Inositol hexafosfato aumenta a apoptose no câncer de próstata

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Inositol hexaphosphate downregulates both constitutive and ligand-induced mitogenic and cell survival signaling, and causes caspase-mediated apoptotic death of human prostate carcinoma PC-3 cells.

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Abstract

Constitutively active mitogenic and prosurvival signaling cascades due to aberrant expression and interaction of growth factors and their receptors are well documented in human prostate cancer (PCa). Epidermal growth factor (EGF) and insulin-like growth factor-1 (IGF-1) are potent mitogens that regulate proliferation and survival of PCa cells via autocrine and paracrine loops involving both mitogen-activated protein kinase (MAPK)- and Akt-mediated signaling. Accordingly, here we assessed the effect of inositol hexaphosphate (IP6) on constitutive and ligand (EGF and IGF-1)-induced biological responses and associated signaling cascades in advanced and androgen-independent human PCa PC-3 cells. Treatment of PC-3 cells with 2 mM IP6 strongly inhibited both growth and proliferation and decreased cell viability; similar effects were also observed in other human PCa DU145 and LNCaP cells. IP6 also caused a strong apoptotic death of PC-3 cells together with caspase 3 and PARP cleavage. Mechanistic studies showed that biological effects of IP6 were associated with inhibition of both constitutive and ligand-induced Akt phosphorylation together with a decrease in total Akt levels, but a differential inhibitory effect on MAPKs extra cellular signal-regulated kinase 1/2 (ERK1/2), c-Jun N-terminal protein kinase (JNK1/2), and p38 under constitutive and ligand-activated conditions. Under similar condition, IP6 also inhibited AP-1 DNA-binding activity and decreased nuclear levels of both phospho and total c-Fos and c-Jun. Together, these findings for the first time establish IP6 efficacy in inhibiting aberrant EGF receptor (EGFR) or IGF-1 receptor (IGF-1R) pathway-mediated sustained growth promoting and survival signaling cascades in advanced and androgen-independent human PCa PC-3 cells, which might have translational implications in advanced human PCa control and management.

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