IL-1ß and IL-18 processing and release, inflammasome components are involved in pyroptosis and also in caspase-independent functions, such as the role of transcriptional co-factor for a Th2 polarization proposed for NLRP3 (Dieude et al. Supplementary File 3; Additional References) or the inhibitory role toward NF-kB of NLRP6, NLRP7 [20], so these alternative roles could be taken in account in the interpretation of genetic association results. All these consideration have been graphically resumed in Fig. 4.

Unfortunately, to our knowledge, no functional studies linking inflammasome polymorphisms and pyroptosis or alternative functions have been yet performed. The only indirect data originated from the work of Booiman et al. [44], which reported the association between a IFI16 SNP and the level of CD4+ T lymphocytes in HIV-infected patients, linking the polymorphism with the loss of this lymphocytes population, therefore assuming a increased IFI16-mediated pyroptosis.

Even if sometimes limited by the ethnic background or sample size, association studies involving inflammasome genes and polymorphic variants are greatly contributing to our knowledge about the role of inflammasome in multifactorial diseases and about the selective pressure made by pathogens on inflammasome components and the possible heterozygote advantage that leads to increase variant frequency in the general population.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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