Circulation Research

RESEARCH LETTER

Circulating Th17 and Th22 Cells Are Associated With CMR Imaging Biosignatures of Diffuse Myocardial Interstitial Remodeling in Chronic Coronary Artery Disease

Jedrzej Hoffmann, Valentina O. Puntmann, Karel Fišer, Tina Rasper, Alexander Berkowitsch, Maria Ludovica Carerj, Eike Nagel, Stefanie Dimmeler, Andreas M. Zeiher

Myocardial fibrosis is the common pathophysiologic denominator between myocardial remodeling and the failing heart. Experimental evidence points toward a prominent role of CD4+ T helper (Th) lymphocytes, particularly Th17 and Th22 cells, as key players in myocardial remodeling, hence their involvement in humans remains unclear. Quantitative tissue characterization by cardiac magnetic resonance imaging supports noninvasive detection of diffuse myocardial interstitial remodeling by measurement of rates of T1 relaxation.[1] We have previously shown that characterization of noninfarcted myocardium by T1 mapping is predictive of outcome in patients with coronary artery disease (CAD), over and above traditional imaging measures.[2] We hypothesized that expansion of specific T-cell subsets would be associated with myocardial T1 mapping measurements. Therefore, circulating T cells were measured in forty-six patients with chronic CAD, who were enrolled in the prospective T1 mapping outcome study (NCT03749343). Exclusion criteria were neoplastic/autoimmune/infectious disease, specific nonischemic cardiomyopathies, myocarditis, and immunosuppressive medication. Patients were categorized into 2 groups, based on sequence-specific ranges for native T1 of noninfarcted myocardium[2]: normal native T1, indicating no remodeling (n=24; median age: 64 [IQR, 52–68] years; LVEF (left ventricular function): 58 [54–62]%) and abnormal native T1 (n=22; 61 [52–69] years; LVEF: 55 [41–64]%) as indicative for diffuse interstitial remodeling and fibrosis. Twelve subjects of similar age (57 [52–66] years) and sex mix with no known cardiac disease and with normal cardiac magnetic resonance findings served as controls. Blood samples were analyzed for standard cardiac and inflammatory biomarkers. Th-cell subsets were analyzed using multiparameter flow cytometry, and the raw data were subjected to hierarchical cluster analysis as described previously.[3] Hierarchical cluster analysis detected a marked expansion of 2 specific Th-cell clusters, phenotypically corresponding to Th22 and Th17 (Figure 1B) in patients with diffuse remodeling. We further confirmed a significant increase in Th17 and Th22 cell counts in patients with abnormal T1 signatures (Figure 1C). Among patients with CAD, there were no significant relationships

Key Words: coronary artery disease ■ myocardium ■ T-lymphocytes ■ T1 mapping

Meet the First Author, see p 592

Correspondence to: Jedrzej Hoffmann, Department of Cardiology, Center of Internal Medicine, University Hospital Frankfurt, Germany. Email jedrzej.hoffmann@kgu.de

The data that support the findings of this study are available from the corresponding author upon reasonable request by email.

Registration: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02407197.

This manuscript was sent to Francesco Violi, Consulting Editor, for review by expert referees, editorial decision, and final disposition.

For Sources of Funding and Disclosures, see page 700.

Nonstandard Abbreviations and Acronyms

CAD	coronary artery disease
LVEF	left ventricular function

between Th-cell subsets and age, sex, CV risk factors, cardiac magnetic resonance cardiac structure or function or the presence of postinfarction scar by late gadolinium enhancement. The latter indicates that expansions of proinflammatory T lymphocytes were indicative for diffuse fibrosis but not for replacement fibrosis.

High-sensitive troponin T (Controls versus CAD normal versus CAD abnormal T1: 4.5 [3–5.9] versus 5.9 [4.5–11] vs 12 [6.8–20] pg/mL; P=0.002) and high-sensitivity C-reactive protein (0.09 [0.05–0.21] versus 0.08 [0.05–0.18] versus 0.22 [0.09–0.50] mg/dL; P=0.018) were significantly higher in the group with diffuse remodeling, whereas N-terminal pro-brain natriuretic peptide (94 [39–122] versus 64 [32–179] versus 201 [79–566] pg/mL; P=0.052) was not significantly different. The groups were similar for total blood leukocyte (P=0.18), granulocyte (P=0.25), or monocyte (P=0.09) counts. In summary, our results indicate that Th17 and Th22 cells may relate to diffuse interstitial remodeling of noninfarcted myocardium in the context of CAD. Despite its novelty, this study is limited by the small sample size and therefore potentially biased by reverse causation and confounding. Future studies are needed to prove the prognostic value of Th17/Th22 polarization, as well as the therapeutic potential of anti-inflammatory treatments to prevent progression of diffuse myocardial remodeling.

ARTICLE INFORMATION

Affiliations

From the Departments of Medicine and Cardiology (J.H., V.O.P., A.B., E.N., A.M.Z.), Institute for Experimental and Translational Cardiovascular Imaging (J.H., V.O.P., M.L.C., E.N., S.D.), and Institute of Cardiovascular Regeneration, Center of Molecular Medicine (T.R., S.D.), Goethe University, Frankfurt, Germany; German Center for Cardiovascular Research DZHK, Berlin, Germany, partner site Rhine-Main (J.H., V.O.P., E.N., S.D., A.M.Z.); and Department of Pediatric Haematology and Oncology, CLIP—Childhood Leukemia Investigation Prague, Charles University, Czech Republic (K.F.).

Sources of Funding

This work was supported by the Adolf-Messer-Stiftung. K. Fišer is supported by Czech Health Research Council (NV18-08-00385).

