

## **Glutathione-redox balance regulates c-rel driven IL-12 production in macrophages: possible implications in anti-tuberculosis immunotherapy<sup>1</sup>**

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The glutathione-redox balance, expressed as the ratio of intracellular reduced (GSH) and oxidized (GSSG) glutathione plays central roles in regulating cellular immune responses. In the present study, we demonstrate that alteration of glutathione-redox balance in macrophages by GSH donors like cell permeable glutathione ethyl ester (GSH-OEt) or N-acetyl cysteine (NAC) have a potent effect on intracellular I-kappaB alpha ( $I\kappa B\alpha$ ) and calmodulin (CaM) signaling which critically regulates interleukin (IL)-12 induction. However, levels of IL-10 and tumor necrosis factor-alpha are not significantly affected in these macrophages. In an environment rich in GSH, an increased  $I\kappa B\alpha$  phosphorylation and degradation results in more accumulation of c-rel in the nucleus that increases IL-12 p40/p70 production. When intracellular GSSG concentration is higher, both nuclear c-rel and IL-12 levels are decreased due to increased CaM expression that binds and sequesters c-rel in the cytoplasm. The glutathione-redox involves the p38 MAP kinase pathway to regulate CaM signaling. We demonstrate that NAC at 3 mM concentration increases BCG-induced IFN-gamma production by PBMCs from patients with active tuberculosis and shifts the anti-BCG immune response towards the Th1-type. Our results indicate that redox balance of glutathione plays a critical role to regulate  $I\kappa B\alpha$  and CaM signaling important for regulation of c-rel translocation to nucleus and IL-12 induction in native macrophages. These findings are important in tailoring macrophages for IL-12 induction and Th1 response to control tuberculosis and other pathophysiological disorders.