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Activation of the regulatory T-cell-indoleamine 2,3 dioxygenase Axis promotes vascular tolerance mechanisms and reduces atherosclerosis

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T-cell activation is characteristic during the development of atherosclerotic plaques. Whereas overall T-cell responses have been implicated in acceleration of disease, regulatory T cells (Tregs) showed atheroprotective effects. The expression of the enzyme indoleamine 2,3 dioxygenase-1 (IDO), which catalyzes the tryptophan (Trp) degradation along the Kynurenine pathway, has been implicated in the induction and expansion of Treg populations. Hence, it has been shown that Tregs can promote IDO expression on dendritic cells, through reverse signaling mechanisms. In this study, we hypothesize that triggering the Treg-IDO axis in the artery wall is atheroprotective. We show that apolipoprotein B100-pulsed TGFβ2-treated tolerogenic dendritic cells promote de novo FoxP3+ Treg expansion in vitro and in vivo. Notably, we observed that local increase in Treg numbers is associated with increased vascular IDO expression, and a robust reduction in the atherosclerotic burden. Using human primary cell cultures, we show for the first time that IDO expression and activity can be regulated by cytotoxic T-lymphocyte associated protein-4, a constitutive molecule expressed and secreted by Tregs, on human macrophages, smooth muscle cells and endothelial cells. Our data suggest that Tregs and IDO-mediated Trp metabolism can mutually regulate each other in the vessel wall, promoting vascular tolerance mechanisms that limit inflammation and atherosclerosis.