

**P062** The effect of dexamethasone on the transcription factor IRF3

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Toll-like receptors (TLRs) are important for the detection of invading pathogens, resulting in the initiation of signalling pathways that culminate in the expression of immune and inflammatory genes. Almost all TLRs activate the transcription factor nuclear factor- $\kappa$ B (NF- $\kappa$ B). TLR3 and TLR4 also have the ability to activate another transcription factor, interferon-regulatory factor 3 (IRF3).

Recently it has been shown that anti-inflammatory steroids such as dexamethasone may inhibit IRF3 activation. Proposed mechanisms involve the inhibition of a protein called glucocorticoid receptor-interacting protein (GRIP) to interact with IRF3, thereby suppressing IRF3 dependent genes. The second is the targeting of an IRF3/p65 complex exclusively activated by TLR4. We have subsequently shown that in response to TLR3 and TLR4 stimulation, dexamethasone can inhibit phosphorylation of Ser396, a residue crucial for IRF3 activation, as well as inhibiting activation of ISRE luciferase, and the production of key IRF3 dependent cytokines. Dexamethasone appears to inhibit autophosphorylation of the upstream kinase TBK1, thereby providing a mechanism for how dexamethasone may be affecting IRF3 activation. We also have preliminary evidence to suggest that IRF3 can not only be activated downstream of TLR3 and TLR4 but can also be activated downstream of the IL-1 signalling pathway, suggesting a potential role for MyD88 in the activation of IRF3.