NOD2 Signaling and Its Relation to Inflammation of the Mucosa

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Over the past several years we have conducted studies to determine the mechanisms underlying the fact that mutations of *CARD15* (encoding NOD2) is a susceptibility factor in Crohn's disease. In initial studies we showed with in vitro studies that activation of NOD2 by its ligand, muramyl dipeptide (MDP) causes negative regulation of peptidoglycan-mediated stimulation of Toll-like receptor (TLR) 2 and that in the absence of such activation (i.e., in cells from NOD2-deficient mice), TLR2 signaling leads to heightened Th1 responses. To support this concept in vivo, we then showed that mice deficient in NOD2 but not normal mice were susceptible to a transient Th1 colitis if they were exposed to recombinant E.coli organisms expressing ovalbumin peptide and were infused with T cells recognizing this peptide; in addition, this colitis was not seen in mice who were deficient in both NOD2 and TLR2.

In further studies we determined the susceptibility of mice to experimental colitis if they bore a transgene that expressed CARD15 or were administered expression plasmids expressing wild-type NOD2 or NOD2 with a Crohns-like mutation. We found that mice expressing increasing amounts of NOD1 due to the presence of a transgene or an expression plasmid was less susceptible to colitis induction than wild-type mice; in addition mice administered an expression plasmid expressing NOD2 with a Crohns-like mutation did not confer reduced susceptibility. Then in our most recent studies we have shown that pre-stimulation of dendritic cells with MDP dramatically reduces subsequent cytokine responses to multiple TLR ligands through the induction of enhanced IFN-regulatory factor 4 (IRF4) activity. This is mirrored in the finding that pre-treatment with MDP administration protects mice from trinitrobenzene sulphonic acid or dextran sodium sulfate-induced colitis, again via induction of IRF4. Finally, tying these findings to Crohn's disease, we showed that repletion of NOD2 in NOD2-deficient mice with a NOD2 expression plasmid expressing wild-type NOD2 restores their ability to be protected from colitis by MDP administration, whereas, repletion of NOD2 in these mice with an expression plasmid expressing a NOD2 with a Crohns-like mutation did not bring about restoration.

Taken together, these studies provide solid evidence that mutations in CARD15 are susceptibility factors in Crohn's disease because in the absence of normal NOD2 function one has reduced regulation of TLR signaling involving multiple TLR ligands.

References:

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