A novel copper(I) complex induces ER-stress-mediated apoptosis and sensitizes B-acute lymphoblastic leukemia cells to chemotherapeutic agents

Roberta Bortolozzi , Giampietro Viola , Elena Porcù , Francesca Consolaro , Cristina Marzano , Maura Pellei , Valentina Gandin and Giuseppe Basso

A phosphine copper(I) complex $[Cu(thp)_4][PF_6]$ (CP) was recently identified as an efficient *in vitro* antitumor agent. In this study, we evaluated the antiproliferative activity of CP in leukemia cell lines finding a significant efficacy, especially against SEM and RS4;11 cells. Immunoblot analysis showed the activation of caspase-12 and caspase-9 and of the two effector caspase-3 and -7, suggesting that cell death occurred in a caspase-dependent manner. Interestingly we did not observe mitochondrial involvement in the process of cell death. Measures on semipurified proteasome from RS4;11 and SEM cell extracts demonstrated that chymotrypsin-, trypsin- and caspase-like activity decreased in the presence of CP. Moreover, we found an accumulation of ubiquitinated proteins and a remarkable increase of ER stress markers: GRP78, CHOP, and the spliced form of XBP1. Accordingly, the protein synthesis inhibitor cycloheximide significantly protected cancer cells from CP-induced cell death, suggesting that protein synthesis machinery was involved. In well agreement with results obtained on stabilized cell lines, CP induced ER-stress and apoptosis also in primary cells from B-acute lymphoblastic leukemia patients. Importantly, we showed that the combination of CP with some chemotherapeutic drugs displayed a good synergy that strongly affected the survival of both RS4;11 and SEM cells.