Regulation of mindin expression and the signaling pathway

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Mindin has an indispensable role in both innate and adaptive immunity. A research group in China investigated regulation of mindin expression and the signaling pathway involved. mRNA expression of mindin was upregulated during dextran sulfate sodium induced mouse intestinal inflammation. Stimulation with CpG-ODN (a known TLR-9 ligand) induced upregulation of mindin expression in RAW 264.7 cells and significantly increased the NF-κB-luciferase activity in vitro.

Body of Text: Mindin is a member of the mindin-F-spondin family of secreted extracellular matrix proteins. Mindin mRNA is abundantly expressed in the spleen and lymph nodes. Mindin-deficient mice are resistant to lipopolysaccharide (LPS)-induced septic shock and exhibit an impaired ability to clear bacterial infections. Mindin-deficient macrophages and mast cells show defective responses to a broad spectrum of microbial stimuli. Mindin also functions as an opsonin for macrophage phagocytosis of bacteria. Despite these studies indicating that mindin is important in both innate and adaptive immunity, information regarding its regulation is poorly understood and activation of signaling pathways are not well investigated.

A research article to be published on March 7, 2010 in the *World Journal of Gastroenterology* addresses this question. The research team led by Professor Jian-Lin Ren from Division of Gastroenterology, Zhongshan Hospital affiliated to Xiamen University, using a mouse model and in vitro experiments, demonstrated that mRNA expression of mindin is upregulated during dextran sulfate sodium (DSS)-induced

acute intestinal inflammation and the in vitro co-stimulating data suggested that mindin may induce NF-κB promoter activation in a TLR-9 mediated manner.

A mouse colitis model was used, in which 3% of DSS was added to drinking water for six days, which resulted in epithelial damage and acute inflammation. HE staining of the colon tissue revealed that DSS treatment induced severe colitis characterized by epithelial and muscle hypertrophy with patchy lymphocytic infiltrates extending into the muscle layers. Quantitative mRNA expression of NF-kB p65 showed over 15 ± 2.5 fold upregulation supporting the development of inflammation at the mRNA level. Then the same cDNA samples were used to analyze the mindin expression, and, surprisingly, mRNA expression of mindin was upregulated by 4.7 ± 1.1 fold compared with the baseline during intestinal inflammation.

RAW 264.7 and CMT93 cells were transfected with pNF-κB-luciferase Firefly, pRL-0 vector and pCMV-mindin-Flag or pCMV-Flag control vectors. 12 hours after transfection, cells were stimulated with the different TLR ligands of Pam3-CSK4, PGN, LPS, flagellin and CpG-ODN 1585 for an additional 12 h, and then luciferase assays were performed. Luciferase activity of NF-κB promoter was significantly increased by 2.5 ± 0.3 fold and 4.5 ± 0.5 fold, in cells transfected with mindin and stimulated with CpG-ODN, for RAW264.7 and CMT93 cells respectively compared with the control. No significant induction of NF-κB luciferase activation was noted in mindin-transfected cells which underwent stimulation with other TLR ligands. This result suggests that mindin induces NF-κB promoter activation through a TLR-9 mediated manner.

While mindin binds to some kinds of bacteria and integrins, it is still unclear whether mindin functions as a coreceptor for several pattern-recognition receptors or other novel receptors and we urge further broad

studies to address these questions. These results raise the importance of the TLR-9 mediated pathway and provide a clue to help define more precisely the function and signaling pathways of the mindin protein.

More information: Guleng B, Lian YM, Ren JL. Mindin is upregulated during colitis and may activate NF-κB in a TLR-9 mediated manner. World J Gastroenterol 2010; 16(9): 1070-1075 www.wjgnet.com/1007-9327/16/1070.asp

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