Disclosures

None.

REFERENCES

1. Child N, Suna G, Dabir D, Yap ML, Rogers T, Kathirgamanathan M, Arroyo-Ucar E, Hinojar R, Mahmoud I, Young C, et al. Comparison of MOLLI, shMOLLLI, and SASHA in discrimination between health and disease and relationship with histologically derived collagen volume fraction. *Eur Heart J Cardiovasc Imaging.* 2018;19:768–776. doi: 10.1093/ehjci/jex309
2. Puntmann VO, Carr-White G, Jabbour A, Yu CY, Gebker R, Kelle S, Rolf A, Zitzmann S, Peker E, D'Angelo T, et al; International T1 Multicentre CMR Outcome Study. Native T1 and ECV of noninfarcted myocardium and outcome in patients with coronary artery disease. *J Am Coll Cardiol.* 2018;71:766–778. doi: 10.1016/j.jacc.2017.12.020
3. Fišer K, Sieger T, Schumich A, Wood B, Irving J, Mejstříková E, Dworzak MN. Detection and monitoring of normal and leukemic cell populations with hierarchical clustering of flow cytometry data. *Cytometry A.* 2012;81:25–34. doi: 10.1002/cyto.a.21148

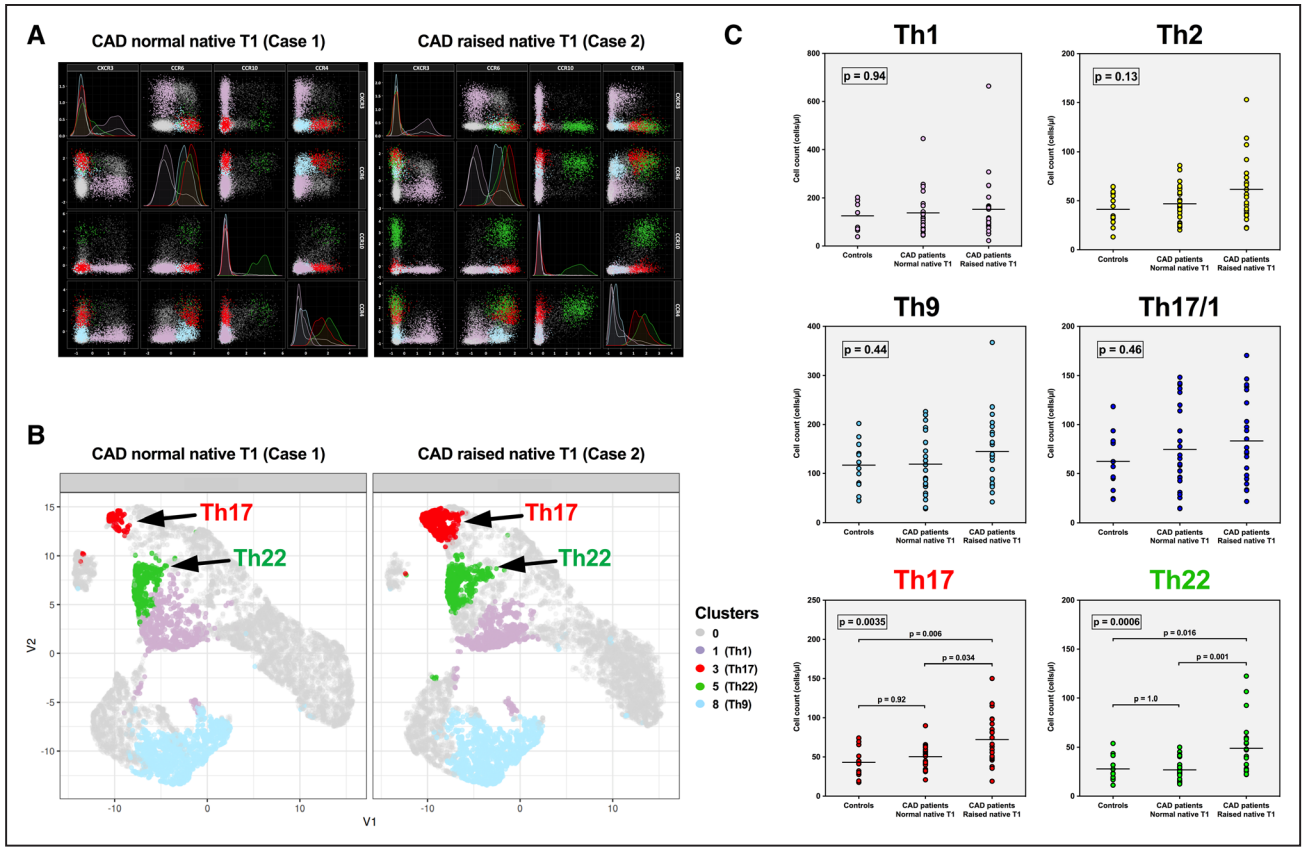

Figure. Inflammatory T-cell signatures of cardiac fibrosis.
A, Scatter plots of Th-cell clusters (as identified by hierarchical cluster analysis) and (**B**) Uniform Manifold Approximation and Projection dimensionality reduction plots showing expansion of Th17 ($CD194^+CD196^+CCR10^-CD183^-$, red cluster) and Th22 ($CD194^+CD196^+CCR10^+CD183^-$, green cluster) cells from representative patients with normal (Case 1) and raised (Case 2) native T1. **C**, Absolute Th-cell counts (Kruskal-Wallis H-test followed by Dunn test). CAD indicates coronary artery disease.