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Sphk2 inhibitor ABC294640 enhances cell death in NSCLC cells via downregulation and proteasome-dependent degradation of c-FLIPL

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Background: Treatment of non-small cell lung cancer (NSCLC) with chemotherapeutic agents gives a poor clinical response due to strong resistance to these drugs. Therefore, there is an unmet need for development of novel targets to overcome chemoresistance. Sphingosine kinase-2 (SphK2) has been rationalized as an important therapeutic target. This study evaluated the impact of SphK2 inhibitor ABC294640, on cell death of lung adenocarcinoma-driven A549 cells via altering cellular FLICE inhibitory protein long variant (c-FLIPL), an important anti-apoptotic protein conferring resistance to apoptosis.

Methods: Cell viability and apoptosis were examined by MTT assay and flow cytometry analysis, respectively. Quantification of morphological changes in nuclei and visualization of apoptotic bodies were studied by DAPI staining. Gene and protein expression levels of anti-apoptotic and autophagy markers were examined by real time RT-PCR and western blot analysis, respectively.

Results: ABC294640 markedly decreased cell viability and enhanced apoptosis in A549 cells accompanied by down-regulating c-FLIPL at both gene and protein expression levels in a concentration-dependent manner. Small interfering RNA-mediated suppression of c-FLIPL increased ABC294640-induced cytotoxicity in A549 cancer cells. ABC294640 promoted proteasome-dependent degradation of c-FLIPL and proteasome inhibitor MG132 partially protected c-FLIPL from degradation induced by ABC294640. Although ABC294640 increased expression of autophagy markers, autophagy inhibition by chloroquine, had no significant effect in altering c-FLIPL protein level.

Conclusion: Altogether, these results suggest that ABC294640 via altering c-FLIPL at both transcription and proteasome degradation level may be an attractive therapeutic target to overcome drug resistance in NSCLC and probably in other solid tumors.

Biography

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