

**P014** Search of possible targets of PI3K/Akt pro-apoptotic signaling in muscle-derived primary cell lines after cisplatin treatment

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The signaling pathway of PI3K/AKT is known as cell survival pathway. In this study we have shown the pro-apoptotic role of PI3K/AKT signaling in primary myogenic cells after cisplatin treatment. Cisplatin-induced apoptosis in myogenic cells was estimated by DNA fragmentation, caspase 3 cleavage and morphological changes. The inhibitors of PI3K/Akt pathway, wortmanin, Ly294002 and Akt inhibitor VIII attenuated the cisplatin-induced apoptosis and the phosphorylation of Akt. Moreover, myogenic cells over-expressing wild type AKT kinase stimulated cisplatin induced apoptosis. Our results indicate that Akt, the downstream target of PI3K is positively involved in cisplatin-induced myogenic cell apoptosis. The previously mentioned inhibitors of PI3K/AKT signaling pathway and N-acetyl cysteine, **had additive effect on the** protection of cells from cisplatin-induced apoptosis. It indicates that PI3K/AKT pathway and ROS are two independent pro-apoptotic pathways in myogenic cells. The activation of eNOS by PI3K/AKT signaling leads to the increased production of intracellular NO. In our case, the inhibitor of NOS, L-NMMA, slightly intensified cisplatin-induced apoptosis and weakened cell protection effect of PI3K/AKT inhibitors indicating the anti-apoptotic role of NO. Involvement of Fas/FasL death pathway in PI3K/AKT signaling has been considered as a possible target as well. We have found that previously mentioned inhibitors of PI3K/AKT signaling pathway reduced cisplatin-induced Fas expression on myogenic cells.