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EDITORIAL COMMENT

Myocardial Inflammation and Arrhythmogenic Cardiomyopathy

Toward a Promising Disease-Modifying Therapy?

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Arrhythmogenic cardiomyopathy (ACM) is a genetic heart muscle disease characterized by loss of ventricular myocardium with replacement by fibrofatty scar, which underlies global and/or regional ventricular dysfunction and predisposes to ventricular arrhythmias and sudden cardiac death.[1] The current designation of ACM represents the evolution of the original term *arrhythmogenic right ventricular cardiomyopathy*, reflecting the modern concept of a biventricular disease with left ventricular involvement, which may parallel (biventricular ACM) or exceed (left-dominant ACM) the severity of right ventricular disease. The disease is frequently caused by genetically defective desmosomal-proteins, like desmoplakin, plakophilin-2, and desmoglein-2. Current treatment of ACM is largely based on drugs, catheter ablation, and device/surgical interventions aimed to prevent and manage heart failure and arrhythmias, but disease-modifying therapies are lacking. The improvement of our knowledge of the molecular mechanisms involved in onset and progression of myocardial lesions is essential for developing disease-specific curative therapies. There is growing evidence of a complex interplay between genetic background and myocardial inflammation,[2] with inflammation being identified as a crucial biologic process that may mediate/promote myocyte damage. In clinical settings, acute myocarditis-like episodes of chest pain with electrocardiographic changes and cardiac troponin (cTn) release may represent the initial clinical presentation and/or a disease progression modality ("hot phase") in patients with genetic ACM, frequently in desmoplakin variants.[3]

In this context, the study by Penna et al[4] is timely and relevant. Their study addressed whether inflammation is an epiphenomenon of myocardial injury or represents a determinant process of disease progression and a potentially actionable pathway. The authors combined single-nucleus RNA sequencing and spatial transcriptomics of human ACM myocardial samples with mechanistic validation in a mouse model harboring homozygous knock-in of a variant in the desmoglein-2 gene ($Dsg2^{mut/mut}$).

The main findings can be summarized as follows. First, in samples from explanted human ACM hearts, myocardial lesions (ie, areas of fibrous replacement) were characterized by enrichment of inflammatory myeloid cells and activated fibroblasts, whereas cardiomyocytes were depleted and, when present, displayed gene programs associated with cell failure. Spatial analyses showed that inflammatory macrophages and activated fibroblasts were colocalized within diseased areas, forming an inflammatory-fibrotic niche. Second, the $Dsg2^{mut/mut}$ mouse model reproduced a similar cellular and transcriptional architecture, including macrophage populations expressing interleukin (IL)-1β and fibroblast populations with profibrotic signatures. Third, pharmacologic blockade of IL-1β in the mouse model attenuated fibrosis, improved ventricular function, reduced ventricular ectopy, and had a greater impact on the outcome when the treatment was started earlier in the disease course. These observations support the idea that IL-1β may act as a relevant mediator of disease progression. The novelty of the study by Penna et al[4] lies in the integration of human spatial and transcriptomic data with preclinical

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therapeutic targeting, rather than in the recognition of causal role of inflammation in the pathogenesis of ACM lesions, which was already demonstrated by prior experimental, pathological, and clinical observations.[5]

The authors are to be congratulated for taking an important step toward our better understanding of ACM pathobiology and for generating a new hypothesis for disease-modifying therapy. From a mechanistic perspective, their study links histology, transcriptomics, spatial organization of cell populations, and interventional preclinical data in a coherent framework. From the bedside perspective, their data support the view that myocardial inflammation may directly contribute to the development of myocardial injury, myocyte death, and fibrofatty scar repair. The paper adds further evidence that ACM is not a "static" scar cardiomyopathy, but is a dynamic myocardial disease that may progress through phases of active inflammation.

