

TAMing Inflammation

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The activation of Toll-like receptors (TLRs) in dendritic cells (DCs) triggers a rapid inflammatory response to pathogens. However, this response must be tightly regulated, since unrestrained TLR signaling generates a chronic inflammatory milieu that often leads to autoimmunity. We have found that the TAM receptor tyrosine kinases - Tyro3, Axl, and Mer - broadly inhibit both TLR and TLR-induced cytokine receptor cascades. Remarkably, TAM inhibition of inflammation is transduced through an essential stimulator of inflammation - the type I interferon receptor (IFNAR) and its associated transcription factor STAT1. TLR induction of IFNAR-STAT1 signaling up-regulates components of the TAM system, which in turn usurp the IFNAR-STAT1 cassette to induce the cytokine and TLR suppressors SOCS1 and SOCS3. These results illuminate a self-regulating cycle of inflammation, in which the obligatory, cytokine-dependent activation of TAM signaling hijacks a pro-inflammatory pathway to provide an intrinsic feedback inhibitor of both TLR- and cytokine-driven immune responses.

Lemke, G., and Rothlin, C.V. (2008). Immunobiology of the TAM receptors. *Nat Rev Immunol* 8, 327-336.

Rothlin, C.V., Ghosh, S., Zuniga, E.I., Oldstone, M.B., and Lemke, G. (2007). TAM Receptors Are Pleiotropic Inhibitors of the Innate Immune Response. *Cell* 131, 1124-1136.