REGULATION OF PULMONARY ARTERY INFLAMMATION BY PPARβ/δ

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Introduction: The peroxisome proliferator activated receptor beta delta (PPARβ/δ) is a transcription factor ubiquitously expressed, although more highly active in skeletal muscle, arteries and endothelium. Signalling via PPARβ/δ is involved in lipid metabolism, glucose metabolism, insulin sensitivity, inflammation, and cell proliferation; however, there are great discrepancies in the literature about the role of PPARβ/δ and scientists describe anti- and pro-effects on inflammation, cell migration and cell proliferation after the activation of PPARβ/δ.

As nuclear transcription factor, PPARβ/δ can regulate genes by directly binding the DNA forming a heterodimer with RXR (induction), or alternatively can repress other nuclear transcription factors (trans-repression) and thus indirectly regulate a different group of genes (Figure 1). Lately it is emerging the theory that PPARβ/δ has a dual effect in the cell and indeed acts as a molecular switch between induction and trans-repression having both pro- and anti- effects in inflammation.

Understanding how PPARβ/δ switches between induction and trans-repression mode of action is of great interest and may provide new molecular targets for treating a variety of inflammation-dependent diseases, including atherosclerosis, diabetes, and cancer.

We hypothesised that PPARβ/δ acts as a molecular switch between induction and trans-repression and depending on which mechanism is triggered it will have pro- or anti-effects.

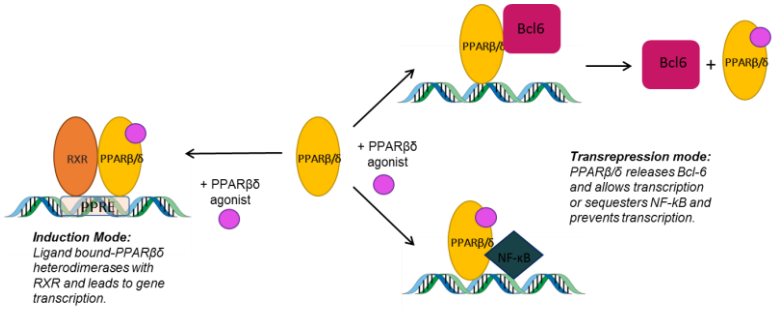

Figure 1. **Switch between induction and trans-repression mode of PPARβ/δ.**

Methods: Pulmonary artery rings from rat were dissected and incubated for 24h under different treatments: vehicle, LPS, LPS+GW0742, LPS+GSK3787, LPS+GW0742+GSK3787, where LPS induces inflammation, GW0742 is a PPARβ/δ agonist and GSK3787 is a PPARβ/δ antagonist. The regulation of the inflammation by PPARβ/δ was examined by measuring the production of the inflammatory biomarkers NO by Griess Assay and IL-6 by ELISA. The switch between induction/trans-repression was analysed through qRT-PCR of target genes.

Results: The presence of GW0742 and GSK3787 together shows the greatest anti-inflammatory effects among all the treatments. GW0742 alone triggers the induction and trans-repression mechanisms of action of PPARβ/δ, but the presence of GW0742 and GSK3787 together only triggers the trans-repression mode of action.

Discussion or Conclusions: Taken all together it suggests that the trans-repression mode of action is responsible for the anti-inflammatory effects of LPS-induced inflammation in the pulmonary artery.