The autoinflammatory side of recurrent pericarditis: enlightening the pathogenesis for a more rational treatment

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Highlights

- Recurrent pericarditis is a troublesome and debilitating event subsequent to a first episode of acute pericarditis.
- The pathogenesis of recurrent pericarditis is still obscure, standing at a crossroad between autoimmune and autoinflammatory pathways.
- Several observations including the presence of anti-nuclear, anti-heart and anti-intercalated disk antibodies as well as the association with specific human leukocyte antigen haplotypes suggest the existence of autoimmune mechanisms in the pathogenesis of recurrent pericarditis.
- The clinical resemblance with autoinflammatory diseases, especially tumor necrosis factor receptor-associated periodic syndrome, familial Mediterranean fever and adult onset Still's disease, all marked by symptomatic serositis, high fevers and raised inflammatory parameters, support the involvement of innate immunity into the pathogenesis of recurrent pericarditis.
- Neutrophils and monocytes are key-effector cells capable of producing a large amount of interleukin-1 via inflammasome activation in patients with recurrent pericarditis.
- Anakinra is an effective therapeutic choice to manage refractory cases of recurrent pericarditis, though other anti-interleukin agents may enrich the therapeutic armamentarium currently available for this disorder in the near future.

The autoinflammatory side of recurrent pericarditis: enlightening the pathogenesis for a more rational treatment

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Declaration of interest

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Ethical Statement

Not applicable for this work.

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ABSTRACT

Recurrent pericarditis (RP) is a troublesome and debilitating complication of acute pericarditis. Although the etiopathogenesis of this condition remains unknown, an intricate overlap of autoimmune and autoinflammatory pathways has been hypothesized to explain its beginning and recurrence over time. The majority of cases are defined as "idiopathic", reflecting our awkwardness to unravel the intimate mechanisms of RP. Given the possible occurrence of anti-nuclear, anti-heart and anti-intercalated disk antibodies as well as the association with peculiar human leukocyte antigen haplotypes, an autoimmune contribution has been claimed to specify the nature of RP. However, the most innovative pathogenic scenario of RP has been conferred to the innate immune system, mainly involving neutrophils and macrophages that produce a large amount of interleukin (IL)-1 via inflammasome activation. The clinical resemblance of RP with autoinflammatory diseases that may be marked by symptomatic serositis, high fevers and strikingly increased inflammatory parameters further suggests a similar inflammasome-mediated pathogenesis. Aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) remain the mainstay of therapy in RP, whereas colchicine is recommended on top of standard anti-inflammatory therapy, due to its role in inhibiting the IL-1 converting enzyme (caspase 1) within the inflammasome as well as the release of additional pro-inflammatory mediators and reactive oxygen species. With regard to treatment of RP refractory to NSAIDs and colchicine, blockade of IL-1 is the most relevant advance achieved in the last decade: the outstanding effect of the short-acting IL-1 receptor antagonist anakinra has been first recognized in the pediatric population,

giving a proof of its practical feasibility. Over a more recent time, a growing experience with anakinra deriving from both large and small studies has further confirmed that RP might be regarded as an IL-1-mediated disease. This review aims to provide a contemporary insight into the mechanisms leading to RP as well as into the most recent literature data showing the beneficial approach originating from IL-1 blockade in this intriguing disorder.

Keywords: Recurrent pericarditis, pericardial disease, pericardium, autoinflammation, autoinflammatory disease, interleukin-1, anakinra, personalized medicine, innovative biotechnologies

Contents

1. Recurrent pericarditis: the size of the problem
2. An interplay of autoimmune and autoinflammatory phenomena within the pericardium
3. A putative role of innate immunity in recurrent pericarditis
4. Recurrent pericarditis in the autoinflammatory diseases
5. Management of recurrent pericarditis
   - 5.a General hints for treatment of recurrent pericarditis
   - 5.b Interleukin-1 blockade in recurrent pericarditis

6. Conclusive remarks

7. References

1. RECURRENT PERICARDITIS: THE SIZE OF THE PROBLEM

Acute pericarditis accounts for about 5% of emergency department admissions due to chest pain, and the estimated recurrence rate of this disorder ranges from 15 to 50% [1] within 18 months after the first acute episode of pericarditis [2]. Recurrent pericarditis (RP) is a troublesome and debilitating complication of acute pericarditis that is defined as *recurrent* when a symptom-free interval of 4-6 weeks or longer occurs between the first acute episode and a relapse [3]. Moreover, RP should be differentiated from *incessant pericarditis*, in which symptoms persist for more than 4-6 weeks but less than 3 months, and *chronic pericarditis* that lasts for more than 3 months [1]. The overall incidence of RP can be estimated around 5-35/10^5 per year [4]. The cause of RP is believed to rely in a misdirected immune mechanism triggered by some microbial agents, mostly viruses, or by their antigens working as key-determinants contributing to both onset and recurrence of pericarditis [5]. Clinically speaking, chest pain, often sharp, improved by sitting up and leaning forward, is the most common symptom of both acute pericarditis and RP. Conversely, other clinical features including pericardial friction rub, electrocardiographic changes such as new widespread ST-elevation or PR segment depression and pericardial effusions may be present in a variable percentage of

