Repression of Macrophage Inflammatory Response Genes by Ncor

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Understanding the mechanisms involved in the inflammatory response of macrophages can help elucidate their possible function in the progression of chronic inflammatory diseases such as atherosclerosis, type II diabetes and obesity. Previous studies have shown that PPAR (peroxisome proliferator activated receptors) acts to inhibit inflammatory mediated genes such as the inducible nitric oxide synthase gene (iNOS) through ligands. It has also been shown that PPAR may inhibit inflammatory response genes in an Ncor dependent mechanism. In the current study we sought to find how the nuclear co-repressor (Ncor), a large adapter protein, interacts with PPAR. Although Ncor does not directly bind to DNA, it interacts with sequence-specific genes. Thus, the purpose of the study was to confirm that iNOS expression is repressed by Ncor and also to find, through transfections, sequences within iNOS that Ncor represses. This was approached by looking for a promoter that was not regulated by Ncor and inserting pieces of the iNOS promoter -750 to +50bp. This region was selected because it contains an AP1 site which has been found to interact with Ncor. The transfections confirmed that iNOS was negatively regulated by Ncor. The results for the regulation of the TK promoter are ambiguous and further studies are needed. The results of the proposed study could be used to screen transcription factors that recruit Ncor. Also, they can be used to screen for other genes that may be repressed by Ncor.