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Idiopathic Recurrent Acute Pericarditis: A Cross Talk between Autoimmunity and Autoinflammation

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Abstract

Idiopathic recurrent acute pericarditis is the most baffling drawback occurring in around 1/3 of patients who have suffered from acute pericarditis or complicating a host of systemic medical conditions. Various autoimmune diseases can involve the pericardium during the acute phase of the disease, even with no specific signs, and different cases of postviral pericarditis display an autoimmune background. In addition, some autoinflammatory disorders might display self-limited pericardial effusions, which are characterized by chronic recurrence. The clinical efficacy of corticosteroids should give support to the autoimmune origin of idiopathic recurrent acute pericarditis, but the dramatic response to interleukin-1 antagonists in patients with steroid-dependent idiopathic recurrent pericarditis should corroborate its autoinflammatory beginnings. The dividing line between the two medical settings is undefined and both autoimmune and autoinflammatory mechanisms should be advocated in the evaluation of this challenging pericardial disease.

Keywords: Idiopathic recurrent acute pericarditis (IRAP); Autoimmunity; Autoinflammatory disorders; Interleukin (IL)-1; *MEFV* gene; *TNFRSF1A* gene; Familial Mediterranean fever (FMF); Tumour necrosis factor receptor-associated periodic syndrome (TRAPS)

Abbreviations: FMF: familial Mediterranean Fever; TRAPS: Tumor Necrosis Factor Receptor-Associated Periodic Syndrome; HIDS: Hyper-Immunoglobulinemia D Syndrome; FCAS: Familial Cold Autoinflammatory Syndrome; MWS: Muckle-Wells Syndrome; NOMID: Neonatal Onset Multisystem Inflammatory Disease; NLRP12-ad: NLRP12-Associated Autoinflammatory Disorder; PAPAs: PAPA (Pyogenic Arthritis, Pyoderma Gangrenosum, And Acne) syndrome; MS: Majeed Syndrome; DIRA: Deficiency Of Interleukin-1 Receptor Antagonist; BS: Blau Syndrome; CANDLEs: CANDLE (Chronic Atypical Neutrophilic Dermatitis With Lipodystrophy And Elevated Temperature) syndrome - AR: Autosomic Recessive; AD: Autosomic Dominant

Introduction

Acute pericarditis might recur over time and unexpectedly even years after recovery of a typical first attack. Recurrences occur in up to 1/3 of patients who have suffered from acute pericarditis [1], while the number of recurrences and the interval between the episodes vary among patients and are not predictable in any cases [2]. The traditional approach to pericarditis may result inconclusive, especially with reference to infectious agents, even from pericardial tap or biopsy: therefore, most of these cases are labeled as idiopathic. Rarely a cardiac tamponade might emerge as a complication of idiopathic recurrent acute pericarditis (IRAP), and failure to respond to standard treatment should require hospitalization to perform a pericardiocentesis or go ahead with extensive investigation and exclude gout, myxedema, uremia, but mostly primary or secondary neoplasms [3]. Diagnosis of pericarditis can be made when chest pain is variably combined with pericardial friction rub, suggestive electrocardiographic changes, new or worsening pericardial effusion, normal creatine kinase-MB, and increased C-reactive protein, but the minimum criteria for diagnosis of IRAP are the combination of typical chest pain, ECG and/or echocardiographic abnormalities, and increased C-reactive protein [4]. There are no controlled clinical trials about the appropriate doses of nonsteroidal anti-inflammatory drugs (as aspirin, indomethacin, or ibuprofen) or optimal duration of treatment in a pericarditis, and inadequate dosage of the index attack can explain the relapses in some cases [5]. Colchicine has been added to the standard treatment of acute pericarditis in a large randomized prospective trial, producing a 2/3 reduction of the recurrence rate [6]. Administration of corticosteroids to maintain for at least 4 weeks and slowly taper in the following months is required in different cases of recurrent pericarditis, legitimating the many concerns of both patients and physicians related to steroid-side effects, but corticosteroid therapy is even an independent risk factor for recurrences [7]. Also intrapericardial administration of triamcinolone has been attempted in the treatment of recalcitrant forms of IRAP [8].

