

**P015** SOCS-1 negatively regulates TLR signalling by mediating MAL degradation

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TLR activation is a double edged sword. It is essential for provoking the innate immune response and enhancing the adaptive immunity against pathogens, but TLR family members are also involved in the pathogenesis of autoimmune, chronic inflammatory and infectious diseases. Therefore, the intensity and duration of TLR responses must be tightly controlled.

We recently characterized a mechanism of degradation of Mal by SOCS-1 that occurs upon signalling by TLR2/4. Mal associated with SOCS-1, which acts as an E3 ligase to mediate polyubiquitination of Mal; polyubiquitination of Mal results in its degradation via the 26S proteasome. Perturbed regulation of these events results in potentiated Mal-dependent NF- $\kappa$ B transactivation and prolonged pro-inflammatory response. Targeted degradation of Mal by SOCS-1 therefore regulates TLR activation of NF- $\kappa$ B, causing instead rapid refractoriness to prolonged TLR2/4 signalling.

Recently we have found that SOCS-1 may also bind tyrosine phosphorylated TLR2/4. Mutation of TLR2 Y761F (TLR4 Y794F) results in potentiated TLR2-mediated activation of NF- $\kappa$ B and ablated SOCS-1-mediated polyubiquitination of Mal. These data suggest a novel mechanism of SOCS-1 target recognition as SOCS-1 may directly bind TLR2Y761 proximally associating with Mal, facilitating E3-ligase-mediated Mal polyubiquitination and subsequent degradation to negatively regulate signalling.