Annexin A1: checkpoint between blood brain barrier and leukocytes trafficking

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Annexin A1 (ANXA1) is expressed in the endothelial cells of the brain microvasculature[1], where it plays a major role in promoting the integrity of the blood brain barrier (BBB)[2]. In particular, ANXA1$^{-/-}$ mice exhibit significantly increased BBB permeability due to disrupted inter-endothelial cell tight junctions, essentially related to changes in the actin cytoskeleton, which stabilizes tight and adherens junctions[2]. Furthermore, ANXA1 is selectively lost in the BBB endothelium in multiple sclerosis (MS), but not in other neuropathologies including Parkinson's and Alzheimer's diseases. We have previously shown ANXA1 to exert a powerful anti-inflammatory action by limiting leukocyte extravasation via binding to and blockade of the α4β1 integrin; hence its absence removes an endogenous braking mechanism in situations of an ongoing immune response[3]. Here we studied the involvement of ANXA1 in leukocyte-BBB interactions and migration, utilising the immortalised human brain microvascular cell line (hCEMC/D3) stably infected with shRNA for ANXA1, in a transwell system under shear stress conditions to ensure the correct cellular polarity and formation of tight junctions. Significantly greater numbers of peripheral blood mononuclear cells (PBMCs) (25±3.1 vs 13±1.6; p=0.0263; n=3) adhered to endothelial monolayers lacking ANXA1 under inflammatory conditions. Furthermore endothelial ANXA1 loss correlated with higher expression of ICAM1 measured by flow cytometry (MIF 903±17 vs 600±15; p=0.0002; n=3) and constitutively higher CD4 migration in non-inflammatory condition. We present here evidence for a dual role of ANXA1 in leukocyte migration into the central nervous system: 1) as a safeguard at the level of the endothelium in non-inflammatory conditions and 2) as a blocker of leukocytes extravasation in the presence of circulating cytokines and inflammatory conditions.

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