The Role of Autoimmunity

A significant subset of IRAP cases are determined by autoimmune reactions to different microorganisms, frequently viruses, and microbial toxins [9]. Most of agents detected in postviral recurrent pericarditis are echovirus, coxsackie-virus, Epstein-Barr virus, cytomegalovirus, adenovirus, and parvovirus B19; a bacterial origin is on the other hand mostly related to *Mycobacterium tuberculosis*, basically as a result of the human immunodeficiency virus epidemic [10]. Different experts advocate that once collagen vascular diseases or a previous myocardial infarction have been ruled out, most cases of IRAP are usually triggered by autoimmune mechanisms with or without an initial viral agent [11]. However, it is misleading to consider all cases of IRAP as autoimmune,

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and definite evidence of an autoimmune basis should be indeed documented, while polymerase chain reaction for cardiotropic viruses and other infectious agents should be negative, and immunoglobulin M against these agents should not be evident [12]. Autoimmunity can play a role in the pathogenesis of recurrent postviral pericarditis through the activation of the innate and adaptive immunity pathway in predisposed hosts, and it is known that microbial DNA can potently stimulate the immune system, activating both toll-like receptors (TLRs), crucial key receptors in response to pathogen recognition, as well as other germline-encoded receptors [13]. Following the response of activated dendritic cells, naïve $CD4^+$ T cells may differentiate into different Th subsets with distinct effector functions and variable cytokine release: recent data have shown that dendritic cells can break an expected state of tolerance and induce autoimmune reactions by priming autoreactive T cells [14]. Critical appears the role of tissue-resident dendritic cells in orchestrating the adaptive components of the immune system, so that appropriate responses are mounted through the recruitment of natural killer cells and imbalance in the feedback control of TLR-activated cells. The induction of autoimmune reactions might also depend on several biohumoral factors, not yet fully identified, which might implicate the pericardium. Different self-antigens may be overexposed following damage to pericardial or myocardial tissues and act as endogenous triggers interacting with TLRs and stimulating B and T cells to elicit an autoimmune process [15].

Immunopathologic mechanisms are evident in the recurrent pericarditis of vasculitides and connective tissue diseases, especially systemic lupus erythematosus. It is well-known that the pericardium can be involved in patients with flares of systemic lupus erythematosus, rheumatoid arthritis, progressive systemic sclerosis, Sjögren's syndrome, polyarteritis nodosa, or other systemic vasculitis. In many cases, pericardial involvement may be subclinical with a silent pericardial effusion or clinically overt with symptoms of different severity. An autoimmune background in some cases of IRAP is also suggested by the presence of proinflammatory cytokines in the pericardial fluid and antinuclear auto antibodies (ANA) in patients' sera, sometimes associated with the occurrence of new autoimmune diagnoses and good response to anti-inflammatory or immunosuppressive therapy [16].

The relationship existing between IRAP and detectable autoantibodies is still unclear: ANA have been detected in 43.4% of patients with IRAP and in only 9.8% of controls [17]. However, a positive result for ANA, even at low titres (1/40 to 1/80), is nonspecific, though its confirmation in patients with IRAP might suggest a potential autoimmune origin. In addition, the clinical significance of ANA in IRAP is limited, as they are equally distributed in patients with or without a definite rheumatological diagnosis, with higher prevalence among females, older individuals, and people of African or American descent [18]. The functional relevance of auto antibodies against cardiac myosin in idiopathic dilated cardiomyopathy remains to be unraveled [19], and no studies exist evaluating their role in IRAP. In 2010, Caforio et al. evaluated by indirect immunofluorescence the frequency of serum anti-heart (AHA), anti-intercalated-disk (AIDA), and non-cardiac autoantibodies in a series of 40 Italian patients with IRAP [20]: three of the autoantigens recognized by the AHA were identified as α and β myosin heavy chain and myosin light chain-1v isoforms, while the autoantigen(s) responsible for AIDA were not yet identified [21]. AHA and/or AIDA represent autoimmune markers in patients with biopsy-proven myocarditis or dilated cardiomyopathy and have been found in 67.5% patients with IRAP: a higher frequency of AHA and AIDA (respectively, 50 and 25%) has been found in IRAP, in comparison with non-inflammatory or ischaemic cardiac diseases. With reference to non-cardiac autoantibodies, only ANA at titres exceeding 1/160 were found in patients with IRAP (5%). In addition, a higher number of recurrences and hospitalizations was documented in IRAP, whereas high titre-AHA were only associated with a higher number of recurrences [20]. Whether or not these autoantibodies may provide clinically actionable biomarkers of IRAP requires future assessment. In spite of these findings, actual guidelines still suggest that the diagnosis of autoimmune pericarditis should be based upon a pericardial biopsy [22].