The translational implications of the study regard not only IL-1β as an inflammation biomarker in ACM, but also its potential causative involvement in the disease progression that offers the possibility for a targeted curative therapy. The present study extends findings from previous investigations showing that IL-1β and related pathways are implicated in cardiac remodeling and fibrosis in heart failure, including a potential therapeutic outlook.[6] A scientific advance of the present study was the reproducibility of the inflammatory-fibrotic niche in the $Dsg2^{mut/mut}$ mouse transgenic model, with similar molecular profiles and biomarkers expression.

The study results underline the need of multimodality imaging not only for diagnostic purposes in ACM, but also for tissue characterization of myocardial scar and scar-related inflammation. CMR already plays a central role for definition of ACM phenotypes, thanks to its ability to provide, beside morphofunctional evaluation, a structural myocardial tissue characterization that is crucial for detection of inflammatory myocardial edema and myocyte death in the context of hot phases.[7] In selected scenarios, additional tools for the study of myocardial inflammation include nuclear medicine imaging, such as positron emission tomography, which may offer complementary information, although the additional value in ACM remains to be established.[8]

A similar argument applies to circulating biomarkers. Conventional markers such as cTn and natriuretic peptides already have practical value, reflecting different domains of disease. cTn, particularly measured with high-sensitivity assays, is the marker of myocardial injury and is particularly informative during hot phase episodes[3]; natriuretic peptides reflect hemodynamic stress and overload. It is unknown, however, if these biomarkers could be sufficiently accurate to capture and monitor the dynamic biologic process of inflammatory-related myocardial depletion and scarring detailed in the present study. Emerging data from previous and present study on the pathobiological importance of inflammatory mediators, fibrosis-related proteins, autoantibodies, and microRNA profiles suggest the need for future research to focus on the additional role of a biomarker-based approach for identification of disease activity, monitoring progression, and guiding treatment selection in patients with ACM.[2]

Although the murine data make IL-1β inhibition an attractive therapeutic approach, they do not justify a generalized anti-inflammatory approach. Human ACM is highly heterogeneous across genes, phenotypes, age, stages, exercise exposure, and rate of progression.[5] Accordingly, the anti-inflammatory treatment could potentially—in the future—be applied in carefully selected patients during a well-defined window of the disease course.

Some study limitations should be considered. The human myocardial samples were obtained at transplantation and therefore represent advanced disease, as the authors recognized, even though reproducible in the murine model. Whether the same cellular programs are also observed during concealed disease, early phenotypic expression, and acute hot phases is not established. The number of samples was limited, and the analysis was largely based on left ventricular tissue. Moreover, samples came from patients of various ages and without information on the clinical features (Did the patients present with "hot phases"? Did they have a more arrhythmic or heart-failure profile?). Also, controls were not deeply characterized. In addition, the animal model was based on homozygous $Dsg2^{mut/mut}$ disease and cannot capture the full complexity of human ACM, with different genetic defects, heterozygous variants, modifier genes, variable expression, and environmental influences.

There is also a translational limitation in the clinical use of biomarkers. Tissue-level transcriptomic signatures are highly informative mechanistically, but they are not bedside tools that would need proper validation.[9] The crucial next step is to determine whether the biology identified in myocardial lesions can be tracked reliably through circulating biomarkers or imaging. For clinicians, the value of this work will ultimately depend on whether it helps generate practical tools for longitudinal assessment and therapeutic decision-making. IL-1β itself may not

be the optimal blood biomarker because of low circulating levels, biological variability, and limited disease specificity. Likewise, macrophage-fibroblast signatures detected in tissue may not translate into useful peripheral blood assays.

In conclusion, the study by Penna et al[4] provides additional support to the perspective that inflammation may contribute to expression/progression of ACM and underlines the need to accurately investigate the inflammatory processes "in vivo" for risk stratification and targeted therapy. The results need to be validated in broader and clinically well-characterized human cohorts, to confirm that similar findings are observed in earlier stages and to identify imaging or circulating markers that can reliably track these pathophysiological aspects. At present, IL-1β inhibition remains a preclinical hypothesis, but the study provides a rational basis for future translational work.

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