Melanoma is the deadliest form of skin cancer in the United States. Recent FDA-approved therapies for melanoma have increased patient survival. However, new or optimized therapeutic approaches are needed to improve treatment outcomes. 15-deoxy-Delta12,14-Prostamide J2 (15d-PMJ) is an investigational small molecule that induces ER stress-mediated apoptosis selectively in tumor cells. Additionally, 15d-PMJ significantly reduces melanoma growth in vivo. The goal of this study was to investigate mechanisms underlying the antitumor activity of 15d-PMJ. We found that the ER stress sensor, PERK, was required for 15d-PMJ-induced apoptosis. PERK activation triggered the release of ER-resident Ca\(^{2+}\) through an IP\(_3\)-sensitive pathway. Increased calcium mobilization led to the accumulation of Ca\(^{2+}\) in the mitochondria followed by the induction of the mitochondrial permeability transition pore (mPTP) and the deterioration of mitochondrial respiration. Finally, we demonstrated that the electronegative double bond located within the cyclopentene ring of 15d-PMJ was required for its activity. Taken together, the present study identifies PERK/IP3R3/mPTP signaling as a mechanism of 15d-PMJ anti-melanoma activity.

INTRODUCTION

- Melanoma is the deadliest form of skin cancer with roughly 7,000 individuals dying from the disease annually.
- 15-deoxy-Prostamide J2 (15d-PMJ) is a novel anti-cancer agent that eliminates melanoma by inducing ER-stress mediated programmed cell death.
- ER-stress occurs when unfolded proteins exceed the cellular folding capacity.
- Activation of ER-stress is known to cause Ca\(^{2+}\) mobilization and subsequent induction of programmed cell death.

Hypothesis:

ER-stress → PERK → ER to Ca\(^{2+}\) flux → Mitochondrial Ca\(^{2+}\) Overload → Cytochrome C release → Cell Death

RESULTS

PERK is required for 15d-PMJ-induced ER stress apoptosis

CONCLUSION

- PERK activity is necessary for the apoptotic action of 15d-PMJ.
- 15d-PMJ increases cytoplasmic Ca\(^{2+}\) through ER-stress which is required for its cytotoxicity.
- ER-stress induced by 15d-PMJ increases mitochondrial Ca\(^{2+}\) levels and mPTP opening.

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