Clinical Immunology

Volume 143, Issue 2, May 2012, Pages 162-169

Immuno-inhibitory PD-L1 can be induced by a Peptidoglycan/NOD2 mediated pathway in primary monocytic cells and is deficient in Crohn's patients with homozygous NOD2 mutations.

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https://doi.org/10.1016/j.clim.2012.01.016

Abstract

Peptidoglycan (PGN) is a ubiquitous bacterial membrane product that, despite its well known pro-inflammatory properties, has also been invoked in immuno-tolerance of the gastrointestinal tract. PGN-induced mucosal IL-10 secretion and downregulation of Toll like receptors are potential mechanisms of action in the gut but there are few data on tolerogenic adaptive immune responses and PGN. Here, using blood-derived mononuclear cells, we showed that PGN induced marked cell surface expression of PD-

L1 but not PD-L2 or CD80/CD86, and specifically in the CD14^{+} monocytic fraction. This was reproduced at the gene level with rapid induction (<Â 4Â h) and, unlike for LPS stimulation, was still sustained at 24Â h. Using transfected and native muramyl dipeptide (MDP), which is a cleavage product of PGN and a specific NOD2 agonist, in assays with wild type cells or those from patients with Crohn's disease carrying the Leu1007 frameshift mutation of NOD2, we showed that (i) both NOD2 dependent and independent signalling (appearing TLR2 mediated) occurred for PGN upregulation of PD-L1 (ii) upregulation is lost in response to MDP in patients with the homozygous mutation and (iii) PD-L1 upregulation was unaffected in patients with heterozygous mutations as previously reported for cytokine responses to MDP. The uptake of PGN and its cleavage products by the intestinal mucosa is well recognised and further work should consider PD-L1 upregulation as one potential mechanism of the commensal flora-driven intestinal immuno-tolerance. Indeed, recent work has shown that loss of PD-L1 signalling in the gut breaks CD8^{+} T cell tolerance to self antigen and leads to severe autoimmune enteritis.

Highlights

â–º Expression of PD-L1 following PGN stimulation of mononuclear cells in health and disease. â–º PGN and MDP induce the upregulation of PD-L1 in healthy monocytic cells. â–º Unlike PGN, MDP does not induce PD-L1 in NOD2 Leu1007fs cells. â–º NOD2 dependent and NOD2 independent signalling pathways are apparent. â–º PGN-induced PD-L1 upregulation may play a role in tolerogenic signalling of the gut.

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Keywords

Peptidoglycan; NOD2; TLR2; PD-L1; CD14; Crohn's disease

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[1] Equal co-authorship.

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