PALLADACYCLE COMPLEX INDUCES CELL DEATH IN HUMAN LEUKEMIA CELLS

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We have been dedicated to develop biphosphinic palladacycle complex (BPC), antineoplasic agent that triggers apoptosis in leukemic human cells independently of the p53 way. We have demonstrated that the BPC compounds are efficient to provoke cell death on HL-60, K562 and Jurkat line but not in normal mononuclear cells. The potency of induction of cell death is related to the structure of the drugs. We have observed that the isomer S(-) is about five times more potent than the isomer R(+) in its capacity to raise lysosomal membrane permeability (LMP) and cause cell death on K562 and HL-60 lines. BPC was capable of inducing the activation of effectors caspase-3 and caspase-6 of HL-60 apoptosis. Also, we observed that the activation of caspases-3 and caspase-6 is dependent of cytoplasmatic release of cathepsin B, since this activation was inhibited by CA074. Confocal images of leukemic cells loaded with acridine orange showed that BPC treatment induced classical apoptosis hallmarks with concomitant relocation of the acridine orange probe from lysosomes to cytosol. BPC compounds induce apoptosis on human leukemia cells by promoting rupture of lysosomal membrane and release of cathepsin enzymes to cytoplasm. Supported by FAPESP, CNPq and FAEP.