THE ANTI-APOPTOTIC EFFECT OF INSULIN-LIKE GROWTH FACTOR-I INVOLVES KINASE PATHWAYS IN C2C12 MYOBLASTS

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Cell cycle progression in mammalian cells is strictly regulated by both integrin-mediated adhesion to the extracellular matrix and by binding of growth factors to their receptors. Progression through the mammalian cell cycle requires the mitogen-stimulated induction of cyclin D1. In the presence of growth factor, cyclin D1 accumulates in G1 phase of the cell cycle and assembles with its catalytic partner CDK4 or CDK-6. This complex controls transit through the G1/S phase transition. Loss of adhesion generally results in complete G1 phase cell cycle arrest and for susceptible cell types loss of adhesion leads to apoptosis. Cell-matrix interactions occur at the focal adhesion which is a complex network of cytoskeletal proteins that links the filamentous actin (F-actin) cytoskeletal network through integrin to the extracellular matrix. In C2C12 cells the apoptotic agent staurosporine (ST) induces a dramatic decrease in the expression of focal adhesion kinase (FAK) which is a widely expressed cytosolic tyrosine kinase involved in trasmission of signals from the focal adhesion to the cytoplasm and in signal trasduction of a number of growth factors. In C2C12 IGF-I treatment is able to counteract FAK decrease and to maintain FAK levels at the same value as control cells. The activity of this tyrosine kinase is enhanced in ST-treated cells as a compensation for its expression decrease. FAK interacts with a variety of focal adhesion macromolecules. Integrin activation of PI3-kinase, and extracellular signal-regulated kinase (ERK) signaling pathways require FAK. In C2C12 cells phosphoinositide 3-kinase (PI3K) activity is inhibited by ST as shown by decreased phosphorylation of its downstream signaling substrate Akt/PKB. IGF-I treatment results in the activation of Akt/PKB which serves as anti-apoptotic stimuli. ST exposure also reduces ERK-1 levels, but this decrease is well counteracted by IGF-I incubation. IGF-I exposure of ST-treated C2C12 cells promotes an increased expression of cyclin D1 bound to CDK-4. It is known that ST induce an accumulation of cells in G1 or G0 phases of the cell cycle associated with a reduction of cyclin D1 expression and activity. As cyclin D1 expression and activation has most frequently been attributed to the activation of ERK and PI3K, the IGF-I anti-apoptotic action on ST-treated C2C12 cells could be explained as an IGF-I mediated stimulation of cell reentry into the cell cycle which was blocked by 16 h exposure to ST.