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SMAD-3 is Involved in TGF-b1 Inhibition of Class II Transactivator and Class II MHC Expression in Human Glomerular Endothelial Cells

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The most of renal diseases are caused by immunologic alterations. The expression of class II molecule (MHC-II) on endothelial cells probably plays a pivotal role in mediating the immune response, eventually renal diseases. The effect of TGF-β1 on MHC-II expression is known to be dependent on cell type, tissue of origin and possibly stage of differentiation. Depending on variety of factors, TGF-β1 can have either proinflammatory or immunosuppressive properties. Previously, we reported that TGF-β1 reduced IFN-γ-induced MHC-II expression in human glomerular endothelial cells (HGEC) in ELISA method (ERA-EDTA 35th congress A12, 1998). However, so far little has been evaluated for the intracellular signal transduction pathway of TGF-β1 on the expression of MHC-II in HGEC. In the present study, we investigated the intracellular mechanism of TGF-β1 in antagonizing IFN-γ effect on the expression of MHC-II in HGEC.

Like the previous results of ELISA, MHC-II mRNA was increased in 24 and 48h after stimulation of INF-γ (20ng/ml) (n=2) in Northern blot, and the expression of MHC-II mRNA was partially inhibited by the treatment of TGF-β1 (10ng/ml) (n=2). The mRNA of class II transactivator, a master regulator that controls MHC-II expression, was also partially decreased by TGF-β1 (10ng/ml) that was coincubated with IFN-γ (20ng/ml) for 6 and 24h in HGEC. However, INF-γ-induced STAT-1α phosphorylation (tyrosine 701 phosphorylation), which is essential for cells to respond fully to IFN-γ, was not affected by TGF-β1 (10ng/ml) in Western blot using total cell lysates (n=3). In HGEC, while Smad3 was induced in nuclear protein after stimulation of TGF-β1 (10ng/ml) for 30min (n=3), Smad3 was not induced by pretreatment of INF-γ (20ng/ml) (n=3) in Western blot, which means that IFN-γ has an antagonizing activity with TGF-β1 via Smad3, and Smad3 might be involved in TGF-β1 inhibition of class II transactivator and MHC II expression.

In conclusion, our study showed that TGF-β1 has an immunosuppressive activity in HGEC that is mediated via SMAD-3.