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THE PEPTIDE INHIBITOR OF TRANS-ENDOTHELIAL MIGRATION, PEPITEM, A NOVEL IMMUNE REGUALTORY AGENT, CONTROLS T-CELL TRAFFICKING DURING INFLAMMATION, A TONIC INHIBITORY PATHWAY THAT IS LOST IN CHRONIC DISEASE

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T-cells are recruited from the blood into extra-vascular tissues during acute inflammation. However, in chronic inflammatory diseases, including atherosclerosis, an inappropriate accumulation of T-cells in the diseased tissue contributes to pathogenesis. Very little is known about the mechanisms by which T-cell trafficking is regulated during inflammation, and it is thus difficult to target this aspect of pathology for the development of new anti-atherogenic therapies. Here we describe a unique immune regulatory peptide that imposes a tonic inhibition of T-cell trafficking during inflammation. PEPtide Inhibitor of Trans-Endothelial Migration (PEPITEM) introduces a new paradigm into the pathways that regulate the inflammatory response. We propose that loss of this regulatory pathway makes the immune system 'leaky', allowing inappropriate access of T-cells to vulnerable tissues in chronic diseases. Lymphocyte trafficking was assessed *in vitro* using videomicroscopy on TNF-α/IFN-γ activated endothelial cells (EC) and lymphocytes isolated from healthy donors or patients with chronic inflammatory disease. *In vivo*, lymphocyte recruitment was assessed in a model of zymosan-driven peritoneal inflammation. PEPITEM was identified using mass spectrometry. Our studies began with an interest in adiponectin, an anti-inflammatory adipose tissue-derived cytokine. Using an *in vitro* migration assay, we observed that the migration of human lymphocytes was dose-dependently blocked by adiponectin. Adiponectin achieves its effects on T-cell migration by the induction of a novel mediator released from B-cells. Thus, the effect of adiponectin was lost when B cells are absent, but could be regained by the addition of supernatants from adiponectin stimulated B-cells. Interestingly, the B-cell derived product did not act directly on T-cells; rather, it stimulated EC to release the lipid mediator sphingosine-1-phosphate, which in turn inhibited the migration of T-cells. We used mass spectrometry to isolate a B-cell derived peptide, corresponding uniquely in the human genome to a proteolytic excision product of the 14.3.3ζδ protein. Synthetic PEPITEM could also effectively inhibit T-cell migration. In zymosan-induced peritonitis in the mouse, T-cell recruitment was significantly increased in a strain lacking B cells when compared to wild-type animals. This excess of T-cell recruitment was ameliorated by treatment with PEPITEM. Lymphocytes isolated from patients with chronic inflammatory disease (type-1-diabetes) were released from the inhibitory effects of adiponectin, but this regulatory pathway could be re-established by the addition of exogenous PEPITEM. We believe that PEPITEM and its associated pathway may have therapeutic efficacy in a number of disease scenarios including atherosclerosis.

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