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Interaction of ANG II and EGF Receptor in Proliferation of Mouse Embryonic Stem Cells

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Effect of ANG II on mouse embryonic stem (ES) cell proliferation was examined. ANG II increased [^{3}H] thymidine incorporation in a time- (>4 hr) and dose- (>10^{-9} M) dependent manner. The ANG II-induced increase in [^{3}H] thymidine incorporation was blocked by inhibition of ANG II type 1 (AT_1) receptor but not by ANG II type 2 (AT_2) receptor. AT_1 receptor was expressed in mouse ES cells. ANG II increased inositol phosphates formation and $[Ca^{2+}]_i$. ANG II translocated PKC α, δ, and ζ to the membrane fraction. Consequently, the inhibition of PLC/PKC suppressed ANG II-induced increase in [^{3}H] thymidine incorporation. The inhibition of EGF receptor kinase or tyrosine kinase prevented ANG II-induced increase in [^{3}H] thymidine incorporation. ANG II phosphorylated EGF receptor, which was blocked by AG 1478 (EGF receptor kinase blocker). ANG II-induced increase in [^{3}H] thymidine incorporation was blocked by the inhibition of p44/42 MAPKs but not by p38 MAPK inhibition. ANG II phosphorylated p44/42 MAPKs, which was prevented by the inhibition of the PKC and AT1 receptor. ANG II increased c-fos, c-jun, and c-myc levels. ANG II also increased the protein levels of cyclin D1, cyclin E, cyclin-dependent kinase (CDK) 2, and CDK4 but decreased the $p21^{cip1/waf1}$ and $p27^{kip1}$, CDK inhibitory proteins. These proteins were blocked by the inhibition of AT1 receptor, PLC/PKC, p44/42 MAPKs, EGF receptor, or tyrosine kinase. In conclusion, ANG II increased mouse embryonic stem cell proliferation by activation of PKC and p44/42 MAPKs via the AT_1 receptor as well as EGF receptor transactivation.