論 文 要 旨

Human neutrophil peptides induce interleukin-8 in intestinal epithelial cells through the P2 receptor and ERK1/2 signaling pathways

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Human neutrophil peptides (HNPs) are antimicrobial peptides produced predominantly by neutrophils. We have previously reported that HNP 1-3 levels are increased in the sera and plasma of patients with active ulcerative colitis. The increased expression of interleukin-8 (IL-8) has also been demonstrated in the colonic mucosa of patients with active ulcerative colitis. HNPs induce IL-8 in lung epithelial cells and monocytes through the P2Y6 signaling pathway. However, the association between HNPs and IL-8 in the intestinal mucosa has not yet been investigated. In the present study, we investigated the effects of HNP-1 on the production of IL-8 by human intestinal epithelial cells and the underlying signaling mechanisms. We observed a significant increase in IL-8 expression in the human colon carcinoma cell line, Caco-2, following treatment with HNP-1. The non-selective P2 receptor antagonists, suramin and pyridoxal phosphate6-azo (benzene-2,4-disulfonic acid) tetrasodium salt hydrate (PPADS), significantly blocked the HNP-1-induced expression of IL-8 in the Caco-2 cells. The P2Y6-specific antagonist, MRs2578, led to a significant but partial decrease in IL-8 expression, suggesting that P2 receptors in addition to P2Y6 are involved in the HNP-1-induced production of IL-8 by Caco-2 cells. In agreement with this finding, HNP-1 also significantly increased IL-8 production in the P2Y6-negative human colon cancer cell line, HT-29, and this increase was blocked by treatment with suramin and PPADS. HNP-1 significantly increased the phosphorylation of extracellular signal-regulated kinase 1/2
(ERk1/2) and p38 mitogen-activated protein kinase (MAPk) in the HT-29 cells. However, the HNP-1-induced production of IL-8 was suppressed by the ERk1/2 inhibitor, U0126, but not by the p38 MAPk inhibitor, sb203580. In conclusion, our data demonstrate that HNP-1 induces IL-8 production not only through P2Y6, but also through additional P2 receptors via an ERK1/2-dependent mechanism in intestinal epithelial cells.