Hepatitis A virus cellular receptor 2 (HAVCR2), also known as T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), is a protein that in humans is encoded by the HAVCR2 gene. HAVCR2 was first described in 2002 as a cell surface molecule expressed on IFNγ producing CD4+ Th1 and CD8+ Tc1 cells.

Later, the expression was detected in Th17 cells, regulatory T-cells, and innate immune cells (dendritic cells, NK cells, monocytes).

Tim-3 is a molecule selectively expressed on IFN-γ–producing CD4+ T helper 1 (Th1) and CD8+ T cytotoxic 1 (Tc1) T cells.

The T-cell inhibitory receptor Tim-3 (T-cell immunoglobulin and mucin-domain containing-3) is currently receiving much attention due to its demonstrated success in multiple preclinical cancer models.

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 a study of Zhang et al. from the Department of Neurosurgery, General Hospital of Shenyang Military, the frequency and function of regulatory T 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 [1)].

1)
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.