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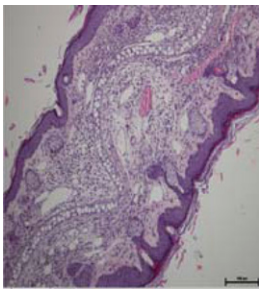
Tempering IL-17 in Psoriasis

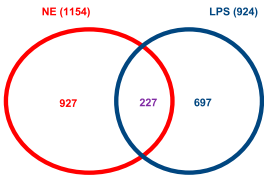


Interleukin-17–producing T cells, which include $CD4^+$ Th17 T cells, $CD8^+$Tc17 T cells, and subsets of γδ T cells, require the activity of the transcription factor retinoic acid receptor–related orphan nuclear receptor (ROR) γt for their differentiation. These RORγt$^+$ IL-17$^+$ cell types have all been implicated in psoriasis pathogenesis, suggesting that therapeutics targeting RORγt might effectively treat this autoimmune skin disease. With this goal in mind, Skepner et al. (p. 2564) identified TMP778, a specific, potent human RORγt inverse agonist, and TMP776, a structurally related but inactive diastereomer of TMP778. TMP778, but not TMP776, inhibited the differentiation of human Th17 and Tc17 cells and the production of IL-17A by effector/memory Th17 and Tc17 cells in vitro. Whole genome transcriptional profiling revealed that TMP778 selectively inhibited the expression of genes associated with a Th17 signature in memory and naive $CD4^+$ T cells under Th17-skewing conditions. TMP778, but not TMP776, also inhibited the production of IL-17A and the expression of IL-17–related genes in human γδ T cells. In mice, imiquimod-induced skin inflammation, which is γδ T cell– and IL-17A–dependent, was inhibited by s.c. TMP778 treatment, which also reduced IL-17A–producing γδ T cells and Th17 gene signature expression in skin-infiltrating cells. Finally, TMP778 inhibited IL-17A production and the expression of Th17 signature genes in cultured PBMCs and skin-derived mononuclear cells of psoriasis patients. Taken together, these data provide insight into RORγt function and suggest that, given its high degree of specificity, TMP778 might be a relatively low-toxicity option for the clinical treatment of psoriasis.

TLR Signaling TAKedown

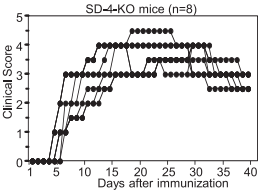
Toll-like receptors play a key role in innate immune host defense against pathogens, but the mechanism that prevents excessive activation of these receptors and consequent harmful inflammatory responses is not completely understood. Gu et al. (p. 2846) set out to determine if protein phosphatase-1 (PP1), a protein abundant in immune cells that has regulatory functions in the inflammatory TNFR pathway, negatively regulates TLR signaling pathways. Using overexpression of phosphatase activity–competent or –deficient PP1, the authors found that PP1 inhibits MAPK and NF-κB pathways activation and production of inflammatory cytokines in RAW264.7 cells that were stimulated with ligands for TLR3, 4, or 9. PP1 inhibition of TLR pathways was mediated by DNA damage-inducible protein 34 (GADD34), a regulatory subunit of PP1, which dephosphorylated TGF-β–activated kinase 1 (TAK1) at serine 412 (Ser412). GADD34 depletion abolished TAK1–PP1 interactions, reversed PP1 overexpression–induced inhibition of TLR signaling, and promoted TLR signaling–induced TAK1 Ser412 phosphorylation, downstream MAPK and NF-κB pathways activation, and proinflammatory cytokine production. These data were corroborated in vivo, as pretreating mice with tautomycetin, a PP1-specific inhibitor, exacerbated LPS-induced endotoxin shock in mice. Together, these results suggest that PP1 and its subunit GADD34 provide an important regulatory checkpoint that tempers TLR signaling and prevents overactive, potentially deleterious, inflammatory immune responses.

Nasal NE Takes a Toll



Activation of both innate and adaptive immune pathways is essential to the efficacy of many mucosal vaccine adjuvants; however, the mechanism of action for many of these adjuvants is not well characterized. In this issue, Bielinska et al. (p. 2722) identify innate and costimulatory pathways integral to immune responses stimulated by mucosal adjuvant $W_{80}5EC$ (NE), an oil-in-water nanoemulsion known to induce potent systemic and mucosal Th1 and Th17 cellular responses. Despite the lack of known innate immune receptor ligands in NE, using in vitro cell-based reporter assays and whole genome microarrays, the authors determined that NE modulates NF-κB activity via TLR2 and TLR4 by a mechanism distinct from other TLR agonists. MyD88-, TLR2-, or TLR4-deficient mice immunized intranasally (i.n.) with recombinant protective Ag of anthrax combined with NE (PA-NE), revealed that these innate molecules were dispensable for PA-NE–elicited Ab responses, but were required for full Th1- and Th17-biased cellular immune responses. To determine if costimulatory pathways were also required for NE-induced immune responses, the authors examined PA-NE–immunized mice lacking both CD86 and CD80 or CD40 and found that these mice displayed defective PA-NE–specific Ab responses compared with wild-type mice, whereas CD86-deficient mice did not. All three groups exhibited defective Th1 and IL-17 cytokine production. Mice deficient for the p35/p40 subunits of IL-12, a potent stimulator of Th1 cytokine responses, or for IL-12Rβ1 also failed to produce Th1 or IL-17 cytokines when immunized i.n. with NA-PE. Together, these results suggest that cellular immune responses stimulated by mucosally administered NE are dependent on both TLR2 and TLR4 innate receptor signaling and adaptive costimulatory molecules, but that many of these pathways are dispensable for NE-induced humoral immunity, revealing previously unknown details about the mechanism of action of NE adjuvant.

Mighty MDSCs Suppress EAE



T cell activation can be downregulated by coinhibitory signals including those initiated by interactions between syndecan-4 (SD-4) on T cells and dendritic cell–associated heparan sulfate proteoglycan-dependent integrin ligand (DC-HIL) on APCs. T cell activity can also be inhibited by the activity of suppressive cell types such as regulatory T cells and myeloid-derived suppressor cells (MDSCs). Chung et al. (p. 2576) investigated whether the DC-HIL/SD-4 interaction plays a role in autoimmune disease using a mouse model of multiple sclerosis, experimental autoimmune encephalomyelitis (EAE). Following myelin oligodendrocyte glycoprotein (MOG) immunization to induce EAE, SD-4 was upregulated on $CD4^+$ and $CD8^+$ T cells in wild-type (WT) mice. In mice lacking either SD-4 or DC-HIL, EAE severity and the numbers of effector T cells in the spleen were significantly increased relative to immunized WT mice. Exacerbated EAE in MOG-immunized Rag2-deficient recipients of adoptively transferred SD-$4^{-/-}$ T cells, but not SD-$4^{+/+}$ T cells, indicated that deletion of SD-4 increased T cell reactivity to MOG. MDSCs from MOG-immunized WT mice potently suppressed T cell activation through DC-HIL–induced production of IFN-γ and NO. Further confirming the relevance of these cells to EAE, DC-HIL–expressing MDSCs from MOG-immunized WT mice were able to ameliorate the exacerbated EAE observed in immunized DC-$HIL^{-/-}$ mice. Thus, interactions between DC-HIL^+ MDSCs and SD-4^+ effector T cells appear to reduce autoreactive T cell activity in EAE, and this pathway may therefore be a useful target to ameliorate autoimmune disease severity.