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Editorial

Cardiac cytokine therapy? Relevance of targeting inflammatory mediators to combat cardiac arrhythmogenic remodeling

1. Evidence of profibrillatory inflammation-signaling in AF

Inflammation is a normal reaction in response to cardiac injury or infection [1]. The ultimate role of inflammation is to repair damaged tissue and restore homeostatic functions [2]. Inflammation can be described as a complex succession of active cellular processes, characterized by an initiation phase and a resolution phase, involving specific endogenous bioactive mediators (cytokines, lipoxins, resolvins), aiming to promote adapted homeostasis [3]. Failures in the resolution machinery in response to inflammation can provoke an unresolved inflammatory status leading to aggravation of structural damages, development of fibrosis, and loss of function [2,3]. Multiple cardiac conditions share an uncontrolled chronic inflammatory profile, including atherosclerosis, myocardial infarction, or atrial fibrillation (AF) [4,5].

In AF, the most commonly diagnosed form of arrhythmia, chronic inflammation is suspected of contributing to structural and electrical atrial remodeling [5]. Among proinflammatory components of interest, the NLRP3 inflammasome has been shown to play an important role in the development of AF [6]. It has been shown that NLRP3 inflammasome activity is increased in the atria from patients with paroxysmal and long-standing persistent AF [6]. Abnormalities affecting the structure (connexins lateralization, cellular hypertrophy) and the function (calcium [Ca^{2+}] handling, cellular contractility) of atrial cardiomyocytes (CM) contribute to the development and the maintenance of AF substrate [7]. NLRP3 inflammasome activity has been demonstrated to be higher in atrial CM from patients with AF compared to patients with no history of AF [6,7,8]. In addition, recent investigations from Jordi Heijman and colleagues revealed that patients developing post-operative AF showed increased atrial CM's activation of the NLRP3-CamKII (Ca^{2+}/calmodulin-dependent protein kinase-II) signaling axis, associated with Ca^{2+}-handling abnormalities [9]. These significant insights helped to clarify the mode of action of arrhythmogenic NLRP3 inflammasome activities. In response to damage-, pathogen-, or lifestyle-associated stimuli, NLRP3 is activated, and NFκB signaling promotes the upregulation of IL-1β and IL-18, which induce the production of further inflammatory cytokines, including IL6, IL-17A, IFN-γ, or CCL2 [10]. Recent study from Larry Scott Jr. and collaborators have demonstrated that obesity-induced atrial arrhythmogenic remodeling is associated with increased NLRP3 activity [11]. In addition, diabetes-associated thromboinflammation was shown to be accompanied by increased activity of NLRP3 inflammasome and IL-1β expression [12]. These data suggest a pivotal role of NLRP3 inflammasome in the activation of cytokine-induced atrial arrhythmogenic inflammation-signaling. In this context, IL6 levels have been shown to be elevated in patients with increased left atrial size and increased AF duration [13]. Increased levels of proinflammatory cytokines (IL-1β, CCL2, CXCL1/2, IFN-γ) and fibrosis-related molecules (COL1A1, αSMA, TGF-β) were associated with atrial electrical remodeling, connexin down-regulation, and atrial arrhythmogenicity [14,15]. Inflammation-resolution promoting interventions with specialized pro-resolving mediators (resolvins, maresins, protectins) have the potential to promote cessation of proinflammatory signals to prevent arrhythmogenic fibrosis [3,15] (Fig. 1).

The underlying mechanisms and modes of action of IL-6, IL-17A, or IFN-γ in the promotion of AF remain unclear.

