HHS Public Access

Author manuscript

Semin Immunopathol. Author manuscript; available in PMC 2016 July 01.

Published in final edited form as:

Semin Immunopathol. 2015 July ; 37(4): 403–406. doi:10.1007/s00281-015-0498-0.

Advances in the genetically-complex autoinflammatory diseases

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Abstract

Monogenic diseases usually demonstrate Mendelian inheritance and are caused by highly penetrant genetic variants of a single gene. In contrast, genetically-complex diseases arise from a combination of multiple genetic and environmental factors. The concept of autoinflammation originally emerged from the identification of individual, activating lesions of the innate immune system as the molecular basis of the hereditary periodic fever syndromes. In addition to these rare, monogenic forms of autoinflammation, genetically-complex autoinflammatory diseases like the periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome, chronic recurrent multifocal osteomyelitis (CRMO), Behçet's disease, and systemic arthritis also fulfill the definition of autoinflammatory diseases - namely the development of apparently unprovoked episodes of inflammation without identifiable exogenous triggers and in the absence of autoimmunity. Interestingly, investigations of these genetically-complex autoinflammatory diseases have implicated both innate and adaptive immune abnormalities, blurring the line between autoinflammation and autoimmunity. This reinforces the paradigm of concerted innate and adaptive immune dysfunction leading to genetically-complex autoinflammatory phenotypes.

Keywords

Autoinflammation; polygenic; chronic recurrent multifocal osteomyelitis (CRMO); periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA); Behçet's disease; systemic juvenile idiopathic arthritis (sJIA)

Introduction

The concept of autoinflammation was born in the context of the monogenic hereditary periodic fever syndromes [1], where it was intended as a direct contrast to autoimmunity, referring to instances where inflammation was present in the absence of either high titer autoantibodies or clonally-expanded, autoreactive T cells. This dichotomy has provided a useful framework for the consideration and classification of immune-mediated diseases, with autoimmunity representing adaptive immune dysfunction and autoinflammation representing innate immune dysfunction. However, this construct is limited by the fact that dysfunction of the innate and adaptive immune systems are not mutually exclusive, even among monogenic forms of autoinflammation [2, 3]. Unlike the monogenic

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autoinflammatory diseases, which are caused by highly penetrant mutations of single genes, the group of genetically-complex or polygenic autoinflammatory diseases are influenced by the interactions of multiple genetic and environmental risk factors. In addition to their genetic complexity, these diseases are also immunologically complex, reflecting the interplay of multiple risk factors that contribute to dysfunction of both innate and adaptive immunity. This review highlights recent advances in the understanding of genetically-complex autoinflammatory diseases, including periodic fever with cervical adenitis, pharyngitis, and aphthous stomatitis (PFAPA), the autoinflammatory diseases of the bone, Behçet's disease (BD), and systemic arthritis.

Periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis (PFAPA) syndrome

The PFAPA syndrome is marked by recurrent episodes of oro-pharyngeal and systemic inflammation. Although its name is suggestive of a stereotypical clinical presentation, a recent study of 301 PFAPA patients highlighted the phenotypic heterogeneity of this syndrome, revealing that only 44% of PFAPA patients had all 4 of the namesake features, while 76% of patients presented with additional symptoms [4]. Despite its occasional transmission in an autosomal dominant or autosomal recessive pattern, PFAPA most frequently develops sporadically or clustered within families without a clear Mendelian pattern of inheritance. In one such case, a single child with a syndromic form of PFAPA was found to have a *de novo* chromosomal translocation that included a microdeletion of *SPAG7* (Table 1) [5]. The function of SPAG7 is unknown, but it is expressed in two tissues relevant to PFAPA, the tonsils and the lymph nodes [5]. Additionally, it is overexpressed in peripheral blood mononuclear cells (PBMC) from individuals seropositive for human parvovirus B19, as compared to PBMC from seronegative individuals, pointing to a potential role for SPAG7 in anti-viral immunity [6]. Another recent study examined the hereditary periodic fever syndrome genes in PFAPA patients, identifying enrichment of *NLRP3* and *MEFV* variants among a subset of PFAPA patients [7]. Moreover, this study identified dysregulated IL-1β production in PFAPA patient monocytes [7]. Finally, a recent *ex vivo* investigation of neutrophils identified increased production of intracellular oxygen free radicals, increased priming, and decreased apoptosis in PFAPA neutrophils during disease flares, as compared to either PFAPA neutrophils from periods of quiescent disease or neutrophils from febrile, non-PFAPA patients [8].

Chronic recurrent multifocal osteomyelitis and autoinflammation of the bone

The autoinflammatory syndromes of the bone, which include chronic non-bacterial osteomyelitis (CNO), chronic recurrent multifocal osteomyelitis (CRMO), and the synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome each manifest sterile, inflammatory lesions of the bone. Our genetic understanding of these disorders is largely derived from investigations of human osteoinflammatory syndromes, including those caused by recessively inherited mutations of *LPIN2*, *IL1RN*, and *RAG1* (Table 1) [9-11]. Additionally, there are two murine models of CRMO caused by mutations of *Pstpip2*,

however no causative mutation of *PSTPIP2* has been identified in human disease [12, 13]. Two recent studies of the murine chronic multifocal osteomyelitis (cmo) model have provided insight into the pathophysiology CNO. One study revealed that cmo neutrophils produce excessive amounts of IL-1β, and that its production is inflammasome-independent [14]. Another study demonstrated that by altering the composition of the intestinal microbiome with dietary manipulations, it was possible to modify the expression of sterile osteomyelitis phenotype [15]. Furthermore, recent human immunologic studies have identified increased Th17 cells in the peripheral blood of SAPHO patients [16], reduced IL-10 production by stimulated monocytes from CRMO patients [17], and increased expression of the inflammasome-related genes, *IL1B*, *CAS1*, and *ASC*, in PBMC from CRMO patients [18].

