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PPAR? negatively regulates T cell function

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Keywords

IL-2, NFATc, nuclear factor of activated T cells, PPAR, peroxisome proliferator-activated receptor, proliferation, prostaglandin

Context

PPAR? is a member of the nuclear hormone receptor family of transcription factors. It is activated by naturally occurring ligands such as 15-deoxy-?12,14 prostaglandin J2 (15?-PGJ2), and by thiazolidinedione drugs such as troglitazone. Recent papers suggest that PPAR? is a negative regulator of macrophage function. This paper reports a novel function of PPAR?, the ability to block T cell activation and IL-2 expression. This function may involve negative regulation of the transcription factor NFATc, which plays a critical role in IL-2 gene expression and T cell activation. To investigate the function and mechanism of action of PPAR? in isolated T lymphocytes and in a T cell line.

Significant findings

Human peripheral blood thymocytes were driven to proliferate by treatment with PHA and PMA. Proliferation was dose-dependently inhibited by two PPAR? agonistic ligands (15?-PGJ2 and troglitazone), but not by a PPARa ligand. Inhibition of IL-2 gene expression occurred at the mRNA level. Induction of NFATc DNA binding activity by PHA and PMA was partially blocked by PPAR? agonists. An association of NFATc with PPAR? was demonstrated, and appeared to be dependent upon activation of the nuclear hormone receptor by ligand. Other experiments employed Jurkat cells, a human T cell line. Cells were transfected with a GFP expression vector and with a PPAR? or empty control vector. Transfected cells were selected for GFP expression by FACS analysis, in order to generate PPAR?$^{+}$ and PPAR?$^{-}$ populations. The validity of this approach was confirmed using a luciferase reporter construct driven by PPAR? binding sites. In PPAR?$^{+}$ but not in PPAR?$^{-}$ cells, IL-2 production was inhibited by PPAR? (but not PPARa) ligands. Transcriptional activities of an IL-2 promoter and an NFATc-dependent reporter construct were decreased by PPAR? ligands in PPAR?$^{+}$ but not PPAR?$^{-}$ cells.

Comments

This "accelerated publication" describes a compact and well-designed piece of research. It makes an important addition to the growing list of unexpected immunomodulatory properties of the peroxisome proliferator-activated receptor (PPAR) family of transcription factors, that is, an ability to interfere with activation of T cells by phytohemagglutinin (PHA) and phorbol 12-myristate 13-acetate (PMA). It would be interesting to examine the effects of PPAR? ligands upon other processes such as T cell activation by antigen presenting cells. An association of PPAR? with NFATc (nuclear factor of activated T cells) in human peripheral blood T cells is convincingly shown; however, PPAR? ligands appear to inhibit NFATc activation only partially. Interference with additional transcription factors (such as activator protein 1[AP1] and NF-?B) may contribute to the inhibition of interleukin (IL)-2 transcription by PPAR?, as the authors acknowledge.

Methods

Proliferation was measured by tritiated thymidine incorporation. IL-2 gene expression was measured at protein and mRNA levels by ELISA and ribonuclease protection assay. Activation of NFATc was examined by electrophoretic mobility shift assay (EMSA). Co-immunoprecipitation and western blotting were used to look for an association between NFATc and PPAR?. Jurkat cells were transfected by the DEAE dextran method, and selected for green fluorescent protein (GFP) expression by sterile cell sorting. Luciferase reporter assays were performed using standard techniques.

Additional information

Another recent paper reports that PPAR? agonists inhibit proliferation of, and IL-2 production by, two murine T cell clones (Clark *et al J Immunol* **164:**1364-1371[Abstract]).

References

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