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TRPV2 plays a critical role in hepoxilin A3-medited neutrophil transepithelial chemotaxis

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Neutrophil transepithelial migration and accumulation at mucosal surfaces is a hallmark of many inflammatory conditions. Recent studies have demonstrated lipids secreted from the luminal surface of intestinal epithelial cells to regulate this event with N-acyl ethanolamine-type (NAE) endocannabinoids (eCBs) suppressing and the eicosanoid hepoxilin A3 (HxA3) activating the chemotaxis of neutrophils across this mucosal barrier. We hypothesized that directional chemotaxis of neutrophils mediated by HxA3 should involve cell-surface receptor(s). Here, we identify a role for the transient receptor potential cation channel subfamily V member 2 (TRPV2) in HxA3-mediated chemotaxis that drives neutrophil transepithelial migration.

Methods: Human promyelocytic cells (HL-60), differentiated (dHL-60) into a neutrophil-like phenotype, were used in a surface internalization-biased protocol, and proteomic analysis of internalized materials following HxA3 exposure identified receptor candidates. Cell migration assays were performed in Transwell® polycarbonate membrane plates using dHL-60 cells on the upper chamber, followed by the addition of chemoattractant HxA3 or fMLP or 2-aminoethoxydiphenylborane (2-APB), a non-specific TRP channel activator in the bottom chamber. siRNA-knock-down of CB2R and TRPV2 genes in dHL-60 cells were performed for their ability to block HxA3-dHL-60 cell migration.

Results: TRPV2 was identified in the proteomic screen. The CB2R agonists individually blocked HxA3 and 2-APB-induced migration of dHL-60 cells. Our data suggests TRPV2 interacts with CB2R, linking these two elements in a potentially coordinated chemotactic function that could be used to position neutrophils in the lamina propria in a state of readiness for transepithelial migration induced by the apical epithelial secretion of HxA3.

Keywords: Neutrophil Transepithelial migration, accumulation, mucosal surfaces, endocannabinoids.

Biography

Claudia Feriotti has her expertise in host-pathogens interactions and innate immunity, her current work is on the identification of molecules secreted by the intestinal epithelial cells which can control neutrophil transmigration from the intestinal lamina propria to the lumen in homeostatic environment or in the intestinal inflammatory diseases. She examines epithelial transcytosis mechanisms used by bacterial toxins for the delivery of biotherapeutics such as proteins, peptides, and siRNA. Her previous work was on the study of Klebsiella pneumonia-host interactions in human pulmonary infections. She analysed the Type I interferon function in the intracellular signalling pathways driven by Klebsiella infection in macrophages.

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