DIFFERENTIAL ROLES OF PROTEIN KINASE C ISOENZYMES IN THE REGULATION OF IN VITRO AND IN VIVO GROWTH OF SKELETAL MUSCLE CELLS AND CHONDROCYTES

Gabriella Czifra, Department of Physiology

In our studies we investigated the participation of the protein kinase C (PKC) isoenzyme family and of other signaling systems in the regulation of in vitro and in vivo proliferation and differentiation of skeletal muscle cells and chondrocytes. We found that the nPKCδ isoform plays an exclusive role in the development of the mitogenic effect (i.e. to promote growth and differentiation) of IGF-I, a key molecule of human skeletal muscle regeneration. However, on mouse C2C12 myoblasts, we have also shown that besides the central involvement of nPKCδ-specific activity, the MAPK pathway also participates in mediating the effect of IGF-I. In addition, it was also proven on these cells that the nPKCδ functions as an “upstream” regulator of the MAPK pathway; i.e. its preceding activation is required for the stimulation of the MAPK system. Furthermore, we also found that stable recombinant overexpression of various PKC isoforms in C2C12 myoblasts differentially affected the functional and morphological features of the cells. The overexpression of cPKCα and β decreased the growth rate of the cells whereas that of nPKCε did not exert any effect. As a marked contrast, constitutive overexpression of nPKCδ dramatically stimulated in vitro cellular proliferation, suppressed the expression of the differentiation marker desmin, and promoted the in vivo development of large, malignantly transformed tumors in immunodeficient mice. Finally, using chondrogenic high-density chicken limb bud mesenchymal cultures, we have shown that the unique PKCμ plays a central role in the regulation of the (late) events of chondrogenic differentiation. These findings strongly argue for the specific yet often antagonistic functions of certain PKC isoforms in the regulation of growth and differentiation of skeletal muscle cells and chondrocytes.