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Meeting abstract

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Inverse relationship of TLR/NF-κB signalling and the Wnt/β-catenin pathway during inflammation: Deciphering the role of Frizzled1 in *M. tuberculosis* infection

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Wnt ligands are palmitoylated glycoproteins that regulate essential aspects of early development, including embryonic patterning, cell proliferation and cell fate determination. Wnts are secreted and bind to cell-surface heptahelical receptors termed "Frizzleds". To date 10 Frizzled (Fzd) receptors have been identified in mice and men. Depending on the receptor context, Wnt ligands can initiate at least three different intracellular signaling cascades: The Wnt/β-catenin pathway, the Wnt/Planar cell polarity (PCP) pathway and the Wnt/Ca^{2+} pathway.

Our previous observation that factors of the Wnt/Fzd signaling pathway are differentially expressed after infection with mycobacteria prompted us to study the interdependence of proinflammatory and Wnt/Fzd signaling processes. We analyzed the regulation of the β-catenin pathway in the context of *M. tuberculosis* infections: After aerosol infection of mice we find an inverse regulation of the TLR/NF-κB- and the Wnt/β-catenin pathway: Whereas inducible nitric oxide synthase (iNOS) and IFN-γ formation are increased, β-catenin levels and the transcription of β-catenin dependent target genes are significantly reduced. This demonstrates that Wnt/β-catenin signaling, which is involved in tissue homeostasis, is switched off under proinflammatory conditions. In murine macrophages, we have then identified Fzd1 mRNA to be upregulated in response to mycobacteria and conserved bacterial structures. Fzd1 has previously been shown to mediate β-catenin dependent signaling in response to Wnt3a and Wnt7b. Microbe-induced Fzd1 transcription depends on the presence of Toll-like receptors (TLR) 2 and 4, the myeloid differentiation response gene 88 (MyD88) and the NF-κB pathway. Single cell analysis by flow cytometry demonstrates an enhanced Fzd1 expression on macrophages in response to *M. tb.*, as well as LPS, which was synergistically enhanced in the presence of IFN-γ. The analysis of lung homogenates of *M. tb.*-infected mice also shows an enhanced Fzd1 mRNA expression during the course of infection, indicating that Fzd1 upregulation also occurs under inflammatory conditions in vivo. Transcripts for Wnt3a are also present in lung homogenates of infected mice. In primary macrophages, Wnt3a restores TLR/NF-κB induced downregulation of β-catenin signaling to the level of unstimulated cells. This novel Wnt-mediated feedback mechanism may be involved in preserving cell homeostasis during microbe-induced inflammation. Both Toll and Wnt signaling pathways are evolutionarily highly conserved and have only recently been found to intersect in Drosophila. The current data further support the notion that Wnt signaling is involved in orchestrating the immune response in response to microbial stimulation of innate immune cells of vertebrate origin.

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