Behçet's Disease

BD, which is marked by recurrent oro-genital ulceration, together with ocular, cutaneous, vascular, and gastrointestinal inflammation, has a relatively high heritability among the genetically-complex autoinflammatory diseases. Family- and population-based genetic studies of BD continue to expand the list of known BD susceptibility genes (Table 1), which has grown to include important cytokines, chemokines, and signaling molecules that implicate both innate and adaptive immune mechanisms in its pathogenesis. The largest risk factor for BD remains the class I Human Leukocyte Antigen (HLA) molecule, *HLA-B*51* [19]. However, a recent study of a large Turkish case-control collection identified multiple class I HLA alleles that strongly influenced BD susceptibility, demonstrating that the role of the class I HLA locus in BD extends beyond *HLA-B*51* [20]. Strikingly, many genes implicated in BD also influence susceptibility to the seronegative spondyloarthropathies, including ankylosing spondylitis and psoriasis. For example, in each of these diseases, risk variants of *ERAP1* influence disease risk through epistasis with the disease-associated class I HLA allele [21-23]. Taken together, these observations strongly suggest that shared pathophysiologic mechanisms exist among these class I HLA-associated diseases [21].

Systemic arthritis (Systemic juvenile idiopathic arthritis and adult-onset Still's disease)

Systemic juvenile idiopathic arthritis (sJIA) and adult-onset Still's disease (AOSD) are both forms of systemic arthritis, with the primary difference between them being the age of onset. Systemic arthritis is a rare condition that includes the development of chronic arthritis, together with recurrent episodes of systemic inflammation that are marked by fever, evanescent skin rash, generalized lymphoid hyperplasia, thrombocytosis, and hyperferritinemia. Individuals with systemic arthritis are also at high risk of developing macrophage activation syndrome, a potentially fatal cytokine storm syndrome. Studies of anti-cytokine therapies (anti-IL-1 and anti-IL-6) have demonstrated the beneficial effects of these agents for many sJIA patients [24, 25]. However, because these therapies are neither universally tolerated nor universally effective, there remains a need to develop novel therapeutic agents to treat sJIA. Two recent studies have provided new clues into genetic underpinnings of systemic arthritis (Table 1). The first study, an ongoing genome-wide association study of sJIA patients from 9 countries, has identified a strong association

between sJIA and *HLA-DRB1*11* and has revealed another *bona fide* sJIA susceptibility locus at chr1:p36.32 [26]. The second study investigated a recessively-inherited, sJIA-like inflammatory disease that was identified in several consanguineous Saudi Arabian families [27]. In every affected family member, the authors identified homozygous founder mutations of *LACC1*, which encodes an antioxidant protein that also influences susceptibility to both inflammatory bowel disease and leprosy.

Conclusion

As we continue to pursue the causes of genetically-complex autoinflammatory diseases, we expect to uncover both innate and adaptive immune mechanisms that contribute to their pathogeneses. Because of the rare nature of many of these diseases, population-based genetic studies are challenging, requiring collaborative efforts to assemble adequately powered cohorts in which to perform association studies. Alternatively, monogenic or familial forms of genetically-complex autoinflammatory diseases will continue to provide a unique perspective of disease pathogenesis, given that in these cases a single genetic lesion is capable of producing an otherwise complex, polygenic phenotype.

Acknowledgments

Funding statement: This study was supported by the Intramural Research Program of the National Institute of Arthritis Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, U.S.A.

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Genes involved in the genetically complex autoinflammatory diseases

Disease	Causative genes in monogenic forms of disease	Risk genes in polygenic forms of disease
PFAPA	*SPAG7* [5]	*NLRP3* [7] *MEFV* [7]
Chronic non-bacterial osteomyelitis	*LPIN2* [9] *IL1RN* [10] *RAG1* [11] *Pstpip2* [12, 13]	chr18 q21.3 – chr18 q22 [28]
Behçet's disease	chr12p12 – chr12p13 [29] chr6p22 – chr6p24 [29] *NEMO* [30] *TNFAIP3* [31] *TNFRSF9* [31]	*HLA-B* [19, 20] *HLA-A* [20] *IL10* [32, 33] *IL23R* [32, 33] *CCR1* [21] *STAT4* [21] *KLRC4* [21] *ERAP1* [21] *MEFV* [34] *TLR4* [34] *TNFAIP3* [35] *TRAF5* [36] *TRAF3IP2* [36] *FUT2* [37]
Systemic arthritis • Adult-onset Still's disease • Systemic juvenile idiopathic arthritis)	*LACC1* [27]	*HLA-DRB1* [26] chr1 p36.32 [26]