2. Inflammatory biomarkers as indicators of atrial low voltage zone

In their research article titled: «***Association between serum inflammatory biomarkers and atrial low voltage in patients with atrial fibrillation***» [16], Tetsuma Kawaji and collaborators evaluated the level of expression of inflammatory biomarkers present in peripheral blood (PB) samples, before catheter ablation procedure, in sixteen patients with AF, participating in the ongoing prospective FIB-MARK study (**Fi**brosis **B**iomarker **M**irroring **A**trial Fi**b**rillation severity as **K**ey of Aging) [Jrct1050200007]. They observed that left atrial (LA) low voltage zone (LVZ), characterized by decreased electrical activity, was associated with increased PB level of pro-inflammatory biomarkers including IL-1β, IL-15, IL-16, IL-17A, IL-2, IL-3, IL-4, IL-8, MIP-1α/β/δ, TNF-α, TNF-β, NT-pro BNP; and decreased expression of ICAM-1, IFN-γ, IL-1α, IL-10, RANTES, TGF-β1, TIMP-2 [16]. They reported that serum IL-17A/IFN-γ and MIP-1δ/IFN-γ ratios were associated with severe LVZ in LA from AF patients.

As assessed by the authors, an important limitation in this study is the small number of patients. Therefore, in future work or follow-up studies, it will be interesting to verify whether the reported

Abbreviations: AF, Atrial Fibrillation; CamKII, Calcium/calmodulin-dependent protein kinase-II; CCL2, C-C motif Chemokine Ligand 2; CM, Cardiomyocyte; IFN-γ, Interferon gamma; IL, Interleukin; LA, Left Atrium; LVZ, Low Voltage Zone; NLRP3, NACHT, LRR, and PYD domains-containing protein-3; Th-cell, T helper cell.

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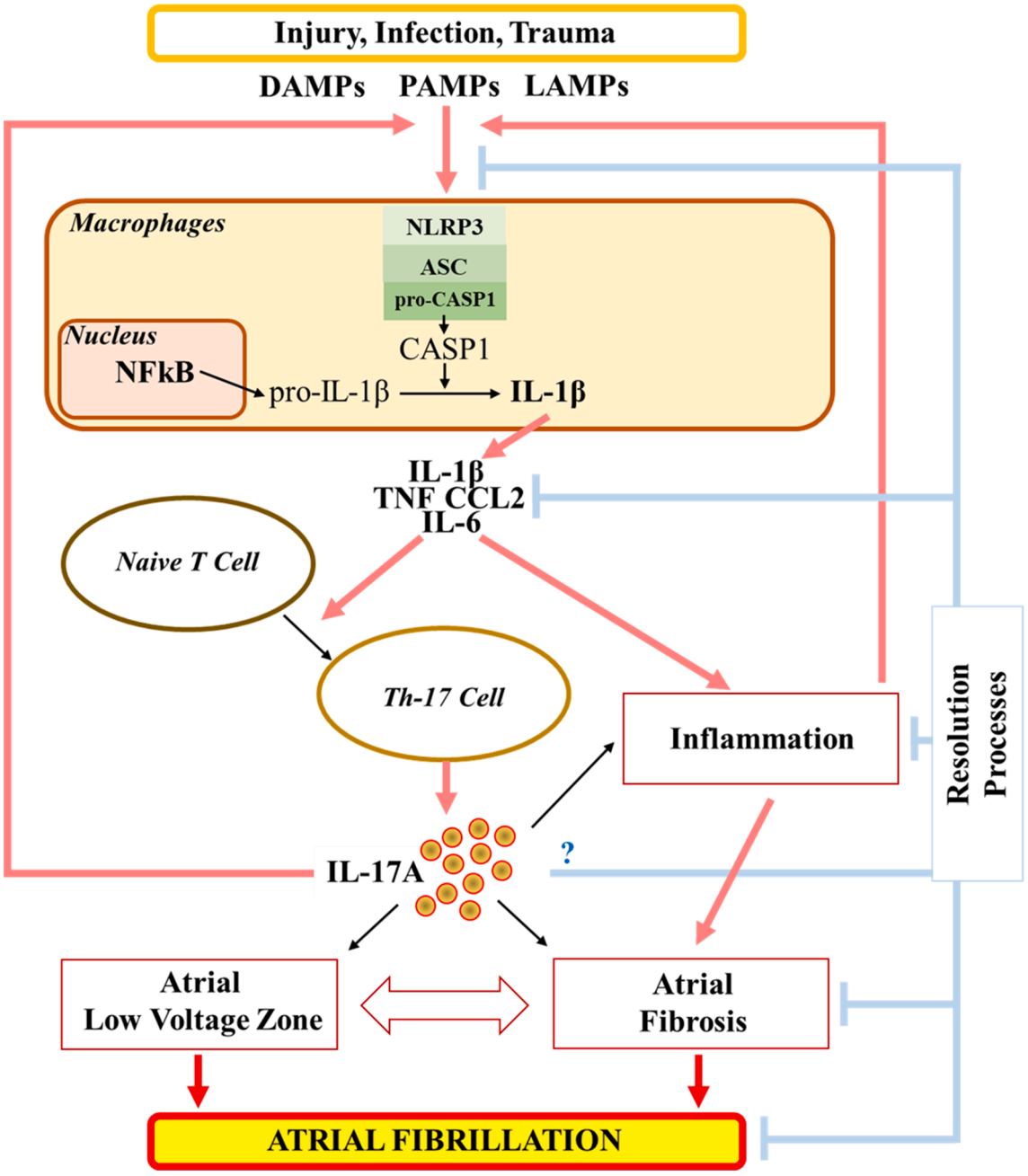

