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DOWN REGULATION OF TGF-β GENE EXPRESSION BY ANTISENSE OLIGODEOXYNUCLEOTIDES INCREASE rIFN-γ-INDUCED NITRIC OXIDE SYNTHESIS IN MURINE PERITONEAL MACROPHAGES

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Increasing evidence indicates that the production of nitric oxide (NO) by inducible NO synthase (NOS) is tightely regulated. Transforming growth factor-β (TGF-β) is a homodimeric protein secreted during macrophage activation, but several lines of evidence suggest that TGF-β is selectively suppressive for macrophage NO production. We therefore reasoned that a strategy employing oligodeoxynucleotides (ODNs) complementally to TGF-β mRNA (antisense ODNs) might increase NO production in IFN-γ-treated murine peritoneal macrophages. To evaluate this concept, we tested the effects of antisense ODNs targeted to TGF-β mRNA (25-mer ODNs complementally to TGF-β mRNA sequences) by introducing it into the medium of cultured macrophages. Phosphorothiolation of ODNs were employed to retard their degradation. Antisense ODNs had no effect on NO production by itself, whereas IFN-γ alone had modest effect. When antisense ODNs were used in combination with IFN-γ, there was a marked cooperative induction of NO production. These effects of antisense ODNs were associated with decreased TGF-β expression in activated macrophages. ODNs with the same nucleotides but a scrambled sequence had no effect. Adding anti-TGF-β antibodies to the IFN-γ-treated macrophages mimicked the positive effect of antisense ODNs on NO production. In addition, the effects of either antisense ODNs or anti-TGF-β antibodies were blocked by adding TGF-β in cultured macrophages. These results indicate that the generation of TGF-β by activated macrophages provides a self-regulating mechanism by which the temporal and perhaps spatial production of NO, a reactive and potentially toxic mediator, can be finely regulated.