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GPR15LG and its derived peptides for the modulation of CXCR4 signaling

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GPR15LG, a chemokine-like ligand for the G-protein coupled receptor 15 (GPR15), is abundantly expressed in the gastrointestinal mucosa and inflamed skin and has been implicated in inflammatory disorders and cancer. The C-X-C chemokine receptor type 4 (CXCR4) plays a critical role in immune cell trafficking and cancer metastasis. Recent evidence suggests a previously unexplored connection between GPR15LG and CXCR4 signaling. We investigated the effects of GPR15LG on CXCR4 function using a combination of binding assays, and functional assays across multiple cell types, including $CD4^+$ T cells and cancer cells. Our results demonstrate that GPR15LG modulates CXCR4 downstream signaling in a context-dependent manner, enhancing CXCL12-mediated CXCR4 signaling and promoting wound healing and cell migration. Gaussian accelerated Molecular Dynamic (GaMD) simulations revealed interaction of GPR15LG within the orthosteric CXCR4 binding pocket. Based on this, we designed a series of GPR15LG-derived peptides that specifically bind to CXCR4. These peptides are currently being optimized to improve their pharmacological properties with the goal of developing new therapeutic agents targeting CXCR4-mediated diseases. Together, our findings reveal a novel regulatory axis between GPR15LG and CXCR4 and highlight new opportunities for therapeutic intervention in inflammation, immune modulation, and cancer metastasis.