Fig. 1. Cytokine orchestration of arrhythmogenic inflammation. In response to injury, infection or lifestyle-induced trauma, DAMPs, PAMPs, or LAMPs can activate the NFκB signaling-pathway and the NLRP3 inflammasome, which contribute to the maturation of pro-IL-1β into IL-1β. IL-1β enhances the production of various proinflammatory cytokines, including IL-6, TNF, or CCL2. The augmentation of proinflammatory signals promotes the differentiation of naïve T cells into Th-17 cells, which produce IL-17A, a bioactive cytokine responsible for further inflammatory signals associated with increased proinflammatory macrophage infiltration and development of cardiac fibrosis. In the atrium, myocardial fibrosis provokes electrical conduction abnormalities, including the development of low voltage zones that contribute to increase the risk of atrial fibrillation (AF). Innate or pharmacologically induced pro-resolution signals and cellular processes have the potential to induce the termination of proinflammatory cells recruitment and differentiation, the diminution of proinflammatory cytokine levels, attenuation of myocardial fibrosis, and inhibition of arrhythmogenic substrate. The role of pro-resolving mediators on IL-17A associated with AF remains unclear. ***Abbreviations:*** ***ASC:*** *apoptosis-associated speck-like protein containing a C-terminal caspase activation and recruitment domain;* ***CCL2:*** *C-C Motif Chemokine Ligand;* ***DAMPs:*** *Damage-associated molecular patterns;* ***IL-1β:*** *Interleukin 1 beta;* ***IL-17A:*** *interleukin 17A;* ***IL-6:*** *Interleukin 6;* ***LAMPs:*** *Lifestyle-associated molecular patterns;* ***NFκB:*** *nuclear factor-kappa B;* ***NLRP3:*** *NACHT, LRR, and PYD domains-containing protein-3;* ***PAMPs:*** *Pathogen-associated molecular patterns;* ***TNF:*** *tumor necrosis factor.*

observations are confirmed in a larger cohort. Furthermore, to better characterize the structural and electrical remodeling suggested by the detection of severe LVZ, it would be interesting to confirm the presence of fibrosis by magnetic resonance imaging (MRI) or/and histopathological analyses of fibrous content on atrial biopsies. Moreover, the analyses of myocardial expression of inflammatory and fibrosis-related genes and proteins would strengthen their approach.

The originality and novelty of this investigation lie in the fact that the authors proposed a quantification of systemic inflammatory biomarkers which, if verified on a larger representative sample of the population, could constitute a potential screening tool to diagnose the susceptibility to severe atrial LVZ. IL-17A is produced by CD4+ T helper cells (Th-17) [17] (Fig. 1). In recent prospective studies involving patients with AF or not, it has been shown that elevated plasma levels of Th17-secreted

cytokines, including IL-17A and IL-6, were associated with an increased risk of AF [18,19]. Elevated serum levels of IL-1β, IL-6 and hs-CRP (high-sensitive C-reactive-Protein) were demonstrated to be associated with increased duration and incidence of AF in patients with cardiac inflammation [20]. Consistent with these observations, Kawaji and collaborators reported that IL-17A and IL-1β were among the top up-regulated cytokines in AF patients with severe LVZ [14]. Interestingly, Kawaji and co-authors reported that IL-6 and IFN-γ were negatively associated with severe LVZ, which seems inconsistent with the previously described proinflammatory, profibrotic and proarrhythmogenic effects of these cytokines [10,13,15]. The paradoxical role of IFN-γ in the myocardium has previously been discussed by Scott P. Levick and Paul H. Goldspink [21]. They reported that although IFN-γ promotes deleterious remodeling on cardiac myocytes and fibroblasts, it may exert protective effects against cardiac hypertrophy [21].

