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Regulatory T-cell homeostasis in patients with coronary artery disease

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Coronary artery disease is a chronic inflammatory disease of the vessel wall. The main interest of this study was to enlighten the T-cell-receptor (TCR)-diversity and thus the anti-inflammatory capacity of Teff and Treg in stable coronary artery disease (CAD), acute coronary syndrome (ACS) patients compared to healthy controls.

Firstly, the distribution of $CD4^+CD25^+FoxP3^{high}$ regulatory T-cells (Treg), $CD4^+IL\text{-}17A^+$ Th17-cells and their ratio in peripheral blood of patients with ACS and stable CAD in comparison to healthy volunteers has been analyzed. No significant difference could be detected in the number of peripheral Treg comparing ACS and CAD patients with healthy controls, suggesting that Treg cell counts do not correlate with the extent of atherosclerosis. But patients with ACS had the significantly higher percentage of Th17-cells and with it an increased Th17/Treg ratio in their peripheral blood lymphocytes. Thus, a numerous Th17/Treg imbalance in patients with unstable atherosclerotic plaques in ACS could be confirmed.

To elucidate whether a restricted TCR repertoire within primarily regulatory T-cells (Treg, $CD4^+CD25^+$), but also effectory acting T-cells (Teff, $CD4^+CD25^-$), might be involved in atherosclerosis and its complications the hypervariable region of their TCR was examined by CDR3 spectratyping. The diversity of the Tregs TCR was significantly decreased in the disease group (ACS and CAD together, P=0.0009) and in both disease subgroups ACS (P=0.0105) and CAD (P=0.0023). Teff's TCR diversity was in line with Tregs showing a reduction in the disease group (ACS and CAD together) compared to healthy controls (P=0.0157), mainly caused by a diminished TCR diversity in CAD patients (P=0.0254). These results suggest that an antigen dependent expansion of single Treg and Teff clones leads to lowering of the overall TCR diversity in the T-cell-pool. A lower TCR diversity may thus impair T-cell function and therefore lead to the diseases. It can be assumed that if the diversity of Treg-TCR is restricted, the crucial Treg clone to sufficiently control the large number of possible T-cells may be underrepresented or absent thereby facilitating pro-inflammatory

processes. A possible reason for the restricted TCR repertoire could be recurrent antigenic stimulation during chronic inflammation such as atherosclerosis which result in a diminish production and TCR-diversity of naïve Treg.

The study further investigated whether a chronic inflammatory process results in an upregulated monoclonal expression of Vβ subunits and by this represents a possible reason of the diminished TCR diversity. Indeed, both patient groups, CAD and ACS had higher amounts of monoclonal CDR3 Vβ subunits in their Teff pool. Within the Treg significant altered monoclonal pattern was also seen in the ACS patients. So the TCR restriction of the Tregs seems to be restricted to the acute phase of atherosclerosis, whereas Teff monoclonal expansion was more likely due to antigen-driven selection during the stable and instable disease progression.

Calculated was also, if TCR diversity was dependent on age. The CS as a major sign for TCR diversity was influenced and significantly reduced in higher age regarding the Teff of all patients together (P=0.0199) and in the group of only CAD (P=0.0117). Whereas focusing on Treg, in the healthy control the opposite phenomenon could be verified (P=0.0310): the higher age the individuals of the healthy control reached, the more diverse appeared their Treg's TCR repertoire and probably this was one reason for their health. So TCR diversity of Teffs and Tregs in healthy is not reduced (but even elevated) in higher age, whereas in patients suffering from atherosclerosis (CAD or ACS) it is more likely diminished.

In summary, the study demonstrates no differences in the amount of occurring Tregs, but restricted TCR-diversity and thus reduced function regarding primarily Tregs, but also Teffs. This might be based most likely recurrent antigen stimulation during the chronic inflammation, but could also be due to thymic involution which leads to diminished production and TCR-diversity of naïve Treg. Measuring or modulating Treg homeostasis may thus represent a promising diagnostic or therapeutic tool in the future.