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The combination of everolimus and terameprocol exerts synergistic anti-proliferative effects in endometrial cancer: Molecular role of insulin-like growth factor binding protein 2

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Oncogenic PIK3CA mutations are common in endometrial cancers and the PI3K/AKT/mTOR pathway is targetable by drugs. We sought to investigate whether the combination of an mTOR inhibitor, everolimus (RAD001) and an AKT inhibitor, terameprocol (M4N), exerts better antiproliferative effects in endometrial cancer. The molecular mechanisms underlying their pharmacological action were also examined. The combination of RAD001 and M4N exerted in vitro synergistic effects on cell viability, apoptosis and expression of IGFBP2 in endometrial cancer cells. The Sp1 site on the IGFBP2 promoter was required for RAD001- and M4N-induced down-regulation. IGFBP2 protein expression was higher in endometrial cancer than in the normal endometrium ($P<0.001$). Furthermore, elevated IGFBP2 histoscores were significantly associated with a lower overall survival ($P=0.021$). In conclusion, our in vitro results demonstrate that RAD001 and M4N exert synergistic anti-proliferative effects against endometrial cancer cells, which appeared to be mediated by the inhibition of IGFBP2, a key anti-apoptotic regulator. Further clinical studies of this drug combination in patients with endometrial cancer may be warranted, especially in the presence of PIK3CA and IGFBP2 aberrations.

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