Altogether, these data confirm the crucial implication of inflammatory signaling in cardiac pathophysiology suggesting that the development of new therapeutic strategies should consider targeting specific cytokine candidates.

3. Conclusion

Unresolved chronic inflammation is suspected of activating arrhythmogenic changes affecting cardiac myocytes and fibroblasts, leading to electrical abnormalities, cardiac fibrosis, and AF. IL-17A, the founding member of IL-17 family, has been found to be associated with severe atrial LVZ, suggesting a potential correlation with the development of cardiac fibrosis and arrhythmogenicity. However, the causal link between elevated levels of IL-17A and the incidence of AF remains unclear.

4. Takeaway points

- NLRP3 inflammasome-induced inflammation signaling is elevated in the atria from AF patients.
- AF patients often show atrial LVZ associated with atrial fibrosis.
- Atrial arrhythmogenic remodeling, including LVZ, is associated with increased levels of circulating inflammatory biomarkers such as IL-17A and IL-1β.
- Therapeutic strategies targeting specific inflammation or resolution mediators may contribute to prevent or treat IL-17A-related profibrillatory atrial remodeling.

5. Call-for-action

- Further investigations are required to clarify the suspected association between systemic levels of IL-17A, IFN-γ, and arrhythmogenic atrial remodeling including NLRP3-inflammasome's up-regulation.
- The inhibitory role of proresolving signaling on Th-17 cells to terminate inflammation is reported, but little is known about their effects on IL-17A production/activity, and eventually on atrial LVZ prevention/reparation.
- It would be interesting to evaluate the levels of circulating IL-17A and IFN-γ in patients treated with recently described medications that have shown promising cardioprotective effects (i.e., low-dose colchicine).