The Role of Autoinflammation

Cases of IRAP which do not match any plausible immunological mechanism have been also related to a growing group of dysfunctions of the innate immune system, called "autoinflammatory disorders" and caused by mutations of genes involved in the regulation or activation of the inflammatory response, without any apparent involvement of antigen-specific T cells and autoantibodies [23]. These patients display periodically-recurring inflammatory attacks, which have a typical onset in the pediatric age, and show classically increased inflammatory parameters, alternating with symptom-free intervals and normal acute phase reactants [24]. Apart from the common recurrent inflammatory attacks, all autoinflammatory disorders have distinct features and specific therapeutic options, which emphasize the need for a specific diagnosis in each case: a synthetic list of hereditary autoinflammatory disorders is shown in the table 1. A host of clinical sceneries can be depicted, and the cardiovascular system might also be involved in two of them, familial Mediterranean fever (FMF), caused by mutations in the *MEFV* gene, which encodes the protein called pyrin, and tumour necrosis factor receptor-associated periodic syndrome (TRAPS), caused by mutations in the *TNFRSF1A* gene, which encodes the 55-kD receptor for tumor necrosis factor (TNF)-alpha, also named TNFRSF1A [25].

FMF is the most common recessive and TRAPS the most common dominant autosomally inherited autoinflammatory disorder. Figure 1 shows FMF-causing mutations in *MEFV* and their location in both exons and protein domains; in particular, the *MEFV* mutations found in patients with IRAP are coloured in red. Figure 2 depicts the mechanisms of pyrin action in the pathogenesis of FMF. Figure 3 shows TRAPS-causing mutations in *TNFRSF1A* and their location in both exons and protein domains; in particular, the *TNFRSF1A* mutations found in patients with IRAP are coloured in red. Figure 4 depicts the mechanisms of TNFRSF1A action in the pathogenesis of TRAPS.

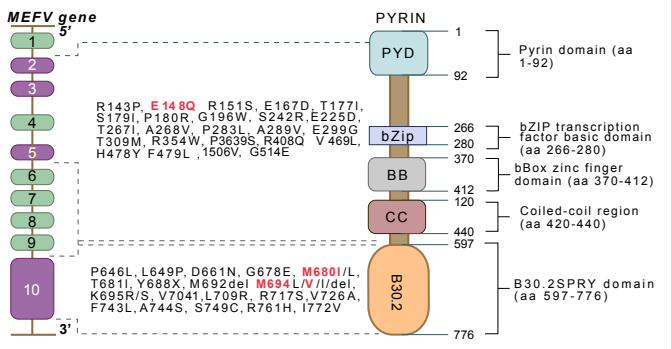

Figure 1: FMF-causing mutations in *MEFV* and their location in both exons and protein domains; in particular, the *MEFV* mutations found in patients with IRAP are coloured in red.

