Regulatory CD4+ T cells from patients with atherosclerosis display pro-inflammatory skewing and enhanced suppressive function

I. E. Dumitriu, S. Dinkla, and J. C. Kaski

Background/Introduction: Regulatory T (Treg) cells have been implicated in atherosclerosis pathogenesis but the mechanisms involved remain poorly defined. Potent suppressive capacity constitutes *the* most important and *defining* Treg feature. 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 in atherosclerosis patients is even scarcer.

Purpose: We aimed to characterise Treg frequency, phenotype and function in atherosclerosis patients.

Methods: $CD4^{+}CD25^{high}CD127^{low}FOXP3^{+}$ Treg were quantified in atherosclerosis patients (myocardial infarction (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 naive $Foxp3^{low}CD45RA^{high}$ Treg ($p<0.0001$), while effector $Foxp3^{high}CD45RA^{low}$ 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. In depth phenotypic and functional characterisation of Treg subsets to identify mechanisms responsible for altered frequency and suppressive activity is ongoing.

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.