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] N.A. Punchard, C.J. Whelan, I. Adcock, J. Inflamm. (Lond.) 1 (2004) 1.
[2] M.O. Freire, T.E. Van Dyke, Natural resolution of inflammation, Periodontol. 63 (1) (2013) 149–164.
[3] C.N. Serhan, Pro-resolving lipid mediators are leads for resolution physiology, Nature 510 (7503) (2014) 92–101.
[4] L.T. Cooper, Myocarditis, N. Engl. J. Med. 360 (15) (2009) 1526–1538.
[5] M. Harada, S. Nattel, Implications of inflammation and fibrosis in atrial fibrillation pathophysiology, Card Electrophysiol. Clin. 13 (1) (2021) 25–35.
[6] C. Yao, T. Veleva, L. Scott, S. Cao, L. Li, G. Chen, P. Jeyabal, X. Pan, K.M. Alsina, I. Abu-Taha, S. Ghezelbash, C.L. Reynolds, Y.H. Shen, S.A. LeMaire, W. Schmitz, F. U. Müller, A. El-Armouche, N. Tony Eissa, C. Beeton, S. Nattel, X.H.T. Wehrens, D. Dobrev, N.a. Li, Enhanced Cardiomyocyte NLRP3 Inflammasome Signaling Promotes Atrial Fibrillation [published correction appears in Circulation. 2019 Apr 23;139(17):e889], Circulation 138 (20) (2018) 2227–2242.
[7] S. Nattel, J. Heijman, L. Zhou, D. Dobrev, Molecular basis of atrial fibrillation pathophysiology and therapy: a translational perspective, Circ. Res. 127 (1) (2020) 51–72.
[8] G. Chen, M.G. Chelu, D. Dobrev, N. Li, Cardiomyocyte inflammasome signaling in cardiomyopathies and atrial fibrillation: mechanisms and potential therapeutic implications, Front. Physiol. 9 (2018) 1115.
[9] J. Heijman, A.P. Muna, T. Veleva, C.E. Molina, H. Sutanto, M. Tekook, Q. Wang, I. H. Abu-Taha, M. Gorka, S. Künzel, A. El-Armouche, H. Reichenspurner, M. Kamler, V. Nikolaev, U. Ravens, N.a. Li, S. Nattel, X.H.T. Wehrens, D. Dobrev, Atrial myocyte NLRP3/CaMKII nexus forms a substrate for postoperative atrial fibrillation, Circ. Res. 127 (8) (2020) 1036–1055.
[10] L. Lin, L. Xu, W. Lv, et al., An NLRP3 inflammasome-triggered cytokine storm contributes to Streptococcal toxic shock-like syndrome (STSLS), PLoS Pathog. 15 (6) (2019) e1007795.
[11] L. Scott Jr, A.C. Fender, A. Saljic, et al., NLRP3 inflammasome is a key driver of obesity-induced atrial arrhythmias, Cardiovasc. Res. 117 (7) (2021) 1746–1759.
[12] A.C. Fender, S. Kleeschulte, S. Stolte, K. Leineweber, M. Kamler, J. Bode, N.a. Li, D. Dobrev, Thrombin receptor PAR4 drives canonical NLRP3 inflammasome signaling in the heart, Basic Res. Cardiol. 115 (2) (2020), https://doi.org/10.1007/s00395-019-0771-9.
[13] G.M. Marcus, M.A. Whooley, D.V. Glidden, L. Pawlikowska, J.G. Zaroff, J.E. Olgin, Interleukin-6 and atrial fibrillation in patients with coronary artery disease: data from the Heart and Soul Study, Am. Heart J. 155 (2) (2008) 303–309.
[14] J. Huang, Y. Xiang, H. Zhang, N.a. Wu, X. Chen, L. Wu, B. Xu, C. Li, Z. Zhang, S. Tong, L.i. Zhong, Y. Li, Plasma level of interferon-γ predicts the prognosis in patients with new-onset atrial fibrillation, Heart Lung Circ. 29 (7) (2020) e168–e176.
[15] R. Hiram, F. Xiong, P. Naud, et al., The inflammation-resolution promoting molecule resolvin-D1 prevents atrial proarrhythmic remodelling in experimental right heart disease, Cardiovasc. Res. 117 (7) (2021) 1776–1789.
[16] T. Kawaji, K. Ono, N. Sowa, et al., Association between serum inflammatory biomarkers and atrial low voltage in patients with atrial fibrillation, IJC Heart Vasc. 37 (2021), 100904.
[17] T. Korn, E. Bettelli, M. Oukka, V.K. Kuchroo, IL-17 and Th17 cells, Annu. Rev. Immunol. 27 (1) (2009) 485–517.
[18] N.a. Wu, B. Xu, Y. Liu, X. Chen, H.e. Tang, L. Wu, Y. Xiang, M. Zhang, M. Shu, Z. Song, Y. Li, L.i. Zhong, Elevated plasma levels of Th17-related cytokines are associated with increased risk of atrial fibrillation, Sci. Rep. 6 (1) (2016), https://doi.org/10.1038/srep26543.
[19] L. Xu, N. Wang, Y. Liang, H. Zhou, J. Yan, Interleukin-17A contributes to atrial fibrillation recurrence and left atrial reservoir function after catheter ablation, Pol. Arch. Intern. Med. 129 (6) (2019) 432–435.
[20] B.-X. Chen, B. Xie, Y. Zhou, L. Shi, Y. Wang, L. Zeng, X. Liu, M.-F. Yang, Association of serum biomarkers and cardiac inflammation in patients with atrial fibrillation: identification by positron emission tomography, Front Cardiovasc Med. 8 (2021), https://doi.org/10.3389/fcvm.2021.73508210.3389/fcvm.2021.735082.s001.
[21] S.P. Levick, P.H. Goldspink, Could interferon-gamma be a therapeutic target for treating heart failure? Heart Fail. Rev. 19 (2) (2014) 227–236.

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