patients [6]. About 80% of pericarditis are considered “idiopathic”, reflecting clinicians’ difficulty in unveiling the actual pathogenic mechanism underlying this disorder. However, an increasing knowledge of the pathways involving adaptive and innate immunity has allowed discriminating different subsets of patients with RP [7]. A clinical phenotype evolving to complete resolution of symptoms, though marked by symptomatic serositis with fever and remarkable increase of inflammatory parameters during acute attacks, tends to show a dramatic response to anti-interleukin (IL)-1 and suggests an autoinflammatory pathogenesis [8]. On the contrary, another phenotype of RP with a subacute course characterized by moderate increase of inflammatory markers, presence of serum autoantibodies including anti-nuclear antibodies (ANA), anti-heart antibodies (AHA) and anti-intercalated disk autoantibodies (AIDA) combined with autoimmune features such as arthralgias, sicca syndrome, Raynaud’s phenomenon and uveitis, would suggest more clearly an autoimmune working [9]. A third and last clinical phenotype of RP includes patients with mild attacks presenting a subacute course, weak elevation of inflammatory markers without autoimmune manifestations and without circulating autoantibodies [8]. Although elevation of inflammatory markers including C-reactive protein (CRP) is not specific for RP, this is important during the management of the disease. In this regard, atypical or subacute cases of RP may be disclosed by imaging techniques, such as computerized tomography scan or cardiac magnetic resonance, which help establishing diagnosis due to pericardial inflammation or edema on T2-weighted images, respectively [1]. More recently, the carcinoembryonic antigen cell adhesion molecule 1 and the major histocompatibility

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Figure captions

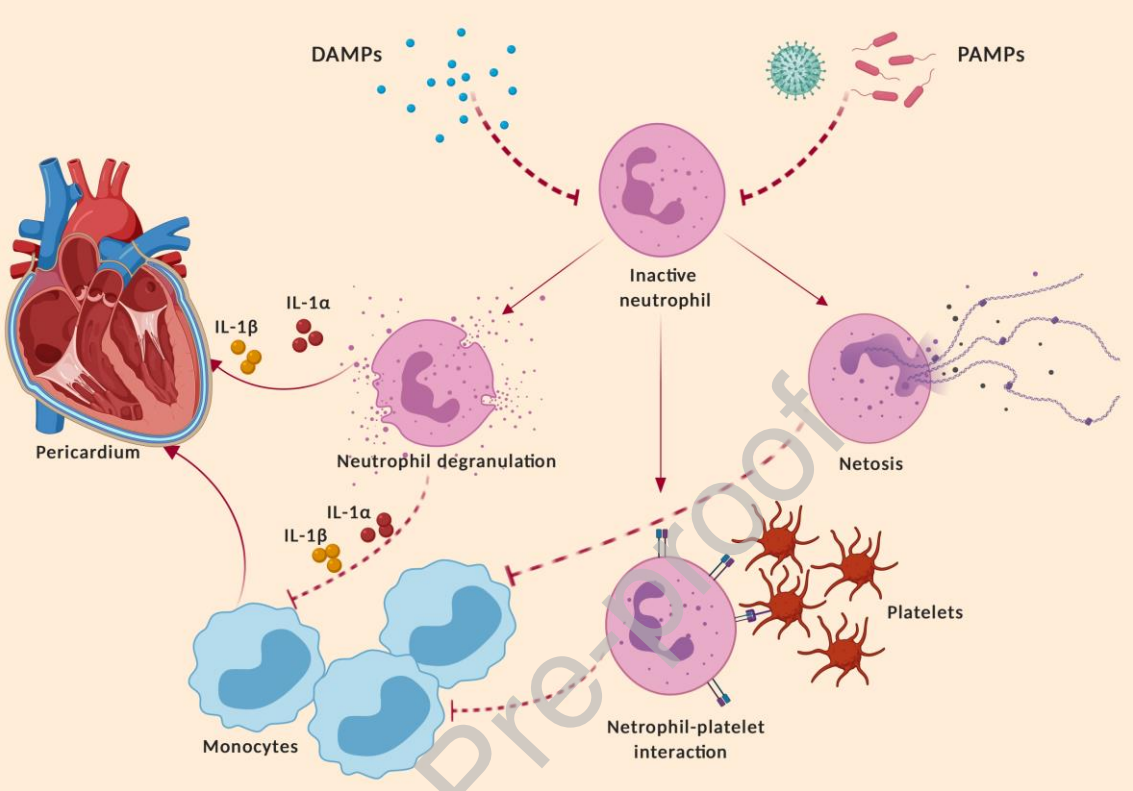

Figure 1 Putative role of neutrophils in the pathogenesis of recurrent pericarditis

