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The poly(adp-ribose) polymerase inhibitor olaparib induces up-regulation of death receptors in primary acute myeloid leukemia blasts by nf-κb activation

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ABSTRACT

Olaparib is a potent orally bioavailable poly(ADP-ribose) polymerase inhibitor (PARPi), approved for BRCA-mutated ovarian and breast cancers. We recently showed that olaparib at clinically achievable concentrations exerts anti-proliferative and pro-apoptotic effects *in vitro* as monotherapy against primary acute myeloid leukemia (AML) blasts, while sparing normal bone marrow (BM) hematopoietic cells. Since AML expresses low levels of death receptors that may contribute to apoptosis resistance, in this study we investigated whether the anti-leukemia activity of olaparib involves modulation of FAS and TRAIL receptors DR5 and DR4. Our data show that the primary AML samples tested express FAS and DR5 transcripts at levels lower than normal BM. In this context, apoptosis triggered by olaparib is associated with a dose-dependent up-regulation of death receptors expression and caspase 8 activation. Olaparib-mediated FAS up-regulation requires NF-κB activation, as indicated by the increase of p65 phosphorylation and decrease of IκBα. Moreover, FAS up-regulation is abrogated by pretreatment of AML cells with two different NF-κB inhibitors. These results indicate that NF-κB activation and consequent induction of death receptor expression contribute to the anti-leukemia effect of olaparib in AML.