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Regulation of Chondrogenesis by Protein Kinase C Signaling

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A role of protein kinase C (PKC) signaling in chondrogenic differentiation of mesenchymes were examined. Multiple PKC isoforms including α, ε, ζ, and λ/ι were expressed in mesenchymes derived from chick limb buds. Among the expressed PKC isoforms, increased expression and activity of PKCα appear to be essential for the induction of chondrogenesis as determined by pharmacological and biochemical studies. The expression of PKCα appears to be mediated by phosphatidylinositol 3-kinase (PI3-kinase)-dependent activation of p70S6 kinase because inhibition of PI3-kinase or p70S6 kinase blocked expression of PKCα and thus chondrogenesis. Inhibition or downregulation of PKCα resulted in the activation of mitogen-activated protein (MAP) kinase subtype, Erk-1, and the inhibition of chondrogenesis. On the other hand, inhibition of Erk-1 enhanced chondrogenesis, and relieved PKC-induced blockage of chondrogenesis suggesting that PKCα regulates chondrogenesis by modulating Erk-1 activity. Inhibition or depletion of PKC inhibited proliferation of chondrogenic competent cells, and Erk-1 inhibition did not affect PKC modulation of cell proliferation. However, PKC-induced modulation of expression of cell adhesion molecules (i.e., N-cadherin, integrins, and fibronectin) involved in precartilage condensation was reversed by the inhibition of Erk-1 indicating that PKC regulates chondrogenesis by modulating expression of these molecules via Erk-1 signaling. Contrast to the role of Erk-1, inhibition of p38 MAP kinase blocked chondrogenesis. The inhibition of Erk-1 or p38 MAP kinase did not affect proliferation of chondrogenic competent cells, however, they regulated expression of cell adhesion molecules involved in precartilage condensation in an opposite way. Since temporal expressions of these adhesion molecules regulate precartilage condensation during chondrogenesis, the results indicate that Erk and p38 MAP kinase subtypes oppositely regulate chondrogenesis at precartilage condensation stage.