Regulatory T cell in aneurysm

Studies have demonstrated that the regulatory T cells (Treg) were functionally impaired in IA patients. Hence, strategies that can improve Treg function in IA patients should be investigated. Based on our previous finding that IL-2 strongly elevated the expression of the checkpoint molecule Tim-3 in Treg cells, we examined the effect of IL-2 in the function of Treg cells from IA patients. External IL-2 significantly improved the proliferation of Treg cells, increased the expression of CTLA-4 and LAG-3, and enhanced Treg-mediated suppression of conventional T cell (Tconv) proliferation. Importantly, compared to the Tim-3- Treg cells, the Tim-3+ Treg cells presented comparable proliferation capacity, but significantly greater expressions of CTLA-4 and LAG-3 and significantly higher capacity to suppress Tconv proliferation. In addition, blocking Tim-3 abrogated IL-2-mediated enhancement of Tim-3+ Treg cells. We then investigated the IL-2 level in IA patients, and found that although IA patients and healthy controls presented similar serum IL-2 concentration, the concentrations of IL-1β and TNF-α were significantly higher in IA patients than in healthy controls, signaling a relative reduction in IL-2 abundance. Together, we found that IL-2 could significantly enhance the function of Treg cells from IA patients in a Tim-3-dependent manner [1].

Pathogenic inflammation contributes to aneurysm formation by mediating the destruction of the endothelium and the extracellular matrix and promoting pathogenic proliferation of smooth muscle cells. In mouse models, tolerance-inducing regulatory T cell (Treg) cells could significantly reduce the incidence and severity of aneurysms. Hence, it should be investigated why in human intracranial aneurysm (IA) patients, Treg cells failed to provide protection against aneurysm formation. In this study, the frequency and function of Treg cells in IA patients were examined. The frequency of Foxp3+ Treg cells was significantly lower in IA patients than in healthy controls. This downregulation was only specific to the Treg subset of CD4+ T cells, as the frequency of total CD4+ T cell was increased in IA patients. Subsequently, we found that the expressions of Treg-associated molecules, including Foxp3, CTLA-4, TGF-β, and IL-10, were significantly lower in Foxp3+ Treg cells from IA patients than in Foxp3+ Treg cells from healthy controls. In both healthy controls and IA patients, Foxp3+ Treg cells were distinguished into a more potent Tim-3+ subset and a less potent Tim-3- subset. The Tim-3+ subset of Foxp3+ Treg cells was significantly reduced in IA patients. Signaling via IL-2, IL-7, IL-15 and IL-21 was shown to promote Tim-3 upregulation in CD4+ and CD8+ T cells. Interestingly, we found that Tim-3 could be upregulated in Treg cells via the same mechanism, but compared to the Treg cells from healthy controls, the Treg cells from IA patients presented defects in Tim-3 upregulation upon cytokine stimulation. Together, our results demonstrated that Foxp3+ Treg cells in IA patients presented reduced function, which was associated with a defect in Tim-3 upregulation [2].

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2)
Zhang HF, Liang GB, Zhao MG, Zhao GF, Luo YH. Patients with intracranial aneurysms presented defects in regulatory T cells, which were associated with impairment in Tim-3 upregulation. Int Immunopharmacol. 2018 Sep 19;64:350-355. doi: 10.1016/j.intimp.2018.09.020. [Epub ahead of print] PubMed PMID: 30243071.