Disorder (OMIM)	Gene Locus	Protein involved	Pattern of inheritance	Major clinical finding	Treatment
FMF (249100)	*MEFV* 16p13.3	Pyrin (marenostrin)	AR	fever, serositis (peritonitis, pleuritis, pericarditis), arthralgias or arthritides, erysipelas-like eruption in the lower extremities, recurrent vasculitides,amyiloidosis in the untreated or noncompliant patients	Colchicine, interleukin-1 antagonists
TRAPS (142680)	*TNFRSF1A* 12p13	Tumor necrosis factor receptor type 1 (TNFRSF1A, or CD120a)	AD	fever, migratory muscle, skin and joint inflammatory signs, abdominal pain, vomiting, serositis (pleuritis, pericarditis), conjunctivitis, periorbital edema, amyloidosis	Etanercept, anakinra
HIDS (260920)	*MVK* 12q24	Mevalonate kinase	AR	fever, polymorphous skin rash, arthralgias, abdominal pain of different severity, diarrhea, lymph node enlargement, splenomegaly, oral aphthosis	Anti-inflammatory drugs, corticosteroids, anakinra
FCAS (120100)	*NLRP3* 1q44	Cryopyrin	AD	fever, cold-induced urticaria-like rash, conjunctivitis, arthralgias	Interleukin-1 antagonists (canakinumab)
MWS (191900)				fever, urticaria-like rash, conjunctivitis, arthralgias, neurosensorial deafness, amyloidosis	
NOMID (607115)				urticaria-like rash, aseptic chronic meningopathy, papilledema, optic nerve atrophy, neurosensorial deafness, deforming osteo-arthropathy of large joints (with abnormal patellar ossification), amyloidosis	
NLRP12-ad (609648)	*NLRP12* 19q13.42	Monarch 1	AD	cold-induced urticaria-like rash	Interleukin-1 antagonists
PAPAs (604416)	*PSTPIP1* 15q24-25	CD2 antigen-binding protein 1	AD	pyogenic sterile arthritis, pyoderma gangrenosus, cystic acne	Corticosteroids, tumor necrosis factor-inhibitors, interleukin-1 antagonists
MS (609628)	*LPIN2* 18p11.31	Lipin 2	AR	recurrent multifocal osteomyelitis, dyserythropoietic anemia, neutrophilic dermatosis	Corticosteroids
DIRA (612852)	*IL1RN* 2q	Interleukin-1 receptor antagonist	AR	sterile multifocal osteomyelitis with neonatal onset, pustular rash with ichthyosis-like changes	Anakinra
BS (186580)	*NOD2 (CARD15)* 16q12.1-13	NOD2 (CARD15)	AD	recurrent symmetric granulomatous polyarthritis, granulomatous panuveitis, brown-coloured and flaky granulomatous rash	Corticosteroids, infliximab
CANDLEs (256040)	*PSMB8* 6p21.3	β5i subunit of the immunoproteasome	AR	recurrent fever, cold-induced pernio-like and vasculitic skin lesions, progressive lipodystrophic changes in the upper body, joint contractures, clubbed fingers	Corticosteroids, interferon-gamma modulators, interleukin-6 antagonists

Table 1: List of the genetic and clinical characteristics of patients with hereditary autoinflammatory disorders [40].

IRAP is the most represented cardiovascular abnormality in FMF and TRAPS, though the role of *MEFV* and *TNFRSF1A* in the initiation of heart involvement has not been demonstrated formally. Patients with IRAP who have no diagnosis of FMF or TRAPS might fall in this category of disorders and, indeed, about 10% of them present a family history of pericarditis, which might at least suggest a genetic predisposition to the pericardial disease [26]. The inflammatory involvement of serosal membranes, combined with joint and skin involvement, is highly reported both for full-blown FMF and TRAPS: pathogen- and danger-associated molecular patterns might be involved in the inflammatory cascade, and it has been proved that frequent triggers of autoinflammation are cold exposure, physical trauma, childhood immunizations, psychological stress, or hormonal changes [27].