Neutrophils activated by cellular sensors like pathogen associated molecular patterns (PAMPs) or damage associated molecular patterns (DAMPs) secrete a large amount of both interleukin (IL)-1α and IL-1β, which in turn can activate monocytes and enhance inflammation in the pericardium. Moreover, neutrophils co-work with platelets for the recruitment of monocytes at the site of inflammation. Finally, the release of neutrophil extracellular traps (Netosis) to neutralize infectious agents can activate monocytes to produce IL-6 and further pro-IL-1β

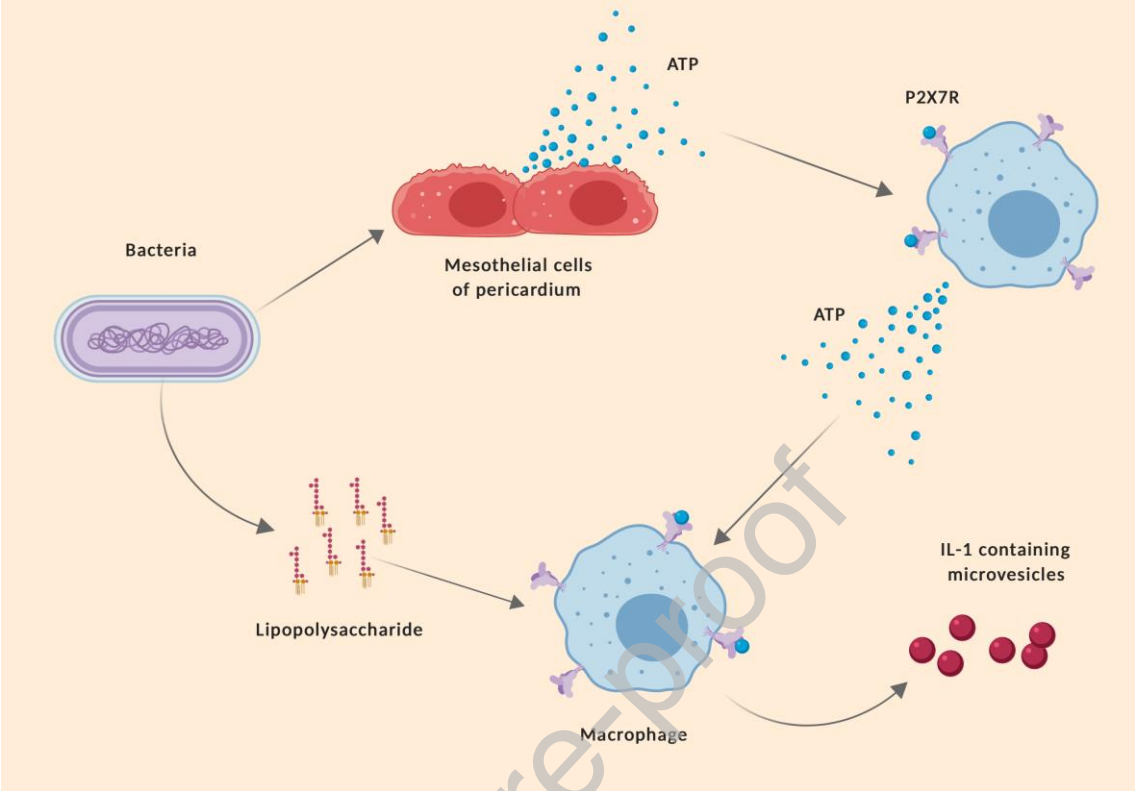

Figure 2 Macrophages and purinergic P2X7 receptor function in recurrent pericarditis

Mesothelial cells of the pericardium appear stressed due to a bacterial infection and release danger signals such as adenosine triphosphate (ATP) that activate monocytes/macrophages. In this context, the purinergic P2X7 receptor (P2X7R) may function as an amplification device to spread the ATP wave, as its activation triggers further ATP release. Finally, macrophages stimulated by lipopolysaccharide and ATP release interleukin (IL)-1-containing microvesicles

Table 1 Synoptic table reporting the main literature data dealing with anti-IL1 agents employed in the treatment of recurrent pericarditis

