Single-Cell Analysis Reveals Regulatory T-Cell Dysfunction in Arrhythmogenic Right Ventricular Cardiomyopathy

Silvia Fanti [1], Alexandros Protonotarios[3], Barbara Szomolay[2], Imogen Heenan[3], Angeliki Asimaki[4], Joseph Westaby[4], Elijah Behr[4], Mary Sheppard[4], Stefania Rizzo[5], Cristina Basso[5], Petros Syrris[3], Perry Elliott[3], Federica Marelli-Berg[1]

[1]Queen Mary University of London; [2]Cardiff University School of Medicine; [3]University College London; [4]St George's, University of London, [5]Azienda Ospedaliera–University of Padua; University of Padua Medical School

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a severe inherited cardiac disorder characterized by fibrofatty myocardial replacement, ventricular arrhythmias, and a high risk of sudden cardiac death (SCD). It is a leading cause of premature mortality, accounting for up to 20% of SCDs in individuals under 35, 5–15% in young adults across Europe, and nearly one-quarter of exercise-related sudden deaths in athletes. Despite advances in genetics and clinical management, there is no curative therapy, and the mechanisms driving disease progression remain poorly understood. Although ARVC is frequently accompanied by inflammatory episodes resembling myocarditis, the contribution of adaptive immunity to disease onset and progression is unclear.

To address this, we investigated T-cell–mediated immune responses in ARVC patients (genotype-positive, phenotype-positive; G^+P^+), genotype-positive relatives without clinical disease (G^+P^-), and healthy controls. We have recently identified a subpopulation of circulating cardiotropic c-Met^+ memory T cells in ARVC patients, also present in the myocardium, with autoimmune specificities. c-Met^+ T cells were similarly observed in the circulation and hearts of mice carrying a pathogenic Desmoglein-2 mutation. Flow cytometry and functional assays revealed increased circulating c-Met^+ cardiotropic T cells mainly in G^+P^+ compare to G^+P^- individuals.

We discovered that regulatory T cells (Tregs), although present at similar frequencies across groups, exhibited reduced expression of key suppressive and activation markers in G^+P^+ patients, indicating functional impairment. Importantly, individuals with higher proportions of activated cardiotropic Tregs showed milder electrical abnormalities, suggesting a protective role. To define the mechanisms underlying Treg dysfunction, we isolated circulating Tregs and performed single-cell RNA sequencing, revealing distinct subpopulations in ARVC patients with altered metabolic programs and acquisition of pro-inflammatory features.

Together, these findings indicate that cardiac autoimmunity emerges in gene carriers before overt disease, while progression to clinical ARVC is associated with loss of effective immune regulation. Dysfunctional Tregs may therefore contribute to disease progression and represent a novel target for immunomodulatory therapy, highlighting the potential for precision immunological interventions in ARVC.