Pericardial involvement in FMF occurs usually late in the course of the disease: in a retrospective study about 4000 FMF patients were studied, finding that pericarditis was rarely observed and self-limited, with a low risk of constriction [28]. The Turkish FMF study group reported that pericarditis was observed in only 1.4% of patients, unlike serositis or synovitis, and independently from the evidence of amyloidosis or congestive heart failure [29]. FMF patients might also present recurrent pericarditis as the unique clinical recurrent manifestation in each inflammatory attack [30]. In addition, IRAP unresponsive to nonsteroidal anti-inflammatory medications and

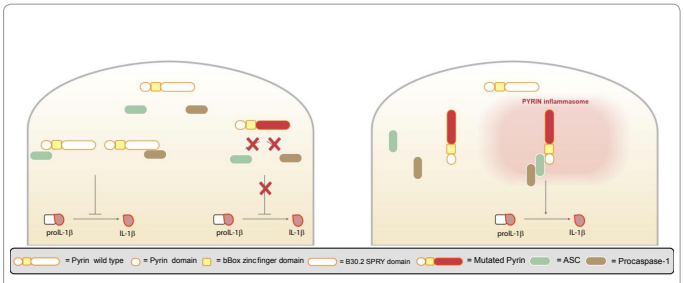

Figure 2: Depicts the mechanisms of pyrin action in the pathogenesis of FMF.

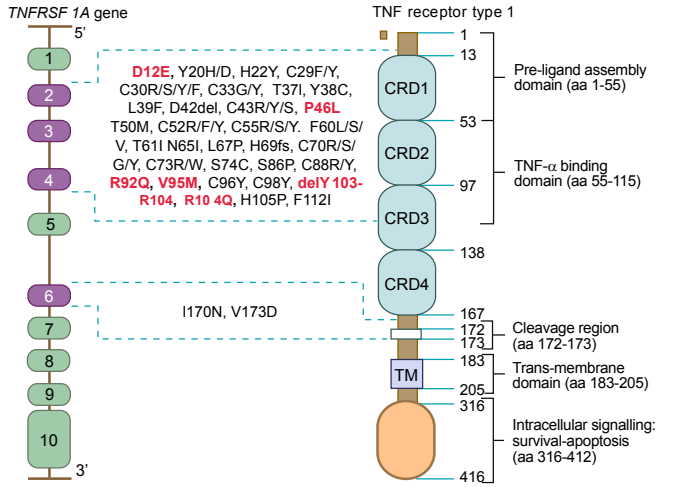

Figure 3: Shows TRAPS-causing mutations in *TNFRSF1A* and their location in both exons and protein domains; in particular, the *TNFRSF1A* mutations found in patients with IRAP are coloured in red.

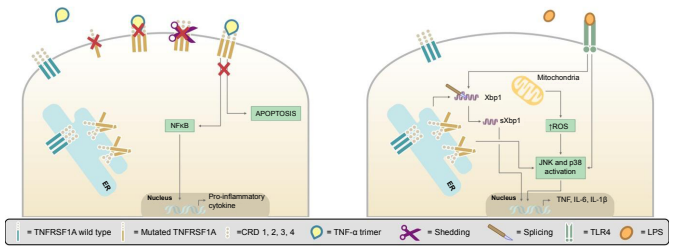

Figure 4: Depicts the mechanisms of TNFRSF1A action in the pathogenesis of TRAPS.

corticosteroids might even be the first onset sign of FMF, justifying a *MEFV* genetic analysis in this subset of patients [31].

Recurrent pericarditis, often in the form of polyserositis, is common in TRAPS, especially when the onset is in adulthood: we have also observed a small group of patients with IRAP who had an atypical or incomplete TRAPS, and more recently we have hypothesized that colchicine resistance and/or familial clustering of pericarditis might be two possible criteria for identifying, among IRAP patients, those with TRAPS, for whom *TNFRSF1A* genetic testing should be contributive [32-34]. With the aim of improving genetic diagnosis in adult patients suspected to have autoinflammatory disorders, we have pointed out some variables strongly related with the probability of detecting mutations in the *MEFV* or *TNFRSF1A* genes, and we have also developed a diagnostic score for selecting high-risk probands [35].

