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Novel signaling paradigm regulating TOLL-like receptors in innate immune cells

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Toll like receptors (TLRs) are essential sensors of microbial attack, and they orchestrate the innate immune response against many microorganisms. The signaling pathways of these mammalian TLRs are well characterized, but the initial molecular mechanisms activated following ligand interactions with their receptors remain poorly defined. Here, we report a novel signaling paradigm initiated by binding of specific TLR ligands (LPS for TLR4, imiquimodfor TLR7, and CpG for TLR9) to potentiate G protein-coupled receptor and matrix metalloproteinase-9 (MMP9) activation to induce mammalian Neu1 sialidase. Central to this process is that Neu1-MMP9 complex is bound to TLR-4, -7 and -9 in naive and ligand stimulated macrophage cells as revealed by co-immunoprecipitation and colocalization assays. Using NFκB dependent secreted alkaline phosphatase (SEAP) analysis, ligand-induced TLR activation was significantly inhibited by oseltamivir phosphate (OP), MMP9 inhibitor and BIM-23127 (a specific NMBR inhibitor). Mal-2 lectin (Maackiaamurensis agglutinin) binding to immunoprecipitated TLRs in cell lysates from naive but not TLR ligand stimulated RAW-blue macrophage cellsindicated the removal of the α-2,3 sialic acid residues from the stimulated receptor ectodomain. OP, MMP9 inhibitor and BIM-23127 blocked MyD88 recruitment to the ligand stimulated TLR receptors. This study reveals an novel identical GPCR signaling platform to potentiate Neu1 and MMP9 cross-talk on the cell surface and in the endosomal compartments of macrophages that is essential for Toll-like receptor activation, cellular signaling and pro-inflammatory responses. Supported by NSERC to MS and CIHR doctoral award to SA.

Biography

Myron R Szewczuk received his PhD (Biology and Immunochemistry) from the University of Windsor, Windsor Ontario in 1974 and completed his postdoctoral studies in Cellular Immunologyunder Dr. Gregory W.Siskind at Cornell University Medical College, New York City, in 1978. From 1978-81, Dr. Szewczuk was an Assistant Professor of Pathology at McMaster University, Hamilton, Ontario. In 1981, he joined the Dept. of Microbiology & Immunology (now Biomedical and Molecular Sciences) as an Associate Professor of Immunology at Queen's University, Kingston, Ontario. In 1986, he received tenure and became full Professor of Immunology and Associate Professor of Medicine. He is presently a full time faculty member at Queen's University with an active teaching and research program in immunology and cancer. He has published over 100 papers, chapters and reviews primarily in the field of immunology and cancer.

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