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氏名	木下　史緒理
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論文審査担当者	主査：　稲垣 宏 副査：　高橋 智，飯田 真介

Abstract

The treatment of multiple myeloma (MM) has been markedly altered by the clinical use of proteasome inhibitors and immunomodulatory drugs (IMiDs). Afuresertib (AFU), a novel inhibitor of the serine/threonine kinase AKT, shows clinical efficacy as a monotherapy against hematological malignancies and is expected to be used in combination with standard therapies for MM. To develop a more effective and less toxic combination of IMiDs for therapy, we examined the anti-tumor effect of sub-optimal doses of AFU, pomalidomide plus dexamethasone (PD), and the AFU-PD combination on MM cells. Two MM cell lines, XG-7 and U266, with low sensitivity to both PD and AFU monotherapies, were subjected to these combinations and analyzed. Although the cell lines showed a slight reduction in viability with the sub-optimal doses of each monotherapy, the combination of the treatments resulted in a reduction in cell viability and the progression of apoptosis. Co-treatment with sub-optimal doses of PD and AFU enhanced caspase activation and highly suppressed the expression of IKZF1 and IKZF3. In addition, this combination promoted the dephosphorylation and stabilization of 4EBP1, an inhibitor of eIF4E activation, which led to the impairment of eIF4E-mediated translational activity. Furthermore, AFU showed a sufficient inhibitory effect on the phosphorylation of FOXO1, a tumor suppressor, in monotherapy or in combination with PD, which may be attributable to the activation of FOXO1, the subsequent inhibition of tumor growth, and the induction of cell death. In conclusion, the combination therapy with sub-optimal doses of PD and AFU exhibited potent anti-tumor activity in MM cells and may provide a novel strategy for the treatment of patients who experienced intolerable toxicity or insufficient response during IMiD therapy.