First author (year) [reference]	Patients number/age	Disease	Study	Anti-IL-1 agent dosage	Outcome	Side effects
Picco (2009) [98]	3 children	2 IRP, 1 Mhyre syndrome/IRP	Case series	ANA from 0.7 mg/kg/day to 1.25 mg/kg/day	Prompt resolution of the clinical symptoms with normalization of acute phase reactants, CCs tapering, relapse in all patients after anakinra withdrawal	NA
Scott (2011) [99]	2 adults	IRP	Case series	ANA 100 mg/day	Remission on anakinra and colchicine in 1 patient, dramatic response and steroid withdrawal without flares in the other patient	NA
Vassilopoulos (2012) [100]	3 adults	IRP	Case series	ANA 150 mg/day in 1 patient, ANA 100 mg/day in 2 patients	Dramatic clinical response with concomitant prompt normalization of acute phase reactants and steroid discontinuation in 2 patients	Increase in aminotransferase levels in 1
Finetti (2014) [101]	12 children, 3 adults	1 Mhyre syndrome/IRP, 1 Sotos syndrome/IRP, 13 IRP	Observational retrospective	ANA from 1 mg/kg/day to 2 mg/kg/day	Complete response within a few days, rapid CCs withdrawal	Skin reactions at the injection site in 5
Lazaros (2014) [102]	10 adults	IRP	Observational prospective	ANA 100 mg/day for 6 months followed by alternate day dosing for further 6 months	Rapid symptom relief, CRP normalization, tapering or discontinuation of CCs, 5/7 patients relapsed shortly after ANA discontinuation	Local reactions at the injection site in 6 patients, transient transaminase elevation in 1
Jain (2015) [103]	13 adults	12 IRP, 1 post-infarction pericarditis	Observational retrospective	ANA 100 mg once daily	Complete improvement of symptoms with ESR and CRP normalization within 2-to-5 days in 12, partial resolution in 1, discontinuation of NSAIDs, colchicine and CCs in 11	Transient injection site reaction in 4
Imazio (2016) [8]	12 children	IRP	Retrospective multicentre cohort study	ANA 1.0 mg/kg/day	Drop in the number of recurrences from 4.2 per year before to 0.1 per year after	NA
Brucato (2016) [104]	20 adults, 1 child	IRP	Randomized, double-blind placebo-controlled	ANA 100 mg/day in adults, 2 mg/kg/day up to 100 mg in children	Reduced risk of pericarditis recurrence and reduced incidence rate of recurrence following ANA	Local reaction at the injection site in 20, herpes zoster in 1, ischemic optic neuropathy in 1,

						elevation of transaminases in 3
Kougkas (2018) [107]	3 adults	2 AOSD, 1 RA	Case series	CANA 150 mg/monthly in AOSD; up to 300 mg/monthly in RA	Prompt and long-standing remission with consequent CCs discontinuation in 2 (with AOSD), partial response in RA	Not reported
Dagan (2019) [105]	7 adults	IRP	Observational retrospective	Anakinra 100 mg/ day in all patients, reduced to 100 mg/every other day in 1	Rapid response within a few days in all patients, prednisone discontinuation in 4 patients, reduction to low-dose in 2, CRP normalization in 6 and decrease in 1	Local reaction at the injection site in 2, herpes zoster in 1
Imazio (2019) [106]	224 adults	167 IRP, 28 post-cardiac injury syndrome, 21 autoimmune diseases, 5 AIDs, 2 pericarditis due to irradiation, 1 post-traumatic pericarditis	Observational cohort study	ANA starting dose of 100 mg/day followed by tapering	Reduction in pericarditis recurrences, emergency department admissions and hospitalizations, CCs sparing effect	Reaction at the injection site in 86, arthralgias/myalgias in 13, transaminase elevation in 7, infections in 6, neutropenia in 3, hypereosinophilia in 1, mild fever in 1, flushes and sweating in 1, perforated diverticulitis in 1, optic neuritis in 1
Caorsi (2019) [108]	55 children	IRP	Observational retrospective	ANA mean dosage of 1.67 mg/kg/day as first-line in 54 CANA 150 mg every 4 weeks in 5 (1 as first-line; 4 after ANA)	50/54 patients had a complete response to ANA combined with NSAIDs and glucocorticoids, colchicine withdrawal in the majority of patients, complete control in 2/5 following CANA, 2 patients discontinued CANA for inefficacy, 1 patient required low-dose CCs to control the disease	Poor compliance in 2, local reaction at the injection site in 1

Abbreviations: AIDs: Autoinflammatory diseases; AOSD: Adult onset Still's disease; RA: Rheumatoid arthritis; ANA: anakinra; CANA: canakinumab; CCs: corticosteroids; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; IRP: Idiopathic recurrent pericarditis; NA: not applicable; NSAIDs: non-steroidal anti-inflammatory drugs