In many autoinflammatory diseases which are driven by inflammasome activation, followed by interlukin-1 (IL-1) oversecretion, the administration of anakinra, the recombinant IL-1 receptor antagonist, has been shown to have a dramatic therapeutic effect: similarly the same impressive effects have been observed in patients with low-penetrance *TNFRSF1A* mutations and isolated IRAP [36], suggesting a strong relationship between pericardial disease and autoinflammation. The identification of a small group of TRAPS-genetically positive patients with IRAP would also allow, in the case of poor response to conventional therapies, to prescribe more specific treatments with the advantage of avoiding the amyloid deposition-related complications of the syndrome.

In addition, the experience of long-course treatment with anakinra in pediatric patients with IRAP, allowing rapid tapering and discontinuation of corticosteroids, with no new disease relapse at a follow-up of 6 months, should suggest that at least a subset of patients with isolated IRAP and no known mutation for FMF or TRAPS might have a not yet identified autoinflammatory disorder, possibly related to gene mutations leading to dysregulation of IL-1 production and secretion [37].

Autoimmunity, Autoinflammation, or a Distinct Explanation?

As we have seen, diagnosis of IRAP is of exclusion, requiring to rule out infectious and non-infectious causes of pericardial inflammation, as systemic autoimmune or immune-related disorders. Since pericarditis may be preexisting and other illuminating signs which might corroborate the diagnosis of an organ-specific immune-related disorder may appear later, IRAP can be mostly diagnosed retrospectively, i.e. after a quite long follow-up, following several therapies which might have led to epitope spreading or change in cardiac antigen specificities. However, the two potential mechanisms explaining IRAP, autoimmune and autoinflammatory, might be unconfirmed in a single patient. Evidence which might ascribe to autoimmunity the origin of IRAP is the presence of serum autoantibodies, while the presence of autoinflammatory gene mutations or a spontaneously occurring-remission of the pericardial inflammation might ascribe the origin of IRAP to autoinflammation [38]. In both autoimmune and autoinflammatory backgrounds we find hypercytokinemia in the pericardial fluid, familial clustering of IRAP, and a good response to empiric anti-inflammatory drugs. In addition, IRAP may represent an independent form of disease, which is from the start neither autoimmune, nor autoinflammatory, but a distinct disorder with distinct pathogenetic mechanisms. Basic efforts of clinical research have provided valuable information and insights on the pathogenetic mechanisms of IRAP, although these mechanisms are far from being completely understood and multiple possible players are still to be identified. In a cohort of 55 patients with a first episode of idiopathic acute pericarditis, followed for a mean period of almost 2 years, genomic human leukocyte antigen (HLA) typing was performed and circulating lymphocyte subpopulations were studied in a subgroup, finding a recurrence rate of 40% and an increased frequency of HLA-A*02, -Cw*07 and -DQB1*0202 alleles in the recurrent forms. Notably, no patient with IRAP exhibited HLA-DRB1*04 and -DQB1*0302 alleles [39]. Thereby, HLA alleles may confer either susceptibility or resistance to IRAP and circulating T-cell subpopulations may also predict the recurrent forms of pericarditis, otherwise a combination of the above alleles might

help to better define patients prone to recurrence. Further studies are needed and are ongoing to define the possible contribution of the major HLA complex and other candidate genes to the recurrence of the disease.

Conclusions

In conclusion, many pathogenetic issues still require investigation in IRAP: we need to find reliable noninvasive methods that will distinguish autoimmune cases from those caused by reinfection or new infection, and even cases suggesting the new family of autoinflammatory disorders, in which innate immunity pathways are disrupted. In addition, clinicians should be aware that IRAP might be a part of the clinical spectrum of both FMF and TRAPS and consider mutation analysis, since the lack of an appropriate treatment in these disorders influences the risk of developing a secondary amyloidosis. Further research will include basic and clinical immunology items and development of more effective drugs, including the evaluation of alternative therapeutic options in the management of this challenging pericardial disease, as pericardiectomy.

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