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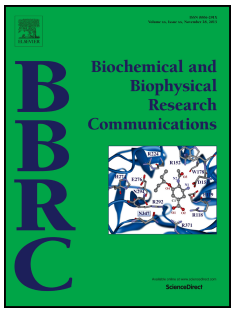

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The anti-osteosarcoma cell activity by a mTORC1/2 dual inhibitor RES-529

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Abstract. mTOR over-activation is important for human osteosarcoma (OS) tumorigenesis and progression. RES-529 is a mTORC1/2 dual inhibitor. Here, our results show that RES-529 inhibited viability, cell cycle progression and proliferation of the established (U2OS line) and primary human OS cells. RES-529 induced apoptosis activation in OS cells. It was yet non-cytotoxic to OB-6 osteoblastic cells and the primary human osteoblasts. RES-529 disrupted assembling of mTORC1 (mTOR-Raptor association) and mTORC2 (mTOR-Rictor-mLST8 association) in human OS cells, blocking mTORC1/2 activation. Significantly, RES-529 induced reactive oxygen species (ROS) production and mitochondrial depolarization in U2OS cells as well. RES-529-induced anti-OS cell activity was more potent than other known Akt-mTOR inhibitors. *In vivo*, RES-529 intraperitoneal injection significantly inhibited U2OS xenograft tumor growth in severe combined immunodeficiency (SCID) mice. mTORC1/2 activation in RES-529-treated tumor tissues was largely inhibited. Collectively, the mTOR inhibitor RES-529 efficiently inhibits human OS cell growth *in vitro* and *in vivo*.

Keywords. Osteosarcoma; mTOR; RES-529; Akt and Molecularly-targeted therapy.