T regulatory cells lose their protective phenotype in patients with coronary artery disease (CAD)

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Background: Atherosclerosis is accompanied by an auto-immune response that involves autoreactive T cells recognizing peptides from ApoB-100, the core protein of LDL-cholesterol. It has been suggested by preclinical animal models that regulatory T-cells (Treg) counteract this pathogenic response by secreting anti-inflammatory cytokines and direct contact inhibition at younger ages, but convert into pathogenic T cells, expressing pro-inflammatory cytokines such as IFN-γ during aging. It has been proposed that Tregs numbers decrease in patients with coronary artery disease (CAD), but clinical evidence remains sparse. Here, we aimed to systematically characterize Tregs in human CAD.

Methods: Patients with a high cardiovascular risk undergoing coronary angiography were included in the Adaptive Immunity in Atherosclerosis (ANIMATE) exploratory biomarker trial at the University Heart-Centre Freiburg-Bad Krozingen, Germany. Peripheral blood mononuclear cells (PBMCs) were isolated from 359 patients. In a case-control design, we selected 80 patients that were matched according to their clinical parameters and divided into 4 groups: younger ≤ 55-year-old patients without (n=19) or with CAD (n=21), and older ≥ 70-year-old patients without (n=18) or with CAD (n=22). We studied Tregs using flow cytometry by targeting extracellular markers, transcription factors, and cytokine expression.

Results: Younger patients without or with CAD did not show significant changes in the frequency of circulating Tregs defined as CD127-/CD25+/FoxP3+ CD4+ T cells. Surprisingly, the number of Tregs in the older patients with CAD was significantly higher (increased by 2-fold) than in patients without CAD (p=0.0036), raising the question of an age-dependent changes in Tregs function that might affect CAD progression. Accordingly, Treg from older patients with CAD showed a lower baseline expression of atheroprotective IL-10, as well as higher IL-17, TNF-a, and INF-γ protein expression as assessed by intracellular flow cytometry. Interestingly, Tregs frequency was significantly increased in patients with arterial hypertension, severe CAD and in patients with previous myocardial infarction. Treg frequencies positively correlated with plasma levels of anti-ApoB IgG autoantibodies. Conversely, Treg fractions negatively correlated with total cholesterol and LDL-C levels.

Conclusion: Here we show that in older patients with CAD, Treg are more frequent and have a more inflammatory phenotype than in controls without CAD. These data support the novel concept of Treg plasticity in CAD and show that protective autoimmunity is lost in the course of disease.