Stimulation by transforming growth factor-α of DNA synthesis and proliferation of adult rat hepatocytes in primary cultures: Modulation by α- and β-adrenoceptor agonists

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We investigated the effects of transforming growth factor-α (TGF-α) on DNA synthesis and proliferation in primary cultures of adult rat hepatocytes and examined the influence of α- and β-adrenoceptor agonists on the TGF-α-induced responses. TGF-α (1.0 ng/ml) produced a 4.1-fold elevation of DNA synthesis during 3 h of culture and a 1.2-fold increase in the nucleus number (proliferation) during 4 h of culture at a cell density of $3.3 \times 10^4$ cells/cm². The TGF-α-induced hepatocyte DNA synthesis and proliferation were dose-dependent at EC₅₀ values of 0.36 ng/ml and 0.45 ng/ml, respectively. Hepatocyte DNA synthesis and proliferation induced by 1.0 ng/ml TGF-α did not reduce even at higher initial plating densities ($5.0 \times 10^4$ and $1.0 \times 10^5$ cells/cm²). Increasing concentrations of a β₂-adrenoceptor agonist, metaproterenol ($10^{-7}$ - $10^{-6}$ M), markedly reduced the proliferative effects of TGF-α, while those of an α₂-adrenoceptor agonist, UK-14304 ($10^{-6}$ - $10^{-5}$ M), and an α₁-adrenoceptor agonist, phenylephrine ($10^{-7}$ - $10^{-6}$ M), significantly potentiated the TGF-α action. The proliferative effects of TGF-α (1.0 ng/ml) were not affected significantly by a monoclonal anti-epidermal growth factor receptor antibody (1-100 ng/ml) and were almost completely blocked by specific inhibitors of signal transducers, such as genistein ($10^{-5}$ M), U-73122 ($10^{-5}$ M), wortmannin ($5 \times 10^{-7}$ M), sphingosine ($5 \times 10^{-6}$ M), PD98059 ($5 \times 10^{-5}$ M), and rapamycin (10 ng/ml). These results suggest that among the elements that link signals of cell surface receptor to the nucleus, the proliferative action of TGF-α is mediated, at least, by tyrosine kinase, phospholipase C, PI (3) kinase, protein kinase C, MAP kinase kinase, and p70 S6K.