

Regulatory T cells from patients with atherosclerosis have enhanced suppression function due to increased effector/resting ratio and pro-inflammatory skewing

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Aim: Regulatory T (Treg) cells have been implicated in atherosclerosis pathogenesis but the mechanisms involved are poorly defined. Potent suppressive capacity remains *the* most important and *defining* Treg characteristic. Data on Treg frequency in atherosclerosis patients is contradictory: some studies found reduced frequencies; others suggested that Treg frequency does not correlate with atherosclerosis severity; and other studies suggested that Treg reduction increases myocardial infarction (MI) risk. Information on Treg suppressive function is even scarcer. We aimed to characterise the frequency, phenotype and function of Tregs in atherosclerosis patients.

Methods: CD4⁺CD25^{high}CD127^{low}FOXP3⁺ Treg were quantified in atherosclerosis patients (MI, n=60; stable angina, SA, n=40), and in healthy subjects (n=30) by flow cytometry. Sorted Treg from atherosclerosis patients and controls were used for direct and cross-suppression assays.

Results: Treg number was significantly lower in MI and SA patients compared to healthy subjects. This was due to reduction of resting/naive Foxp3^{low}CD45RA^{high} Treg (p<0.0001), while effector/activated Foxp3^{high}CD45RA^{low} Treg were not affected. Moreover, we found a significant increase in cytokine-producing Foxp3^{low}CD45RA^{low} Treg (p<0.0001). Strikingly, suppression assays demonstrated that Treg from MI patients display enhanced suppressive function compared to Treg from healthy individuals, in line with increased effector/resting Treg ratio in MI.

Conclusions: Our data indicate that Treg from atherosclerosis patients are potent suppressors and have pro-inflammatory phenotype and functions. These results contrast previous findings that suggested decreased Treg suppressive function in MI. Our results reveal a complex role for Treg in human atherosclerosis beyond generic suppression of inflammation into dynamic cells that exhibit pathogenic traits.