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Neuropeptide CGRP regulates inflammation by increasing lymphangiogenesis

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Lymphatic vessels play an essential role in maintaining tissue fluid homeostasis. In inflamed tissue, the lymphatic vasculature undergoes extensive remodeling and expansion, including lymphangiogenesis, which is the formation of new lymphatic vessels. Accumulating evidence suggests that inflammation-associated lymphangiogenesis is not an endpoint phenotype of inflammation, but rather a dynamic and active reaction that regulates resolution of inflammation and tissue repair. Calcitonin gene-related peptide (CGRP) regulates inflammation through signaling for receptor activity-modifying protein (RAMP) 1, a subunit of CGRP receptor. We have demonstrated that RAMP1 signaling in immune cells, is important for suppression of inflammation. In addition, the recruited immune cells in the inflamed tissue produce pro-lymphangiogenic factors, VEGF-C and VEGF-D to increase lymphangiogenesis as indicated by increased LYVE-1$^+$ vessels during healing of wounds and peritoneal inflammation. Indeed, RAMP1 in macrophages promotes skin wound healing and lymphangiogenesis in the granulation tissues. In the peritonitis, RAMP1 in macrophages and T cells facilitates lymphangiogenesis in the diaphragm tissue and enhances peritoneal drainage function of lymphatics. These findings suggest that RAMP1 signaling in immune cells plays a critical role in enhancement of lymphangiogenesis; therefore, a specific agonist for RAMP1 may be a therapeutic option for wound tissue healing or peritoneal inflammation.