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Curcumin sensitizes kidney cancer cells to TRAIL-mediated apoptosis via ROS-JNK- CHOP activation

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The Holy Grail in cancer therapy is to find an agent that is able to eradicate cancerous tumors without harming normal tissues. Much research has focused on fulfilling this goal. The use of TRAIL in cancer therapy has been considered an attractive option to kill different types of tumors with minimal toxicity on normal cells. However, the development of resistance against TRAIL by many tumor cells is the major obstacle that limits TRAIL's therapeutic applications in clinical settings. Curcumin induces apoptotic cell death through caspase dependent and independent mechanisms. It has been found that curcumin at low doses induces apoptosis by the down-regulation of proteasomes and increasing levels of ROS. The sensitization of the cancerous cell leads to activating many transcriptional factors and signaling pathways, resulting in activating apoptotic pathways and ultimately cell death. We investigated whether the combination of curcumin with TRAIL induced synergistic anti-tumor effects. Also, we assessed if the mechanism of cell death was via the induction of apoptosis and was caspase-dependent. Furthermore, the effect of curcumin or curcumin/TRAIL combination on general oxidative stress of cells was tested. As well as this, we examined whether oxidative stress can induce the activation of Mitogen Activated Kinases (MAPK) and Endoplasmic Reticulum (ER) stress. Curcumin was shown to cause a higher degree of sensitization of ACHN cells to TRAIL induced apoptosis than silymarin. The highest degree of synergy was observed at the combination of 25 μM curcumin with 50 ng/ml TRAIL. Curcumin, by itself or in a combination with TRAIL, did not only cause a cellular inhibition, but they also permanently induced a caspase dependent apoptotic ACHN cell death. The apoptotic cell death process was associated with the activation of both the intrinsic and the extrinsic pathways of apoptosis. Treating ACHN cells with curcumin or curcumin/ TRAIL combination can induce ROS production, therefore, increased the general oxidative stress of the cells. Curcumin induced ROS production was associated with an increase of ER stress and the dysregulation of MAPK pathways. Curcumin, alone or in combination with TRAIL was found to induce the expression of stress associated protein kinases, JNK and P38, while suppressed the expression of the survival kinase ERK. The pretreatment of cells with the free radical scavenger, NAC, abolished the effect of curcumin or curcumin/TRAIL combination on CHOP and MAPK protein expression. The pre-treatment with the JNK inhibitor Sp600125 abolished curcumin-induced CHOP activation.

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