

Abstract

# Target misfolded protein clearance pathway for cancer therapy <sup>†</sup>

Apar Pataer

MD Anderson Cancer Center, Department of Thoracic and Cardiovascular Surgery, Houston, TX 77459, USA; apataer@mdanderson.org

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**Abstract:** The role of RNA-dependent protein kinase R (PKR) and its association with misfolded protein expression in cancer cells are unclear. Herein we report that PKR regulates misfolded protein clearance by preventing its release through exosomes and promoting lysosomal degradation of misfolded prion proteins in cancer cells. We demonstrated that PKR contributes to the lysosome function and regulates misfolded prion protein clearance. We hypothesized that PKR-associated lysosome function is critical for cancer but not normal cell survival, representing an effective approach for highly targeted cancer therapy. In screening a compound library, we identified two PKR-associated compounds. Compound 1 did not affect normal cells but selectively induced cell death in cancer cells depending on their PKR expression status. Compound 1 significantly inhibited the growth of human lung and breast xenograft tumors in mice with no toxicity. Compound 1 binds to PI4K2A and disrupts the PKR/PI4K2A associated lysosome complex, contributing to destabilization of cancer cell lysosomes and triggering cell death. We observed that PKR and PI4K2A play significant prognostic roles in breast cancer patients. These results demonstrate that targeting of a PI4K2A/PKR lysosome complex may be an effective approach for cancer therapy.

**Keywords:** PKR; PI4K2A; lysosome; Compound 1



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